The impact of childhood obesity on long-term health burden in the UK

Min Hae Park

London School of Hygiene and Tropical Medicine

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Full name: Min Hae Park

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ABSTRACT

In the UK, 7-10% of the child and adolescent population are currently considered obese according to International Obesity Task Force (IOTF) definitions, and this proportion is expected to rise to 14% over the next 20 years. Childhood obesity is associated with complications including dyslipidemia, insulin resistance, and respiratory problems, and childhood body mass index (BMI) is correlated with BMI in adulthood. However, the ways in which overweight and obesity in early life impact on long-term health are not well understood.

This thesis reviews the current evidence for the associations between overweight in childhood and disease outcomes in adulthood, and discusses the limitations of methods that have commonly been used to examine this topic. To investigate the effects of childhood and adolescent overweight on long-term health, pooled data from three British National Birth Cohorts (the 1946 National Survey of Health and Development, 1958 National Child Development Study, and 1970 British Cohort Study) are analysed. The findings of this analysis indicate that being overweight in childhood and adolescence may contribute to increased risk of type 2 diabetes and coronary heart disease, but not hypertension or non-cardiovascular outcomes. Projections from a micro-simulation model show that overweight and obesity in the current UK child population could present a substantial burden in terms of disease prevalence and healthcare costs by the year 2050, and the effects of different obesity interventions on long-term burden are explored.

Overweight and obesity in childhood may have important implications for long-term cardiovascular risk, and current trends in childhood obesity prevalence are likely to have a substantial impact on long-term health burden in the UK. Early intervention to reduce overweight in childhood is likely to have an important role in reducing future obesity-related disease burden.

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ABBREVIATIONS AND ACRONYMS

BCS70	British Cohort Study 1970
BMI	Body mass index (also Quetelet Index), a measure of weight for height kg/m^2
BMI SDS	Body mass index standard deviation score
CAPI	Computer assisted personal interviewing
CASI	Computer aided self-interviewing
CHD	Coronary heart disease, includes angina and heart attack
CI	Confidence interval
CIMT	Carotid intima-media thickness
CVD	Cardiovascular disease, includes coronary heart disease and stroke
DAG	Directed acyclic graph
DALY	Disability-adjusted life year
DOHaD	Developmental Origins of Health and Disease
ESRC	Economic and Social Research Council
EU	European Union
GBD	Global Burden of Disease
HDL-C	High-density lipoprotein cholesterol
HR	Hazard ratio
HSE	Health Survey for England
ICD	International Classification of Diseases
IHD	Ischaemic heart disease
IIH	Idiopathic intracranial hypertension
IOTF	International Obesity Task Force
LDL-C	Low-density lipoprotein cholesterol
LOCF	Last observation carried forward
LVM	Left ventricular mass
MEND	Mind, Exercise, Nutrition, Do It!
MetS	Metabolic syndrome
MRC	Medical Research Council
NAFLD	Non-alcoholic fatty liver disease
NCDS	National Child Development Study 1958

NCMP	National Child Measurement Programme
NFBC1966	Northern Finland Birth Cohort 1966
NHF	National Heart Forum
NHS	National Health Service (UK)
NICE	National Institute for Health and Clinical Excellence
NSHD	Medical Research Council National Survey of Health and Development 1946
ONS	Office for National Statistics
OR	Odds ratio
PAF	Population attributable fraction
PCOS	Polycystic ovary syndrome
PDAY	Pathological Determinants of Atherosclerosis in Youth study
QALY	Quality-adjusted life year
RR	Risk ratio
SCE	Slipped capital epiphyses
SD	Standard deviation
SE	Standard error
SEP	Socioeconomic position
SES	Socioeconomic status
UK	United Kingdom
WHO	World Health Organization
YLL	Years of life lost

1. INTRODUCTION

1.1. Background

Childhood obesity prevalence has doubled or tripled in high-income countries since the 1980s,[1-2] and is rapidly rising in a number of low- and middle-income countries.[3-4] It is currently estimated that 155 million children aged 5-17 years worldwide are overweight or obese.[5] Obesity is associated with a number of co-morbidities, including type 2 diabetes, cardiovascular diseases (CVD) and several cancers,[6] and is one of the leading preventable causes of death and disease worldwide.[7-8] Increasing understanding of the progressive nature of many of these co-morbidities,[9-10] and awareness of the difficulties in treating adult obesity,[11] have shifted the focus from adult adiposity and its control to early life factors and prevention.[12] Reducing childhood obesity prevalence is a major priority for the UK government, as outlined in their 'Healthy Weight, Healthy Lives' cross-government strategy.[13]

The impending disease burden associated with childhood obesity has been variously described as 'a health time bomb,'[14] 'a massive tsunami,'[15] and even a national security threat.[16] It is known that childhood obesity is associated with a number of long-term health problems,[17] but the pathways from excess adiposity in early life to outcomes in adulthood are unclear. Furthermore, the scale and nature of the childhood obesity health burden are unknown. Key questions that arise from consideration of these issues include, what does childhood obesity today mean for health tomorrow? What are the wider implications of the childhood obesity epidemic, and what can we do to prevent or mitigate these effects?

As the number of obese children in the UK and worldwide continues to rise, the need for answers to these questions becomes increasingly urgent. Central to understanding the long-term implications of current childhood obesity is an examination of whether obese children who become obese adults are exposed to additional long-term health risks compared to non-obese children who become obese adults. Information about the expected burden of childhood obesity is essential for public services planning, resource allocation, and appropriate strategies for intervention.

1.2. Aims and objectives

The primary aim of this thesis is to investigate the impact of childhood obesity on future health burden in the UK.

Three main objectives are addressed. The first relates to whether overweight and obesity in childhood and adolescence are risk factors for long-term health outcomes; associations between

overweight in childhood and adolescence and morbidity in adulthood are examined to test the hypothesis that overweight in youth is associated with increased risk of obesity-related diseases in adulthood (type 2 diabetes, hypertension, coronary heart disease, stroke, asthma, arthritis, gall bladder disease, and selected cancers). One possible explanation for associations between childhood overweight and adult disease is that obesity tracks into later life, [18] so the effects of adult overweight may account for the observed disease risks. Therefore the second objective of this thesis is to examine the contributions of overweight and obesity at different life stages to disease outcomes, and to test the hypothesis that overweight in childhood and adolescence confer increased risk of obesity-related diseases in adulthood, compared to obesity in adulthood only. In addition to identifying whether childhood obesity contributes to long-term disease risk, it is of interest to know the implications of the current childhood obesity epidemic for long-term health burden. The Department of Health have used a micro-simulation model to estimate obesity burden in the UK in the year 2050 [19]; the final objective of this thesis is to estimate the health burden and healthcare costs associated with current levels of childhood obesity, and to explore the impact of interventions for preventing and treating obesity on future burden of childhood obesity. Addressing these objectives will further our understanding of the relationships between childhood overweight and adult disease, and provide insight into the potential future burden of the current childhood obesity epidemic.

1.3. Overview of the research

In this thesis, pooled secondary data from three British National Birth Cohort studies are analysed to address the first two research objectives, supported by the findings of a systematic review of the literature. The 1946, 1958 and 1970 birth cohorts are prospective studies that have followed up between 5,362 and 17,638 individuals born during one week in each year. Cohort members for whom there are height and weight data in childhood, adolescence and adulthood, and information on disease outcomes in adulthood, form the population for the main analyses. Despite some differences in data collection methods, these datasets have comparable target populations, and provide longitudinal data on participants at several points during childhood, adolescence and adulthood, making them ideal for studying life-course effects. The final objective is examined using a micro-simulation model developed by the National Heart Forum, which was designed to project future disease burden and costs associated with current obesity trends. Estimates generated from this model have been used by the Department of Health as the basis for predictions of future obesity burden in the UK.

Ethical approval for this work was obtained from the London School of Hygiene and Tropical Medicine Ethics Committee (see Appendix 1). Funding to support this work was from an Economic and Social Research Council (UK) 1+3 studentship.

1.4. Structure of the thesis

This thesis is organised as follows: Chapter 2 begins with an overview of the research area, discussing the effects of childhood obesity on health, and approaches to measuring obesity burden. This is followed by a systematic review of studies that have investigated the associations between childhood overweight and adult disease in Chapter 3. Chapter 4 describes the analytical approaches and methods used in the thesis. Chapter 5 describes the British National Birth Cohort data, giving an overview of patterns of response, participant characteristics, and the distributions of the variables used in the main analyses. Chapter 6 presents the results of analyses of the British National Birth Cohort data relating to the effects of childhood and adolescent overweight and obesity on adult disease. Chapter 7 presents the results from examination and application of the National Heart Forum obesity model for projecting disease burden attributable to childhood overweight and obesity in the UK, and assessment of the effects of different approaches to obesity interventions. Finally, Chapter 8 discusses the main findings of the thesis, their strengths and limitations, and their implications.

2. CHILDHOOD OBESITY: EPIDEMIOLOGY AND CONSEQUENCES

2.1. Introduction

The dangers of excess body fat for health were recognised more than two millennia ago in ancient Greece, when Hippocrates wrote that corpulence led to disease and early death, and observed that changes in the diet could lead to improvements in health. [20-21] However, it is only in recent decades that obesity in childhood has occurred on a scale and to an extent that has led to wide concern. In this chapter, I begin with an overview of childhood obesity definitions and epidemiology, and go on examine the evidence on the effects of childhood obesity on health and approaches to measuring obesity burden.

2.2. Childhood obesity: definitions and epidemiology

2.2.1 Measuring childhood obesity

Obesity is a condition in which there is excessive accumulation of body fat, to the extent that health is likely to be compromised. [22] Direct methods for estimating fat mass, such as magnetic resonance imaging (MRI) and dual energy x-ray absorptiometry (DXA), provide detailed information on aspects of body composition but require expensive equipment and skilled technicians. In large population-based studies, obesity is usually assessed using indirect methods, the most common of which is body mass index BMI, a measure of weight for height (weight in kilograms divided by the square of height in metres (kg/m^2)). Obesity in adults is defined by the World Health Organization (WHO) according to BMI cut-off points that relate to increased risk of co-morbidities and mortality (Table 2-1).

Table 2-1: Classification of overweight and obesity in adults (non-Asian populations) [22]

Classification	BMI (kg/m^2)
Underweight	<18.5
Normal range	18.5-24.9
Overweight (pre-obese)	25-29.9
Obese Class I	30-34.9
Obese Class II	35-39.9
Obese Class III	≥40

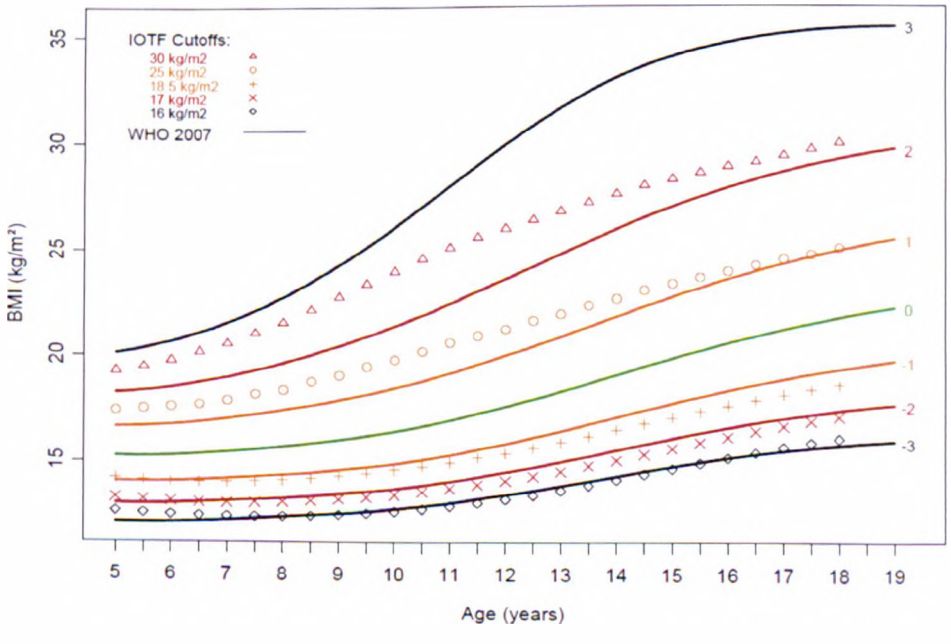
Measuring obesity in children and adolescents (aged <19 years) is complicated by the fact that height and body composition are continually changing. The proportion of fat to lean mass varies with sex, age and physical maturity, [23-24] making it problematic to define physiological norms. Consequently BMI adjusted for age and sex, expressed as centiles or standard deviation scores (BMI SDS or Z-score) of the BMI distribution in a reference population, are the most commonly used measures of adiposity in children and adolescents.

UK clinical guidelines on childhood obesity [25-26] recommend that children with BMI ≥91st centile of the 1990 UK reference population [27] should be considered for clinical intervention, with assessment of co-morbidities at BMI ≥98th centile. This is in contrast to population-based studies such as the National Child Measurement Programme, [28] which use cut-offs at the 85th and 95th centiles of the 1990 reference population to define overweight and obesity respectively. The WHO growth references for children aged up to19 years [29-30] are based largely on US data (more countries were included for development of infant and early childhood references), and use cut-offs at +1 SD and +2 SD to classify overweight and obesity, which are equivalent to BMI 25 kg/m^2 and BMI 30 kg/m^2 at age 19 years.

International definitions of childhood overweight and obesity have been developed for children aged 2-18 years by the International Obesity Task Force (IOTF), based on BMI centiles averaged across six countries (Brazil, USA, Great Britain, Netherlands, Hong Kong and Singapore), and which correspond to BMI 25 and 30 kg/m^2 at age 18 years. [31] Reference centile curves were fitted to these data using Cole's LMS method, an approach which summarises the BMI distribution at a specific age according to its median (M), coefficient of variation (S), and a measure of skewness (L, based on the Box-Cox power needed to transform the data to a normal distribution). [32] L, M and S at each age are used to draw smoothed curves, with the M curve representing the 50th centile curve for BMI.

Examples of child BMI cut-offs can be seen in Figure 2-1. The use of different references produces different estimates of obesity prevalence, [33] which can make comparison of results across studies problematic. The use of standardised definitions of obesity, such as the IOTF references, can avoid this issue.

Figure 2-1: Comparison of WHO and IOTF cut-offs for obesity in boys aged 5-19 years. Source: WHO



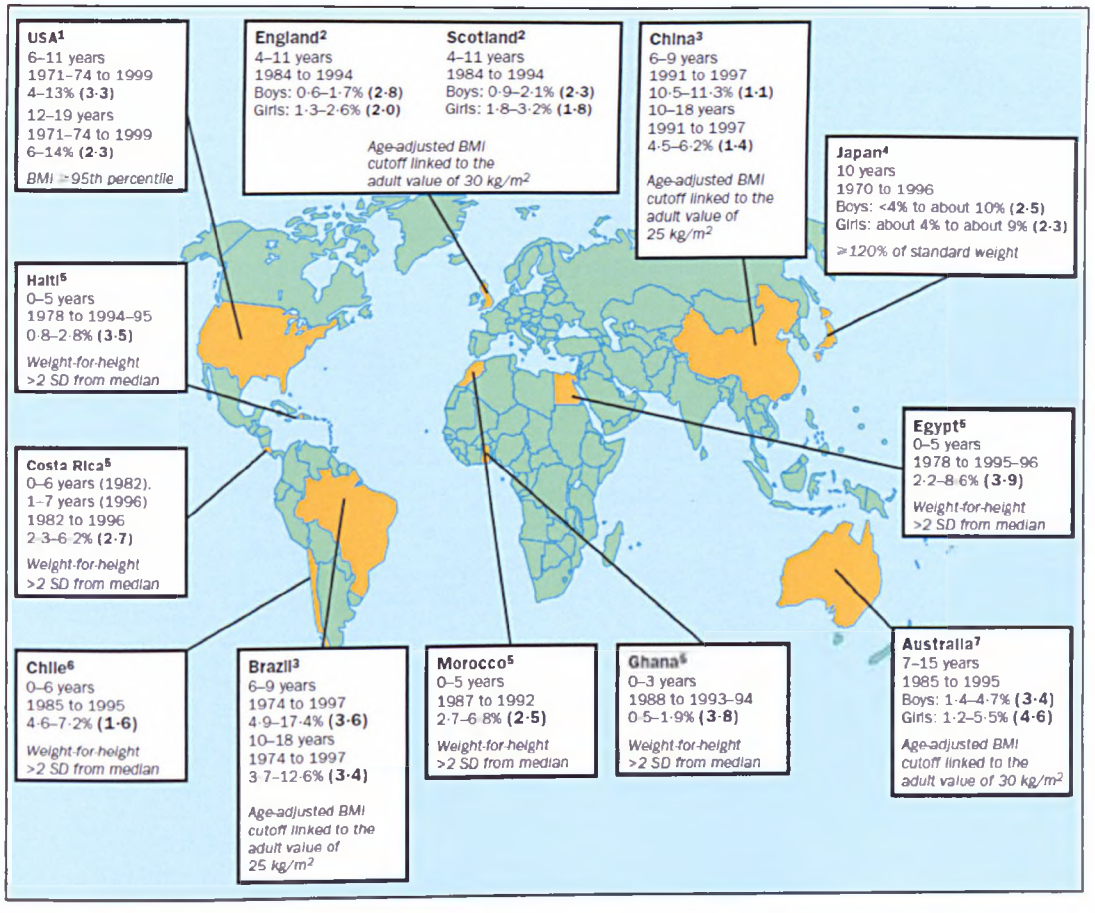
A limitation of BMI as a measure of adiposity is that it does not account for variation in body composition, fat distribution or body proportions. Abdominal fat and visceral adipose tissue (as opposed to subcutaneous adipose tissue) have been shown to be independently associated with increased cardio-metabolic risk, [34-35] and measures of abdominal obesity such as waist circumference can provide additional information on cardio-metabolic risk. [36-40] However, despite its limitations, BMI is highly correlated with adiposity and is a reproducible indicator of cardio-metabolic risk, [41] and its simplicity and reproducibility mean that it is a reliable measure of adiposity in large population-based studies. [42] Furthermore, BMI has been shown to be a stable measure of adiposity change in growing children. [43] For these reasons, BMI and IOTF cut-offs are used as measures of overweight and obesity in childhood, and the WHO cut-offs are used for adults throughout this thesis.

2.2.2 Epidemiology of childhood obesity

At the individual level, obesity can be attributed to an imbalance between energy intake (via diet) and energy expenditure (via physical activity), [44] except in the case of rare genetic or endocrine conditions. However, the etiology of obesity is complex, with influences on diet and physical activity acting at the individual, household, regional and societal levels to contribute to patterns of obesity. [45-46]

Since the 1980s, the prevalence of childhood obesity has doubled or tripled in most regions of the world, regardless of the method used to define obesity (Figure 2-2). The rate of increase in obesity prevalence and the global nature of this trend makes a genetic explanation unlikely, although genetic factors are likely to have an important role in individual variation in adiposity. [47] Changes in lifestyle at the population level have contributed to current trends, characterised by changing energy content, portion sizes and foodstuffs in the diet, decreased levels of physical activity, and increasing sedentary behaviours such as television viewing. [48]

Figure 2-2: Global increases in childhood obesity prevalence. Source: Ebbeling et al 2002 [2]



In the UK, 7-10% of children are considered obese by IOTF definitions, [45] which are among the highest rates in Europe.[1] The distribution of obesity is not uniform across socio-demographic groups, and overweight and obesity among children and adolescents has been associated with a number of factors, including older age, higher parental weight, lower socioeconomic status (although the reverse was true until the latter half of the 20th century, and the opposite effect is observed in many developing countries today [46]), ethnicity, reduced physical activity levels, and sedentary behaviours. [50-53] Data from the NCMP 2007/08 indicate that obesity prevalence at age 10-11 years is double the prevalence at age 4-5 years (18.3% versus 9.6%, ≥95th centile of UK 1990 reference), and is higher among boys than girls. [54] Obesity prevalence among Black (prevalence 26.4%) and Asian (21.5%) children is higher than the national average, and lower among Chinese (13.7%) and White (17.3%) children. There is also variation in prevalence of overweight and obesity between UK constituent countries and regions; analysis of 13,194 children from the UK Millennium Cohort Study at age 3 years showed that children from Northern Ireland and Wales were more likely to be overweight or obese than children in England, while within England, children from the East and South East regions were less likely to be overweight than children from London, even after adjustment for individual socio-demographic characteristics and risk factors for overweight. [55]

Obesity prevalence in England among children aged 2-11 years, defined according to IOTF criteria, increased from 1.7% in 1984 to 5.4% in 2002 among boys, and from 2.6% to 7.8% among girls over the same time period. [56] This is equivalent to an overall annualised change in prevalence of 0.7%, assuming linear change. However, the picture of change is more complex than one of a generalised increase in BMI. For example, the distribution of BMI has become increasingly positively skewed, such that the greatest increases in BMI have occurred amongst the heaviest children at the upper end of the distribution while the BMI distributions at the lower end are relatively unchanged. [57] Children are also becoming obese at younger ages than previous generations. [58-59] More recently, there is evidence from several countries, including the UK, Sweden, France, Australia, Japan and the USA, to indicate a plateauing of childhood obesity trends, although this stabilisation of trends is more apparent in higher socioeconomic status (SES) groups. [60-61]

2.3. Childhood obesity and health

The effects of childhood obesity on health can be divided into those that occur, a) concurrently (in childhood), or b) in the future. Many of the immediate and long-term health effects of childhood obesity have common causes, which are the result of metabolic and endocrine changes associated with obesity. For example, the metabolic syndrome, non-alcoholic fatty liver disease and polycystic ovary syndrome (in girls) share common features. [62] Disorders observed in childhood may also represent early stages of progression to other clinical outcomes that manifest in later life, such as in the case of metabolic syndrome, atherosclerosis and cardiovascular disease. Therefore from a public health perspective, childhood obesity represents a primary through to tertiary prevention challenge.

2.3.1 Concurrent co-morbidities of childhood obesity

Cardio-metabolic complications

Childhood obesity is associated with the development of atherosclerosis and related cardio-metabolic risk factors. Atherosclerosis in youth was first documented by Enos *et al* in an autopsy study which reported the presence of fibrous lesions in the coronary arteries of young US soldiers (mean age 22.1 years) killed in the Korean War. [63] Two contemporary US studies have expanded on these findings by relating atherosclerosis at autopsy to risk factors in childhood, adolescence and young adulthood. [9-10 64-65] The Bogalusa Heart Study, a series of cross-sectional surveys of children followed up into adulthood, found that cardiovascular risk factors observed at age 3-18 years, including BMI, were associated with the severity of atherosclerosis at post-mortem autopsy. [9-10] The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study, a multi-centre autopsy study of more than 2,000 young people who had died at ages 15-34 years of external causes, showed that cardiovascular risk

factors assessed from medical records and at autopsy were associated with atherosclerotic lesions in the arteries. [64-65] These studies confirmed that atherosclerosis begins in early life, and that the severity and extent of lesions is associated with obesity and other cardio-metabolic risk factors.

The metabolic syndrome MetS, also known as the insulin resistance syndrome and syndrome X, describes the clustering (co-occurrence) of risk factors for cardiovascular disease and type 2 diabetes, namely central obesity, hypertension, dyslipidemia (elevated LDL-cholesterol or triglycerides, or lowered HDL-cholesterol), and glucose intolerance or insulin resistance.[66] Clustering of cardio-metabolic risk factors has been observed in several studies of overweight children and adolescents,[37 67-74] and the number of risk factors has been shown to be correlated with the extent of atherosclerosis. [10] In the Bogalusa study, the relationship between obesity and cardio-metabolic markers was studied in a sample of 2,816 children and adolescents (age 5-17 years), and showed that measures of both total and central adiposity were associated with insulin, triglyceride, cholesterol and apolipoprotein levels. [75] Analysis of data from a nationally representative sample of 2,430 US children aged 12-19 years showed that 4% of all adolescents, 7% of overweight, and 29% of obese adolescents (BMI≥95th centile) met the National Cholesterol Education Program criteria for MetS. [70] A clinic-based study of obese children and adolescents in the UK (aged 2-18 years; BMI >95th centile) reported that 70% had at least one other component of the metabolic syndrome (insulin resistance or impaired glucose tolerance, dyslipidemia or hypertension), while 33% had multiple risk factors. [69] The prevalence of MetS has been shown to increase with the degree of overweight, reaching up to 50% among children with significant obesity. [76] Ethnic minority children are at higher risk of metabolic complications than white children. [74 77] Weight loss studies have shown improvements in cardio-metabolic risk factors with reduction in overweight. [78-79]

More recently, noninvasive techniques have been used to assess atherosclerosis in young people, and have confirmed the relationship with classic risk factors. A number of studies have shown increased carotid intima-media thickness (CIMT),[80-83] and increased left ventricular mass (LVM) [36 81 84] in children and adolescents with increased BMI and other risk factors. As an example, analysis of a sample of young people aged 13-27 years from the Bogalusa Heart Study showed that increased insulin levels were associated with increased LVM among participants in the highest tertiles for weight and adiposity. [84]

Type 2 diabetes

Insulin resistance and insulin deficiency can result in high blood glucose levels, and eventually type 2 diabetes. The condition is rare in youth, but prevalence has increased more than 10-fold in recent years, and is strongly associated with obesity. [85] One study of children in the UK and Ireland showed that 95% of those diagnosed with type 2 diabetes at age <17 years were

overweight or obese, while 83% were obese. [86] This study also showed that children of black and South Asian origin were overrepresented, with an incidence of type 2 diabetes that was between 4 and 11 times higher than that in white children (incidence in black children estimated at 3.9 cases per 100,000 per year, compared to 0.35 in white children). The progression from impaired glucose tolerance and MetS to overt type 2 diabetes may be accelerated in youth compared to adults, [87] but children can also revert from impaired to normal glucose tolerance if overweight is reduced, highlighting the importance of early intervention and weight maintenance during childhood. [79 88]

Fatty liver and gallbladder disease

Non-alcoholic fatty liver disease (NAFLD, an early stage of liver disease), is the most common form of liver disease in children and adolescents, and is associated with overweight and obesity.[89-90] A recent review found that there is a growing body of evidence that NAFLD shares many features of the MetS in children and adolescents. [91] The largest of the studies in this review was an autopsy study of 817 individuals who had died of external causes at age 2-19 years, which showed that there was evidence of atherosclerosis in 30% of children with fatty liver, compared to 19% of those without fatty liver (OR 1.8; P <0.001). [92] Other studies in the review showed a relationship between fatty liver and cardio-metabolic risk factors including obesity, dyslipidemia, hypertension, insulin resistance and CIMT. Lifestyle intervention studies have shown that reduction in overweight is associated with improvement in liver enzymes and NAFLD. [93-94]

Gallbladder disease is also related to overweight in youth. One study of pediatric cases of gallstones (cholelithiasis) and inflammation of the gallbladder (cholecystitis) showed that 60% of idiopathic cases were in overweight adolescents. [95] The degree of overweight is also associated with gallstones, with higher risk in obese adolescents than in overweight. [96] However, the relationship is complex, and there is evidence that gallstones may be associated with weight loss as well as overweight. One study of 493 German children and adolescents with BMI Z-score >2, found that those with gallstones had lost an average of 10.1 ±7.0 kg prior to the study, compared to 5.8 ± 5.0 kg among those participants who did not have gallstones. [96]

Respiratory problems

An association between overweight, obesity and asthma has been reported in a handful of prospective studies in children. A systematic review of longitudinal studies examining the relationship between BMI in childhood or adolescence and asthma in adolescence found an association between elevated BMI and persistence and intensity of asthma symptoms in 8 out of 10 studies. [97] As an example, one study of admissions to a US pediatric intensive care unit over a 10-year period showed that children with recurrent asthma exacerbations (asthma attacks)

were twice as likely to be overweight when compared to those with one admission for asthma (OR 2.3; 95% CI 1.1, 4.9). [98] Other components of the metabolic syndrome may also be related to asthma. One study of Mexican adolescents (n=500) showed that the prevalence of MetS was higher among obese adolescent boys with persistent asthma than in those without asthma, but no effect was observed in adolescent girls. [99]

Obstructive sleep apnoea is another problem associated with obesity in childhood. In a case-control study of 399 children and adolescents (age 2-18 years) in the US, obesity was associated with a more than four-fold increase in odds of sleep-disordered breathing (OR 4.59; 95% CI 1.58, 13.33). [100] Sleep apnoea may also be related to other cardiovascular risk factors. In a small study of 28 children and adolescents (age 2-18 years), sleep apnoea was associated with increased LVM and abnormal LV geometry, after adjusting for age, sex and BMI. [101]

Orthopaedic problems

Obese children and adolescents are at greater risk of musculoskeletal discomfort, mobility problems and orthopaedic complications, such as slipped capital epiphyses (SCE) and Blount's disease, than their normal weight peers. It is estimated that up to 80% of children with SCE [102] and Blount's disease [103] are obese. Cross-sectional studies have also indicated a dose-response effect, as children with SCE in both hips have higher BMI than those with unilateral disease. [102]

Gynaecologic problems

Polycystic ovary syndrome (PCOS) has been related to the MetS and NAFLD in women, with obesity as a common factor in both. [104] It is reported to be a growing problem among adolescent girls, and has been associated with elevated BMI in cross-sectional studies. [105-107] Such studies have also shown a higher prevalence of MetS [107-108] and liver dysfunction in obese adolescent patients compared to their normal weight peers. [109]

Neurological problems

Idiopathic intracranial hypertension IIH (or pseudotumor cerebri) is an uncommon condition (prevalence 1 per 100,000) that can lead to visual impairment and blindness. [110] It occurs more frequently in those with obesity than in lean populations. In an Israeli study, it was estimated that up to 60% of children with IIH (aged $\leq$16 years) were overweight or obese. [111]

Psychological well-being

Obese children face stigmatisation and are often subject to negative stereotypes. [112-113] Although evidence for an association between obesity and indicators of psychological well-being such as self-esteem and depression remains equivocal, [114] studies have shown that obese children have lower health-related quality of life,[115-116] greater body dissatisfaction, [114] and more emotional and social problems than their normal weight peers. [117] They are also more likely to

have problems with school attendance and perceived academic performance.[117] These problems are especially common among adolescent girls. [114]

2.3.2 Future health problems associated with childhood obesity

Tracking of obesity into adulthood

Tracking refers to the persistence of values or ranks of continuously distributed traits over repeated measurements over time. [118] BMI in childhood has been shown to track into adulthood, with the strength of associations increasing with childhood age; a systematic review of the literature on the tracking of overweight from childhood into adulthood found that longitudinal studies consistently reported an increased risk of overweight in adulthood for overweight and obese in youth. [18] In one study of children in the US (n=854), overweight or obesity at age 1-2 years was associated with OR 1.3 (95% CI 0.6, 3.0) for obesity in adulthood (age 21-29 years), compared to OR 17.5 (95% CI 7.7, 39.5) for overweight or obesity at age 15-17 years, after adjusting for parental overweight. [52] In another example, analysis of data from 2,610 participants in the Bogalusa Heart Study showed that BMI measured at ages 2-17 years was associated with BMI, adiposity (skinfold thickness) and overweight in adulthood (ages 18-37 years). [119] Analyses of data from the Fels Longitudinal Study have shown that BMI in childhood or adolescence can be used to predict the probability of overweight or obesity in adulthood, with better predictions with increasing age in childhood. [120]

Tracking of childhood overweight into adulthood, with its attendant health risks in later life, and the increasing association with childhood age, emphasize the difficulty of reducing overweight in later life and the benefits of early intervention.

Childhood obesity predicts cardiovascular risk in adulthood

In addition to persisting into adulthood, childhood overweight predicts other components of MetS and markers of atherosclerosis in later life. A recent systematic review of childhood obesity and adult cardiovascular disease risk reported consistent positive associations between BMI in early life and cardiovascular risk factors such as blood pressure and CIMT in adulthood. [121] In the Bogalusa Heart Study, overweight adolescents (age 13- 17 years) had adverse levels of body fatness, blood pressure, serum lipids, insulin and glucose at age 27-31 years, compared to those who were lean in adolescence. [122] The Muscatine Study, a population-based longitudinal study of cardiovascular risk factors in children, young adults and family groups, showed that CIMT in 725 men and women aged 33-42 years was associated with BMI and cholesterol levels in childhood. [123] Analysis of data from the Bogalusa Heart Study and the Cardiovascular Risk in Young Finns Study, a population-based prospective cohort in Finland, showed that high BMI at age 9-18 years was associated with increased risk of high CIMT and type 2 diabetes at age 24-41 years. [124]

Other cardiovascular risk factors that cluster with obesity in childhood have also been shown to track into adulthood in longitudinal studies. Analysis of the Bogalusa Heart Study showed that clustering of systolic blood pressure, insulin level and ratio of total to HDL-cholesterol persisted from childhood (age 5-17 years) to adulthood (up to age 25 years), and also that tracking of multiple risk factors increased with baseline ponderal index (a measure of adiposity, weight/height^3). [125] Multiple risk factors in childhood are associated with increased cardiovascular risk, as demonstrated in the Cardiovascular Risk in Young Finns study; pulse wave velocity and arterial stiffness (markers of atherosclerosis [126-127]) in white adults aged 24-45 years were associated with the number of classic risk factors (obesity, high LDL-cholesterol, low HDL-cholesterol, elevated blood pressure and smoking) in childhood and adolescence. [128-129] Furthermore, a reduction in overweight between childhood and adulthood was associated with lower pulse wave velocity, indicating a beneficial effect of weight management in youth for prevention of atherosclerosis. [128]

Childhood obesity and adult disease

There is some evidence that obesity in youth is associated with increased risk of a number of chronic diseases, including type 2 diabetes, hypertension, asthma, CVD, and cancers, and mortality in adulthood. [130-134] A study of 18,513 Israeli army personnel showed that odds ratios OR for hypertension at age 26-45 years were 1.75 (95% CI 1.66, 1.86) for men who were overweight at age 16-19 years, and 3.75 (95% CI 3.45, 4.07) for those who were obese, after adjusting for age and blood pressure. [135] Similarly, analysis of data from the Muscatine Study showed that childhood adiposity (measured at age 7-18 years) was positively correlated with adult blood pressure (age 20-30 years). [136] Analysis of data from 4,719 participants in the 1966 Northern Finland birth cohort found that obesity in adolescence was associated with a doubling of odds of doctor-diagnosed asthma in adulthood (OR 2.09; 95% CI 1.23, 3.57). [137]

The association between childhood BMI and adult disease may be stronger for BMI measured later in childhood. For example, a systematic review and meta-analysis of studies relating BMI at ages 2-30 years to later CHD risk found no strong evidence for an association with BMI measured in early childhood (age 2-6 years), but there was a positive association with BMI measured at ages 7-18 years (RR of CHD associated with 1 SD increase in BMI: 1.09; 95% CI 1.00, 1.20) and 18-30 years (RR 1.19; 95% CI 1.11-1.29). One study, which used data from the 1958 British birth cohort, showed that BMI measured at ages 11 and 16 predicted obesity and history of diabetes and hypertension at age 33, while BMI at age 7 gave less satisfactory results (using receiver operating characteristic analysis). [138] The evidence on long-term morbidity and mortality associated with childhood obesity is reviewed systematically and discussed in greater detail in Chapter 3.

Childhood obesity and long-term psychosocial outcomes

In addition to the relationship with disease outcomes, longitudinal studies have related childhood obesity to adverse social and economic outcomes in later life, especially among women. As an example, the National Longitudinal Survey of Youth, a US study of 10,000 men and women, showed that women who were obese at age 16-24 years had fewer years of higher education, lower family income, higher rates of poverty and lower rates of marriage than those who were not obese at those ages.[139] These effects remained even after adjusting for parental income and education. Analyses of the 1958 British birth cohort found that obesity at age 16 years was associated with lower hourly earnings at age 23 years among women, after adjustment for parental social class and arithmetic and reading test scores in childhood; this effect remained even among obese adolescents who were no longer obese at age 23. [140] An effect of adolescent obesity on earnings was not observed among male cohort members. Similarly, analysis of data from the 1970 British birth cohort showed that obesity at both ages 10 and 30 years was associated with poorer employment and relationship outcomes in women, but not in men. [141] However, this study did not find an effect in obese children who moved into the normal weight category in adulthood.

2.4. Burden of childhood obesity

The burden of a disease or risk factor can be described as the impact of the health problem in a population, in terms of economic cost, morbidity, premature mortality, quality of life or other indicators. [7] In the case of obesity, its contribution to incidence of type 2 diabetes, CVD, respiratory problems, cancers, liver disease, psychosocial problems, mortality, and the costs associated with these, would all contribute to its burden. Quantification of disease burden enables an assessment of the scale of a problem, monitoring of change over time, and estimation of the impact of various policy options on projected health outcomes. This information is essential for effective prioritization of resources and health services planning.

2.4.1 Measuring health burden

There are a number of ways in which the burden of an exposure or disease may be assessed. The simplest measures describe a single aspect, such as estimates of disease prevalence, incidence, or mortality rates attributable to the exposure in the population. Other summary measures combine different dimensions of ill health, such as disability-adjusted life years (DALYs), which take into account morbidity and mortality [7]; one DALY is conceptually equivalent to one lost year of health in the population. The DALYs for a specific disease are calculated as the sum of years of life lost (YLL) due to premature mortality and ill-health and disability due to the disease or exposure. Quality-adjusted life years (QALYs) or health-adjusted life expectancies (health expectancies) account for the quality of life as well as the amount of life lived [142]; typically, each year of life lived in perfect health is assigned a value of

1, death is assigned a value of 0, and values in between these limits indicate years that are not lived in full health. Other dimensions of burden, principally economic costs associated with ill health, including healthcare expenditure and loss of productivity due to poor health, may be incorporated into the calculation of health burden.

Two general models for attributing health outcomes to causes (exposures) have been described previously [143]: 1) categorical attribution, and 2) counterfactual analysis. Categorical attribution describes an approach in which an outcome is attributed to a single cause (or group of causes) according to defined rules, such as when attributing road traffic accidents to alcohol consumption. This approach has an advantage in that the numbers attributed to each of the causes will add up to 100%, but the main disadvantage is that it cannot account for multi-causal outcomes, such as death due to CVD in a person with type 2 diabetes. In counterfactual analysis, the contribution of a risk factor to the health outcome is estimated by comparing the measure of disease burden with the expected burden in an alternative hypothetical scenario (the counterfactual), such as in the absence or reduction of the risk factor, which provides an insight into the potential gains in population health (or money saved) that may be achieved by reducing an exposure. The contribution of the exposure is usually expressed as a population attributable fraction (PAF), which estimates the reduction in disease or mortality that would occur in the counterfactual scenario, where the distribution of the risk factor is different but all other factors are unchanged.

2.4.2 Obesity burden

Current burden

Studies show that obesity accounts for a substantial and growing proportion of disease burden worldwide. Analysis of the Global Burden of Disease (GBD) database showed that across developed regions, high BMI was the fifth leading cause of disease burden, accounting for 7.4% of DALYs. [144] As the prevalence of obesity has risen, its contribution to mortality has also increased. In one study, it was estimated that more than 40,000 deaths, a loss of 1.05 years of life expectancy, 77% of deaths from diabetes, and 14% of CVD mortality could be attributed to overweight and obesity in England and Wales in 2003 [145]; projections to the year 2015 showed that the contribution of obesity to mortality would be likely to increase over the period.

As a consequence of its contribution to healthcare expenditure, obesity is also associated with a substantial economic burden.[146-148] There is some debate about whether lifetime medical costs for obese individuals may be attenuated to some degree by reduced life expectancy, [149] but studies of elderly populations have indicated that those obese people who survive to age 70 will live as long as their normal weight peers, but with fewer disability-free life years and substantially higher expenditure on healthcare. [150] Recent analyses estimated that overweight

and obesity-related ill health cost the NHS £5.1 billion in 2006-07. [151] In addition to the costs of co-morbidities, the costs of treating obesity itself have risen substantially in recent years, with increases in the number of anti-obesity drug prescriptions [152] and bariatric surgical procedures. [153] The increasing proportion of people with extreme obesity also has implications for other public services, ranging from the need for wider furniture and equipment in schools and hospitals, to increased demand for assistance from fire services to lift patients or housebound individuals. [154-155] Furthermore, obesity presents indirect costs to the economy, such as through working days lost to ill health. [156-158]

Future burden

In the case of childhood obesity, there are both concurrent and long-term contributions to disease burden. A study of concurrent childhood obesity co-morbidities in the European Union (EU) used conservative estimates of disease prevalence from the literature, and estimated that at least 20,000 obese children in EU have type 2 diabetes, over 400,000 have impaired glucose tolerance, over 1 million have increased cardiovascular risk, and more than 1.4 million have early signs of liver disease. [159] The large number of children with risk factors for later disease, including CVD and liver disease, highlights the potential contribution of current childhood obesity to future disease burden.

Studies of future burden associated with obesity incorporate two elements: 1) predicting the nature of the obesity epidemic, based on some assumptions about the association between current and future BMI distribution, and 2) estimating the disease burden and/or costs associated with these. Such studies may also explore the impact of behavioural and environmental influences on obesity and policy interventions. [160] In one example, an Australian study estimated the future costs (in 2024/25) of obesity-related cancer and CVD in a cohort of young adults born 1970-1980. [161] For this, the authors modeled four scenarios of obesity distribution: one in which the prevalence of obesity was projected using an age-cohort logistic regression model (based on cross-sectional surveys at 5-year intervals), one which predicted a linear increase in obesity prevalence (based on two surveys), one in which obesity prevalence in 2024/25 was equal to the age-specific prevalence in 2004/05, and another in which obesity prevalence remained at the same level as in youth (age 25-34). Relative risks of disease from the literature were used to calculate PAFs, and applied to hospital discharge, mortality and direct healthcare cost data. Using this method, it was estimated that if obesity prevalence in 2024/25 remained at the same level as in youth, the number of hospitalisations due to cancer and CVD could be halved, with 200 fewer deaths, and more than $51 million saved, compared to a more than doubling of costs in the worst case scenario.

Using the micro-simulation model (also called an individual-based model) that is used later in this thesis (described in Chapter 7), [162] the 2007 Foresight Obesity report estimated that the

obesity prevalence in the UK would continue to rise over the next forty years, and that by 2050, the direct costs to the NHS would have increased by £5.5 billion. [19 45] This figure did not include the costs of increased disability, work absenteeism, early retirement and early death. In an updated analysis, it was estimated that by 2030, the prevalence of obesity among adults would increase from 26% to 41-48% in men, and from 26% to 35-43% in women, equating to an increase in the number of obese adults of 11 million, [163] which would result in rises in cases of diabetes, CVD and cancer, and a large reduction in the number of disability-free years. Medical costs associated with these diseases were estimated to increase by around $2 billion p.a. by 2030.

2.5. Summary

Childhood obesity prevalence has increased dramatically over the past three decades, and is now present in the population on a scale beyond that which has been seen previously. Due to its associations with health problems in both childhood and in later life, obesity presents a considerable burden and public health challenge.

The emphasis of the UK government is on preventing and reversing the recent trends in childhood obesity. Many of the concurrent and future health problems associated with childhood obesity appear to have common features, and disorders observed in children may represent early stages of progression to chronic diseases in adulthood, such as in the case of metabolic syndrome and cardiovascular disease. These features draw attention to the potential long-term effects of childhood obesity, and the role that early management of childhood obesity may have in the prevention of future chronic diseases. However, the extent to which the childhood obesity epidemic will contribute to future health burden, beyond that attributable to the tracking of overweight into adulthood, is unclear. Characterisation of the relationship between childhood obesity and adult disease, and estimation of the future burden of childhood obesity can contribute to the debate on the effectiveness and cost-effectiveness of early interventions to promote healthy weight, and may inform how resources should be allocated.

3. CHILDHOOD OBESITY AND LONG-TERM HEALTH: A SYSTEMATIC REVIEW OF THE LITERATURE

3.1 Introduction

As discussed in the previous chapter, there is growing evidence to indicate that the most common obesity-related diseases originate in early life, and that risk factors for these diseases track from childhood into adulthood. However, it is unclear whether individuals who were overweight in childhood have increased risk compared to others of the same weight status in adulthood who were not overweight in childhood. Previous reviews have explored the relationship between childhood obesity and disease in adulthood,[17 130] but have not focused on whether the effects of childhood obesity are independent of adult obesity.

In this chapter, I review the evidence on the relationship between childhood or adolescent BMI and morbidity and mortality in adulthood, with particular focus on the effect of early life BMI independent of adult BMI. The objectives were to systematically evaluate the current evidence on the relationship between childhood BMI and morbidity and mortality in adulthood, and to assess whether childhood BMI status contributes to adult disease risk, independent of adult BMI. I also examined the methods used to explore the independent effects of childhood obesity, and considered the strengths and limitations of these approaches, and the implications for future research.

The work that forms this chapter has been published in *Obesity Reviews* journal (Park, M. H., C. Falconer, R. M. Viner and S. Kinra. (2012). "The impact of childhood obesity on morbidity and mortality in adulthood: a systematic review." *Obesity Reviews* doi: 10.1111/j.1467-789X.2012.01015.x).

3.2 Methods

A systematic review of published studies investigating the associations between childhood BMI status and morbidity and mortality in adulthood was conducted. The main outcomes of interest were: type 2 diabetes, hypertension, cardiovascular diseases (coronary heart disease and stroke), asthma, arthritis, gall bladder disease, cancers, and mortality. These outcomes were selected based on background knowledge and previous reviews of the literature. [45 164]

3.2.1 Search strategy

Ovid MEDLINE (1948-July 2011), EMBASE (1980-2011 Week 18) and the Cochrane Library (1990-2011) were searched electronically for relevant publications, and reference lists from selected articles were hand-searched for additional studies. The search terms (shown in Table 3-1) were based on terms used in previous Cochrane reviews of childhood obesity, [165] and

incorporated tested search filters for study design used by the Scottish Intercollegiate Guidelines Network (SIGN) (available at: http://www.sign.ac.uk/methodology/filters.html).

3.2.2 Study selection

Potentially relevant titles were screened for initial assessment of eligibility using the following inclusion criteria:

1) Prospective or historical follow-up or case-control designs (i.e. childhood exposure and adult outcomes measured in the same individuals);
2) BMI from directly measured weight and height at one or more ages in childhood (mean age 2-12 years) or adolescence (mean age 13-19 years). Only studies with data on measured childhood BMI were included as the review by Reilly and Kelly [166] showed that evidence from recalled weight status was less consistent than evidence from measured BMI. Infant size was not included as an exposure of interest, as the relationships between infant size and growth and adult disease may be more complex and distinct from those with weight status in childhood; [167]
3) Childhood BMI status calculated using national reference charts or IOTF criteria [31], or BMI treated as a continuous measure;
4) Any of the outcomes of interest assessed (clinically or self-reported) at one or more stages in adulthood (age >19 years);
5) English language articles published after 1980.

Exclusion criteria were:

1) Studies that recruited participants for an obesity intervention or health promotion programme;
2) Participants from select clinical populations, e.g. preterm babies, childhood cancer survivors;
3) BMI calculated from parent or self-reported height and weight in childhood;
4) Studies that reported risk factors without a disease end-point as the outcome, e.g. blood pressure but not hypertension.

Abstracts were double-screened (by me, MHP and Catherine Falconer, CF) for retrieval of full-text articles, and inter-rater agreement was assessed using kappa coefficients (κ).[168]

Table 3-1: Search terms used in systematic review of childhood and adolescent weight status and adult morbidity

Database		
MEDLINE	**EMBASE**	**Cochrane library**
1. exp Child/	1. child/	"asthma, hypertension, cardiovascular disease, type 2 diabetes, arthritis, gallbladder disease, cancer" AND "child*, adolescen*, teen*" AND "obes*, overweight" in *Title, Abstract or Keywords*
2. exp Adolescent/	2. adolescent/	
3. juvenile.mp.	3. pediatrics/	
4. exp Infant/	4. child$.mp.	
5. child$.mp.	5. adolescen$.mp.	
6. adolescen$.mp.	6. infan$.mp.	
7. infan$.mp.	7. teen$.mp.	
8. teen$.mp.	8. p?ediatric$.mp.	
9. P?ediatric$.mp.	9. juvenile.mp.	
10. Pediatrics/	10. or/1-9	
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	11. exp OBESITY/	
12. (obes$ or obesity).mp.	12. overweight.mp.	
13. exp Obesity/	13. (obes$ or obesity).mp.	
14. exp Overweight/ or exp Body Weight/	14. exp body mass/	
15. (BMI or body mass index or body-mass-index or weight-for-height).mp.	15. (BMI or body mass index or body-mass-index or weight-for-height).mp.	
16. exp Body Mass Index/	16. 11 or 12 or 13 or 14 or 15	
17. 12 or 13 or 14 or 15 or 16	17. exp ASTHMA/	
18.(asthm$ or respiratory condition).mp. or exp Asthma/	18. (asthm$ or respiratory condition).mp.	
19. exp Hypertension/ or hypertension.mp.	19. exp HYPERTENSION/ or hypertension.mp.	
20. cardiovascular disease.mp. or exp Cardiovascular Diseases/	20. cardiovascular disease.mp. or exp cardiovascular disease/	
21. exp Diabetes Mellitus, Type 2/ or type 2 diabetes.mp.	21. exp non insulin dependent diabetes mellitus/ or type 2 diabetes.mp.	
22. arthritis.mp. or exp arthritis/	22. arthritis.mp. or exp ARTHRITIS/	
23. gall bladder disease.mp. or exp Gallbladder Diseases/	23. gall bladder disease.mp. or exp gallbladder disease/	
24. cancer.mp. or exp Neoplasms/	24. cancer.mp. or exp neoplasm/	
25. 18 or 19 or 20 or 21 or 22 or 23 or 24	25. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	

26. exp Case-Control Studies/	26. exp case control study/
27. exp Cohort Studies/	27. exp longitudinal study/
28. case control.tw.	28. exp retrospective study/
29. (cohort adj (study or studies)).tw.	29. exp prospective study/
30. Cohort analy$.tw.	30. exp cohort analysis/
31. (Follow up adj (study or studies)).tw.	31. (Cohort adj (study or studies)).mp.
32. (observational adj (study or studies)).tw.	32. (Case control adj (study or studies)).tw.
33. Longitudinal.tw.	33. (follow up adj (study or studies)).tw.
34. Retrospective.tw.	34. 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35. 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34	35. 10 and 16 and 25 and 34
36. 11 and 17 and 25 and 35	36. limit 35 to (human and yr="1980 -Current")
37. limit 36 to (humans and yr="1980 -Current")	

3.2.3 Study quality

Study quality of case-control and cohort studies was assessed using a checklist adapted from the Newcastle-Ottawa Quality Assessment Scale (available at: http://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf). Studies were assessed based on the following domains:

- Selection bias: one star awarded if overweight/obese children were drawn from the same community as normal weight children; one star awarded if the study demonstrated that the outcome of interest was not present at the start of the study (for cohort studies);
- Comparability: one star awarded if comparison of age and sex at baseline between exposure groups demonstrated comparability, or if analyses controlled for age and sex; one star awarded if analyses controlled for socioeconomic position, a potential confounder of the association between childhood weight status and disease outcomes;
- Assessment of outcomes: one star awarded if outcome in adulthood was assessed by a trained health professional or through health records; one star awarded (for cohort studies) if follow up sufficient for outcomes to manifest – a mean age at follow-up of >35 years was selected as the cut-off as diabetes and hypertension diagnosed at ≤35 years of age has been considered as early onset in the literature [169-170];

- Adequacy of follow-up: for cohort studies, one star awarded if all subjects were accounted for at follow-up, or if subjects lost to follow-up were unlikely to introduce bias (≤20% lost to follow-up, or a description of those lost suggest no difference from those followed up).

3.2.4 Data extraction and synthesis

The data were double-extracted independently using a pre-designed extraction form. The principal outcomes that were extracted from each study were measures of the association between adult disease risk and childhood BMI (expressed as regression or correlation coefficients) or childhood BMI category/status (expressed as risk ratio, hazard ratio or odds ratio and confidence intervals), and these measures after adjustment for adult BMI. The following information was also extracted: study design, exposure(s), disease outcome(s), methods of measuring exposure/outcome, child age, adult age, sample size, sex of participants, country of study, years of birth, measures of tracking of BMI/overweight, and study quality measures (see above). Due to the diverse nature of outcomes, study designs and measures of effect included in the selected studies, data were synthesised and are presented in a narrative fashion. Publication bias was assessed using a funnel-plot in Stata 12 (StataCorp, TX). To assess potential bias due to different methods of assessing outcomes, results of studies using self-reported disease were compared with those using objective measures.

3.3 Results

3.3.1 Search results

The initial search yielded 7,890 results, which were narrowed down to 118 abstracts for full-text screening (Figure 3-1). Studies that did not meet inclusion criteria but which reported outcomes relevant to the review are summarized in Table 3-4. A total of 40 studies were included in the review; two of these were case-control studies, [171-172] and the remaining 38 were cohort studies (including three manuscripts presenting pooled analyses of cohort studies [173-175]). Inter-rater agreement was substantial (84%, κ=0.62). Sample sizes n ranged from 181 [131] to 1,145,467. [176] The majority of studies were from Western Europe (Denmark, Finland, Norway, Sweden, the UK, the Netherlands), and the US (including Hawaii). Two studies were conducted in Australia, [177-178] and a further two in Israel. [135 179] The mean ages at which BMI was measured ranged from birth up to 19 years. Full descriptions of the included studies can be seen in Table 3-2.

Figure 3-1: Study selection process

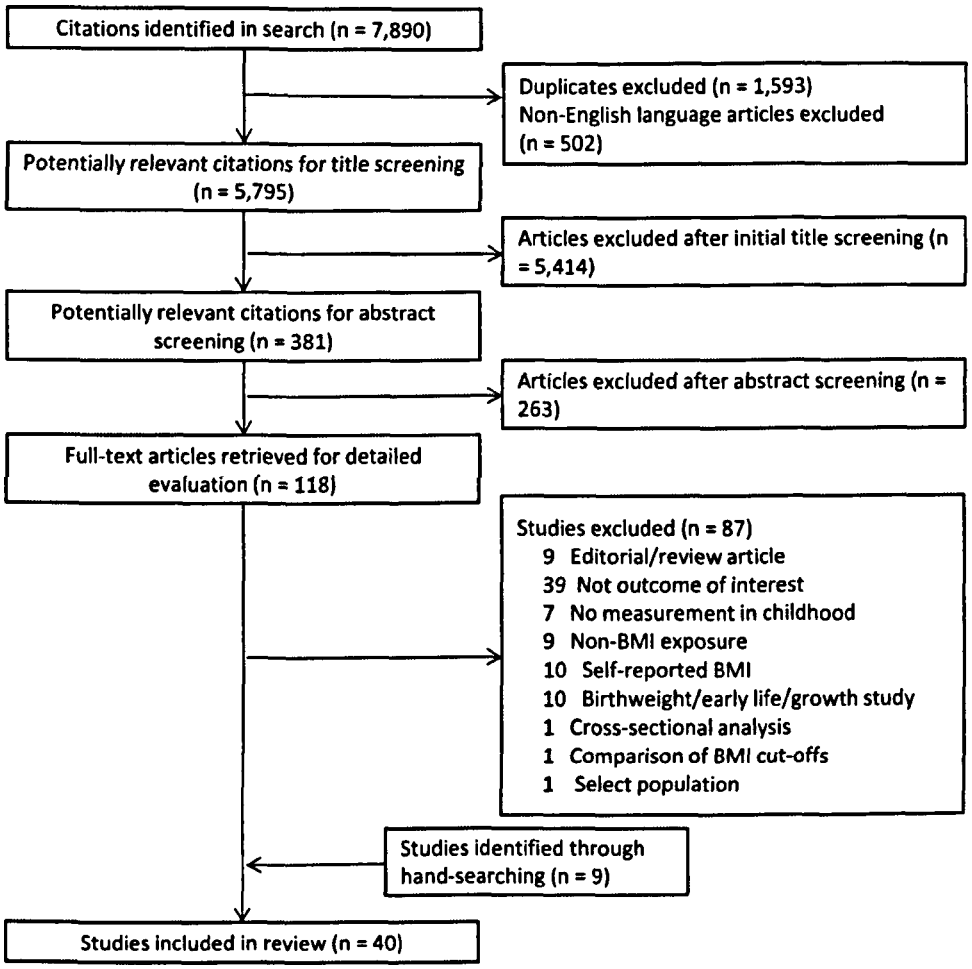


Table 3-2: Description of included studies

Reference (study design)	Exposure measure(s)	Disease outcome(s)	Age at last follow-up, years	Population	Main effect size	Adjustment for adult BMI
Ahlgren 2004 [180] (cohort)	BMI quintiles at age 14 y	Breast cancer (registry data)	Time to event	117,415 Women in Copenhagen, b. 1930-75	Lower BMI at age 14 associated with increased risk of breast cancer: RR per 1 unit increase in BMI: 0.97 (95% CI 0.96, 0.98)	-
Al Mamun 2009 [177] (cohort)	BMI z-score at age 5 y; overweight & obesity (IOTF)	Type 1 and type 2 diabetes (self report)	21	2,639 Men & women (51% ♀) in Australia, b. 1981-84	1 unit increase in BMI z-score at age 5 associated with 60% increase in odds of diabetes (OR 1.61; 95% CI 1.24, 2.09); overweight/obesity vs non-obese: OR 2.60; 1.29, 5.22	-
Andersen 2010 [173] (cohort)	BMI at age 7 y	CHD – nonfatal and fatal (registry data)	Time to event after age 25 y	216,771 Men & women (49% ♀) Copenhagen, b. 1936-76 & Helsinki, b. 1924-44	Each unit increase in BMI at age 7 y associated with ~5-10% increase in odds of CHD event, after adjustment for birth weight	-
Baker 2007 [181] (cohort)	BMI z-score at age 7-13 y	CHD – nonfatal and fatal (registry data)	Time to event	276,835 Men & women (50% ♀) in Copenhagen, Denmark, b. 1930-76	♂: 1 unit increase in BMI z-score associated with 5-17% increased odds of nonfatal event, 10-24% increase for fatal event ♀: 1 unit increase in BMI z-score associated with 2-11% increased odds of nonfatal event, 7-23% increase for fatal event	-
Barker 2002 [182] (cohort)	BMI quartiles at age 11 y	Type 2 diabetes, hypertension, CHD (registry)	20+	13,517 Men & women in Helsinki, Finland, b. 1924-44	ORs for1 unit increase in BMI at age 11: *T2DM* 1.18 (1.13, 1.23); *Hypertension* 1.07 (1.04, 1.09); *CHD* 1.06 (1.03, 1.10) [Adjusted for age and sex]	-

Barker 2002b [183] (cohort)	BMI Z-scores at ages 1-12 y	Hypertension (registry data)	38-39	6,730 Men & women (47% ♀) in Finland, b. 1934-44	From age 8, high BMI associated with hypertension; cumulative incidence 13.7% (11.2-16.2) among men with BMI <16 at age 12 vs 21.1% (18.4-23.8) among men with BMI >18	-
Bjorge 2004 [184] (cohort)	BMI categories at age 14-19 (medium 25-74th; high -84th; v high ≥85th centile, US ref.)	Kidney cancer (registry data)	Time to event; mean age 45 y	227,221 Men & women (49% ♀) in Norway, b. 1943-1950s	♂: Very high BMI at age 14-19 y associated with 2.6 times risk of renal cancer compared to medium BMI category: RR 2.64 (95% CI 1.48, 4.70) ♀: No strong evidence of association between BMI category at age 14-19 y and renal cancer	-
Bjorge 2008 [185] (cohort)	BMI categories at age 14-19 (medium 25-74th; high -84th; very high ≥85th centile, US ref.)	Mortality: cause-specific and all-cause (registry data)	Time to event up to 2005; mean age 40 - 43 y	226,678 Men & women (49% ♀) in Norway, b. 1943-1950s	Highest BMI category vs. medium [RR (95% CI)]. *All-cause mortality*: ♂: 1.4 (1.3, 1.6); ♀: 1.4 (1.2, 1.5) *Cancer (all)*: ♂: 1.2 (0.9, 1.5); ♀: 1.2 (1.1, 1.5) *Ischemic heart disease*: ♂: 2.9 (2.3, 3.6); ♀: 3.7 (2.3, 5.7) *Cerebrovascular diseases*: ♂: 1.9 (1.2, 3.2); ♀: 1.5 (0.9, 2.6)	-
Burgess 2007 [178] (cohort)	BMI z-score quartiles at age 7 y; overweight and obesity (IOTF) vs non-obese	Incident asthma after age 7 y [adult-onset: age>21 y] (self reported)	32	753 Men & women (52% ♀) in Tasmania, Australia, b. 1961	♂: No strong evidence of association between BMI z-score quartile or overweight at age 7 and asthma at age 32 ♀: Each increase in BMI z-score quartile at age 7 associated with OR 1.73 (95% CI 1.17, 2.17); overweight at age 7 OR 3.05; 1.28, 7.29	OR 1.73 →1.51 (0.98, 2.31); 3.05 → 2.13 (0.82, 5.57)

Chu 1991 [77] (case-control)	Overweight (BMI >85th centile) at age 18 y	Breast cancer	20-54	4,742 cases; 5,698 controls. Women in USA b. 1926-1962	No strong evidence of association between BMI category and post-menopausal breast cancer risk; RR pre-menopausal breast cancer for obese women 0.6 (0.2, 0.9), no association with overweight RR premenopausal: not overweight at 18/overweight adult 1.5 (1.2, 1.9); overweight at 18/not overweight adult 0.9 (0.6, 1.5); overweight at 18/overweight adult 0.9 (0.6, 1.2) Menopausal: not overweight at 18/overweight adult 1.8 (1.2, 2.6); overweight at 18/not overweight adult 0.9 (0.4, 2.1); overweight at 18/overweight adult 0.8 (0.4, 1.5)	See results
De Stavola 2004 [186] (cohort)	BMI-SDS at ages 2, 4, 7, 11 and 15 y	Breast cancer (registry data)	53	2,187 Women in UK, b. 1946	No strong evidence of association between BMI-SDS at any age and breast cancer	-
Engeland 2003 [187] (cohort)	BMI categories at age 14-19 (medium 25-74th; high -84th; v high ≥85th centile, US ref.)	Ovarian tumour (registry data)	Time to event, up to age 100 y or 2001	111,883 Women in Norway, b. 1943-61	Being in high and very high BMI categories in adolescence associated with increased risk of ovarian cancer compared with medium BMI category. High: RR 1.43 (1.00, 2.04); Very high: RR (1.56 (1.04, 2.32)	-
Engeland 2003 [188] (cohort)	BMI categories at age 14-19 (85th-94th, ≥95th centile vs. reference category 25th-75th centile)	All-cause mortality (registry data)	Time to event, mean 31.5 years follow-up)	227,003 men and women in Norway, b. 1948-68	Obesity (BMI >95th centile) at age 14-19 was associated with increased risk of all-cause mortality in adulthood (RR in men 1.82; 95% CI 1.48, 2.43, RR in women 2.03; 95% CI 1.51, 2.72)	-
Eriksson 1999 [189] (cohort)	BMI categories at age 11y (BMI ≤15.5; -16.5; -17.5; >17.5)	CHD deaths (registry data)	Deaths during 1971-95	3,641 Men in Finland, b. 1924-33	BMI at age 11 positively associated with risk of CHD death. Compared to baseline group (BMI≤15.5) at age 11 y: BMI 15.5-16.5: HR=1.28; BMI 16.5-17.5: HR=1.35; BMI >17.5: HR=1.53	-
Eriksson 2001 [190] (cohort)	BMI z-score; BMI categories at age 6 (BMI ≤13.6; -14.2; -14.8; -15.4; >15.4)	CHD hospitalizations & deaths (registry)	Events during 1971-97	4,630 Men in Finland, b. 1934-44	No strong evidence of association between BMI z-score and CHD	-

Eriksson 2003a [191] (cohort)	BMI at ages 1-12 y	Type 2 diabetes (registry data)	Diagnoses 1964-98 at age >40 y	8,760 Men & women (47% ♀) in Finland, b. 1934-44	Cumulative incidence of T2DM positively associated with BMI at each age from 4 years onwards	-
Falkstedt 2007 [192] (cohort)	BMI category in late adolescence (BMI <18.5; 18.5-20.9; 21-22.9; 23-24.9; 25-29.9; ≥30)	CHD and stroke, fatal and nonfatal (registry data)	40-55	46,156 Men in Sweden, b. 1949-51	*CHD*: BMI ≥30 kg/m^2 at age 18-20 years associated with 4 times risk compared to BMI 18.5-20.9 (HR 4.3; 95% CI 3.1-5.9). *Stroke*: HR in highest BMI category=2.4 (1.3, 4.5); lowest risk in BMI category 21.0-22.9 (HR 0.9; 95% CI 0.7, 1.1).	-
Field 2005 [193] (cohort)	BMI z-scores and centiles (categories - <10th; -25th; -50th; -75th; -85th; ≥85th centile, US ref.) at age 8-15 y	Hypertension (self report of medication or clinical assessment)	18-26	286 Men & women in Boston USA, b. 1963-73; results reported for male subjects only	Compared to reference group (BMI <75th centile in childhood) individuals with BMI 75th-84th centile had 3 times risk of hypertension in adulthood (OR=3.6; 95% CI 0.7, 18.2); individuals with BMI ≥85th centile had 5 times risk (OR=5.1; 95% CI 1.4, 18.1).	Same point estimate, wider CIs
Forsen 2004 [194] (cohort)	BMI z-score at age 11 y	CHD – hospital admissions and deaths (registry)	27-64	4,130 Women in Finland, b. 1934-44	No strong evidence of association between BMI z-score and CHD risk. Compared to baseline group BMI <15.9 kg/m^2, HR for CHD among BMI >18.4 was 1.79 (0.89, 3.60).	-
Gunnell 1998 [195] (cohort)	BMI categories at ages 2-14 (<25th;25-49th; 50th-75th; >75th centile, UK90 ref.)	Mortality – all cause, CVD, IHD, stroke (registry data)	Up to July 31, 1995	2,990 Men & women (51% ♀) in Britain, b. 1922-37	BMI in 50-75th centile vs. 25th-49th centile: *All cause* HR 1.4 (1.1, 1.8), *CV* HR 1.6 (1.1, 2.5), *IHD* HR 2.1 (1.3, 3.6). BMI >75th centile vs. 25th-49th centile: *All cause* HR 1.6 (1.1, 2.3). No strong evidence of association with stroke mortality.	-
Hoffmans 1989 [196] (cohort)	BMI at age 18 y and BMI categories (≤18.9; 19-19.9; 20-24.9; ≥25 kg/m^2)	Mortality – CHD and cancer (death certificates)	18-49 (32 years follow-up)	78,612 Men in the Netherlands, b. 1932	Compared to reference group with BMI 19-19.9 kg/m^2 *CHD mortality*: BMI 20-24.9 associated with 30% increase in risk (HR 1.31; 1.02, 1.67); BMI ≥25 HR 2.42 (1.36, 4.30). *Cancer mortality*: No association with BMI category.	-

Hypponen 2003 [197] (cohort)	BMI-SDS tertiles at ages 7, 11, 16, 23 y	Type 2 diabetes (self-reported)	41	10,683 Men & women in Britain, b. 1958	Compared to ref. group (BMI-SDS in middle tertile) *Age 7*: Upper tertile OR 3.97 (95% CI 1.7, 9.1); 1 unit increase in BMI-SDS OR 1.44 (1.2, 1.7). *Age 11*: Upper tertile OR 3.59 (1.7, 7.5); BMI-SDS OR 1.78 (1.5, 2.1). *Age 16*: Upper tertile OR 4.18 (2.1, 8.4); BMI-SDS OR 2.04 (1.7, 2.4).	Adjusted for BMI at 23 years → no association
Israeli 2007 [135] (cohort)	Overweight (BMI 25-30 kg/m^2) and obesity (BMI>30) at ages 16.5-19 y	Hypertension (medical history or clinical assessment)	26-45	18,513 Men in Israel, recruited to Israeli Defense Forces 1976-96	Adjusted for age and blood pressure at baseline, compared to normal weight, overweight in adolescence associated with hypertension risk (OR 1.75; 95% CI 1.66, 1.86); obesity associated with nearly 4 times risk (OR 3.75; 3.45, 4.07).	-
Jeffreys 2004 [198] (cohort)	BM-SDS at ages 2-14 y	Cancers: All, breast, colon, prostate, lung; cases and mortality (registry)	Cases up to Dec 2001, deaths to Jan 2003	2,347 Men & women in Britain, b. 1922-37	*All cancers*: Compared to lowest BMI-SDS quartile, being in highest quartile associated w/ 40% increase in risk (OR 1.43; 95% CI 1.01, 2.04); 1 unit increase in BMI-SDS OR 1.14 (1.00, 1.29); stronger association w/ cancers related to smoking. No association w/ other cancers	-
Juonala 2011 [174] (cohort)	Overweight and obesity (IOTF) at ages 4-19 y	Type 2 diabetes and hypertension (clinical assessment)	Mean length of follow-up: 23 y	6,328 men and women in the US, Australia and Finland	*Type 2 diabetes*: RR for overweight or obesity 2.4 (95% CI 1.6, 3.6) Hypertension: RR for overweight or obesity 1.8 (95% CI 1.5, 2.1) Analyses adjusted for age, height, cohort and length of follow-up	Overweight as child but nonobese as adult - similar risk as nonobese as child & adult
Lawlor 2005 [199] (cohort)	BMI z-score at primary school entry (mean 4.9 y); BMI z-score quartiles;overweight & obesity (IOTF)	CHD and stroke hospital admissions and mortality (registry data)	Follow-up period began on January 1, 1981	11,106 Men & women in Scotland, b. 1950-56	*For CHD, stroke and CHD/stroke:* No strong evidence of association with BMI z-score quartile at school entry; no strong evidence of association with overweight/obese status.	-

Lawlor 2006a [200] (cohort)	BMI z-score at primary school entry	Diabetes diagnosis at age >20 y (self-reported)	46-50	5,793 Men & women in UK, b. 1950-56 (*singleton births only*)	Each unit increase in BMI z-score at school entry associated with 22% increase in risk of diabetes in adulthood (OR 1.22; 95% CI 1.10, 1.36)	Adjustment for adult BMI: OR 1.07 (0.96, 1.19)
Lawlor 2006b [201] (cohort)	BMI z-score in childhood and adolescence; overweight and obesity (IOTF)	IHD and stroke (registry data)	Up to 30 Nov 2004	2,586 men & women in Britain b. 1922-37; 1,420 men b. 1936-69; 10,555 men & women b. 1948-68	Pooled results: no strong evidence of an association between BMI z-score in childhood and risk of mortality from IHD or stroke	-
Le Marchand 1988 [172] (case-control)	BMI tertiles at age <25 y	Breast cancer (registry data)	29-65	3,208 Women in Hawaii, b. 1918-43	No strong evidence of association between BMI tertile at age <25 y and breast cancer risk	-
Li 2007 [202] (cohort)	BMI-SDS at ages 7, 11, 16; overweight and obesity (IOTF)	Hypertension (clinical assessment or medication)	45	9,297 Men & women (50% ♀) in Britain, b. 1958	BMI-SDS at all ages positively associated w/ hypertension: Age 7, OR 1.10 (1.04, 1.17); Age 11, OR 1.22 (1.15, 1.28); Age 16, OR 1.27 (1.20, 1.34) Overweight/obese associated w/ increased risk of hypertension: Age 7, OR 1.35 (1.13, 1.64); Age 11, OR 1.66 (1.39, 1.97); Age 16, OR 1.96 (1.64, 2.35)	Adjustment for BMI at age 45 y →no association
Magnussen 2010 [124] (cohort)	BMI Z-scores at ages 9-18 y; overweight and obesity (IOTF)	Type 2 diabetes (clinical assessment)	24-41	1,781 Men & women (56% ♀) in US & Finland	BMI≥75th centile in childhood RR 3.4 (95% CI 1.8-6.4) [adjustment for other MetS components, RR 3.0; 1.6-5.7] IOTF overweight/obesity RR 3.4 (1.7-6.8) [adjustment for other MetS components, RR 3.4; 1.7-6.7]	-

Morrison 2010 [203] (cohort)	BMI at age 12.4±3.3 (Princeton Follow-up Study) 10.0±0.5 (National Growth & Health Study)	Type 2 diabetes (clinical assessment or self-report)	PFS: 38.6±3.6 NGHS: 19.1±0.7	PFS: 822 men & women (53% ♀) in the US b. 1960s NGHS: 1,067 women in the US	PFS: BMI in top fifth centile at baseline associated with 4-fold increase in risk of T2DM (OR 4.00; 95% CI 1.28, 12.5) NGHS: no strong evidence that BMI at baseline associated with T2DM in stepwise logistic regression model	-
Must 1992 [204] (cohort)	BMI categories at ages 13-18 y (overweight: *BMI>75th centile*; lean BMI between 25th and 50th centiles, US ref.)	Mortality; Morbidity: CHD, angina, diabetes, athero-sclerosis, stroke, hip fracture, cancer, arthritis (self-report)	73±1	181 Men & women (55% ♀) in the US, b. 1914-16	♀– no strong evidence of association between overweight in adolescence and mortality ♂– overweight in adolescence associated with all-cause mortality (HR 1.8; 1.2, 2.7); CHD mort. (HR 2.3; 1.4, 4.1); stroke mort. (HR 13.2; 1.6, 108.0); colorectal cancer mort. (HR 9.1; 1.1, 77.5) No strong evidence of association between overweight in adolescence and angina, diabetes, atherosclerosis, stroke, colorectal cancer or stroke; CHD risk increased in men (HR 2.8; 1.1, 7.2)	Adjustment for adult BMI → no association
Neovius 2009 [205] (cohort)	BMI categories at age 16-20 y (under-, normal, overweight, obese; WHO)	Mortality (registry data)	Follow-up to September 2007	45,884 men in Sweden, b. 1949-51	Overweight (HR 1.33; 95% CI 1.15, 1.53) and obesity (HR 2.14; 95% CI 1.61, 2.85) associated with increased risk of death (adjusted for muscular strength, age socioeconomic status and smoking).	-
Nieto 1992 [206] (cohort)	Quintiles of relative weight derived internally at age 5-18 y	Mortality (death certificates)	Follow-up to June 1985	13,146 men and women (50.3% ♀) iu the US, b. 1915-40	Relative weight in highest quintile (prepubertal and postpubertal) associated with increased risk of mortality (OR 1.5; 95% CI 1.0, 2.4)	-
Nguyen 2008 [207] (cohort)	BMI at ages 4-18 y	Type 2 diabetes (clinical assessment)	19-44	1,988 Men & women (57% ♀) in the US, b. late 1950s-1990	Each unit increase in BMI since childhood associated with increased risk of adult diabetes (β 0.09; 0.06, 0.12)	-

Osmond 2007 [208] (cohort)	BMI at ages 1-11 y	Stroke - hospitalization or death (registry data)	59-69	12,439 Men & women (48% ♀) in Finland	Each unit increase in BMI associated with reduced risk of all stroke at ages 2 (HR 0.84; 0.77, 0.92) and 7 y (HR 0.85; 0.76, 0.94) [same pattern with hemorrhagic and thrombotic stroke]; no strong evidence for association with BMI at age 11 y	-
Shaheen 1999 [209] (cohort)	BMI and BMI quintiles at age 10 y	Asthma in the previous year (self reported)	26	6,420 Men & women (55% ♀) in Britain, b. 1970	BMI at age 10 y not associated with asthma at age 26 y	-
Silventoinen 2009 [176] (cohort)	BMI categories at conscription (under-, normal, overweight, obese, very obese; WHO)	CHD and stroke – hospitalization and mortality (registry data)	39-44 (follow-up to end 2006)	1,145,467 Men in Sweden, b. 1951-76	Hazard ratios (reference group: normal weight) *CHD:* Overweight 1.74 (1.64, 1.84); Obese 2.50 (2.22, 2.81); Very obese 3.23 (2.54, 4.10) *Stroke*: Overweight 1.37 (1.26, 1.47); Obese 2.08 (1.78, 2.42); Very obese 3.20 (2.40, 4.26)	-
Tirosh 2011 [210] *(cohort)*	BMI percentile at age 17 y	Type 2 diabetes and coronary heart disease (clinical assessment)	25-45 (mean age 30.6±5.3)	37,674 Men in Israel Defense Forces (IDF) Medical Corps	HR for incident diabetes in adulthood for top decile of BMI in adolescence vs bottom decile: 2.76 (2.12, 3.58) HR for incident CHD: 5.43 (2.77, 10.62)	Diabetes HR 1.01 (.75, 1.4) CHD HR 6.85 (3.3, 14.2)

♂=male; ♀=female; b.=born; ref.=reference population; BMI=body mass index kg/m^2; CHD=coronary heart disease; HR=hazard ratio; OR=odds ratio; RR=risk ratio; 95% CI=95% confidence interval; IOTF=International Obesity Task Force definition of childhood overweight/obesity; NGHS=National Growth and Health Study; PFS=Princeton follow-up study; WHO=World Health Organization definition of overweight/obesity

3.3.2 Childhood or adolescent BMI and long-term health

Of the 40 included studies, 11 reported on type 2 diabetes, six on hypertension, 15 on coronary heart disease (CHD), eight on stroke, two on asthma, three on cancers (multiple), two on colon cancer, one on kidney cancer, four on breast cancer, one on cervical cancer, one on ovarian cancer, and six on all-cause mortality (some studies considered multiple disease outcomes). Evidence of associations between childhood or adolescent BMI status and adult disease outcomes (not accounting for the effect of adult overweight) are summarised by outcome in Table 3-3.

Type 2 diabetes

There was consistent evidence that overweight in early life was associated with increased risk of type 2 diabetes in adulthood. Of 11 studies that analysed the relationship between BMI or BMI status in childhood (ages 0-18 years) and type 2 diabetes in adulthood, 10 reported a positive association (*n* ranged from 822 [203] to 37,674 [179]), including one study which analysed data from the NCDS 1958 cohort. [197] Odds ratios for one unit increase in BMI-SDS ranged from 1.22 (95% CI 1.10 to 1.36) at school entry (*n* 5,793), [200] to 2.04 (1.7 to 2.4) at age 16 (*n* 10,683). [197] One small US study (*n* 181) found no strong evidence of an association between overweight at age 13-18 years and diabetes at age 73. [204] A study from Norway (*n* 226,678) [185] reported mortality from endocrine, nutritional and metabolic diseases as an outcome (mean age at follow-up 40-43 years), and found a positive association with BMI categories at age 14-19 years (RR: 2.5, 95% CI 1.4 to 4.5 in men, RR 5.7, 95% CI 3.0 to 11.0 in women).

When seven studies using objectively assessed type 2 diabetes (from registry data or clinical examination) [124 174 182 191 203 207 210] were considered separately from those using self-reported data, all seven showed that increased BMI or overweight at ages 1-18 years were associated with increased risk of type 2 diabetes in adulthood; the largest effect size was observed in a study of 822 men and women from the US, which reported OR 4 (95% CI 1.28, 12.5) for BMI in the top fifth centile at mean age 12 years; another US study showed that each unit increase in BMI at age 4-18 years was associated with a 9% increase in diabetes risk at age 19-44 years (95% CI 6-12).

Three of the included studies explored the effects of childhood obesity independent of adult BMI by simultaneously adjusting for adult BMI in regression analyses. In an analysis of data from a British birth cohort, associations between BMI-SDS in childhood and adolescence and self-reported type 2 diabetes at age 41 were no longer observed after adjustment for BMI at age 23 years (*n* 10,683).[197] For example, one unit increase in BMI-SDS at age 11 years was associated with OR for type 2 diabetes of 1.78 (95% CI 1.5 to 2.1), while one unit increase in

BMI-SDS at age 23 was associated with OR 2.25 (1.9 to 2.6); after adjustment for BMI at age 23, the odds ratio for one unit increase in BMI-SDS at age 11 was reduced to 1.06 (0.8 to 1.3). Similarly, in a study of BMI z-score at primary school entry and self-reported diabetes at age 46-50, each 5 kg/m^2 increase in adult BMI was associated with an OR of 1.65 (95% CI 1.43 to 1.90); OR per BMI-SDS at school entry decreased from 1.22 (95% CI 1.10 to 1.36) to 1.07 (0.96 to 1.19) after adjustment for adult BMI (*n* 5,793).[200] The same effect was observed in an analysis of Israeli data, when the HR for incident diabetes in adulthood for adolescents with BMI in the top decile compared to the bottom decile was reduced from 2.76 (95% CI 2.12 to 3.58) to 1.01 (0.75 to 1.4) after the inclusion of BMI in adulthood in the regression model (*n* 37,674). [210]

A pooled analysis of four cohort studies compared outcomes for participants categorised into four groups according to their overweight status in childhood and adulthood, [174] and showed that cohort members that had been overweight or obese in childhood but not obese in adulthood had similar risk of diabetes as those who had been normal weight in childhood and adulthood (RR 1.3; 95% CI 0.4, 4.1).

Hypertension

Six studies from Israel, Finland, Britain (NCDS cohort), Australia and the US, reported on hypertension (*n* from 286 [193] to 18,513 [135]); all studies showed that increased BMI or overweight in early life (ages 1-19) was associated with an increased risk of hypertension in adulthood (ages at follow-up ranged 18-45 years). Odds ratios for obesity in childhood ranged from 1.35 (95% CI 1.13, 1.64) [202] at age 7 to 3.75 (3.45, 4.07) at age 16-19 y. [135] All six studies used an objective measure of hypertension as the outcome, although one study used a combination of clinical examination and self-report of use of antihypertensive medication. [193]

Two of the five studies reported findings adjusted for adult BMI. In one study, individuals who had been overweight at age 8-15 years were shown to have five times the risk of hypertension in early adulthood compared to those who were normal weight (OR 5.1, 95% CI 1.4, 18.1); after adjustment for BMI at age 18-26, the effect size remained the same, but the confidence interval was wider and included OR=1. [193] Similarly, in the other study, associations between BMI-SDS at ages 7, 11, and 16 and clinically assessed hypertension at age 45 were no longer observed after controlling for BMI at age 45 years. [202] The pooled analysis of four studies, [174] showed that those who had been overweight or obese in childhood but not obese in adulthood had similar risk of hypertension as those who had been normal weight in childhood and adulthood (RR 0.9; 95% CI 0.6, 1.4).

Coronary heart disease

15 studies explored the relationship between BMI or BMI status in childhood/adolescence and CHD events (fatal and non-fatal). Of these, 10 studies (*n* ranged from 2,990 [132] to 1,145,467 [176]) reported that increased BMI or overweight at ages 2-25 years was associated with increased risk of CHD in later life (ages 39+); half of these studies were in male study populations [176 189 192 196 210] Hazard ratios ranged from 1.53 for CHD mortality associated with high BMI at age 11 [189] to 5.43 (95% CI 2.77, 10.62) for incident CHD associated with high BMI at age 17 [210]). In one US study (*n* 181) higher BMI at ages 13-18 was associated with increased risk of CHD morbidity and mortality in males but not females. [131] The remaining 4 studies (*n* 4,130 [194] to 14,561[175]) found no association between childhood BMI (ages 2-22 years) and CHD at ages 25-80 years. All studies used objective measures of CHD or CHD mortality as outcome measures.

One of the included studies of CHD looked at the effect of childhood obesity independent of BMI in adulthood. In this large study (*n* 37,674), the hazard ratio for incident CHD at age 25-45 for men with BMI in the top decile at age 17 (compared to those with BMI in the bottom decile) increased from 5.43 (95% CI 2.77 to 10.62) to 6.85 (3.3 to 14.2) after adjustment for BMI in adulthood. [210] Another study (*n* 181), which reported an association between overweight in adolescence and CHD mortality among men, found that this association was attenuated to the null after adjustment for adult BMI. [204]

Stroke

Of the 8 studies that reported on stroke outcomes, two large studies from Sweden (*n* 46,156 [211] and 1,145,467 [176]) showed that overweight and obesity in late adolescence (ages 16-25) were associated with increased risk of stroke in adulthood at ages 39-55. HRs ranged from 1.4 (95% CI 1.3, 1.5) for overweight to 3.2 (2.4, 4.3) for very obese children. One study from Norway (*n* 226,678) reported an association between high BMI at age 14-19 years and stroke mortality in males (RR 1.9, 95% CI 1.2, 3.2) at ages up to 62 years; [212] a further study (*n* 181) observed this association in males. [131] One Finnish study reported an inverse relationship [213]; among 12,439 men and women, increased BMI at ages 2 and 7 years was associated with a 15-16% reduction in risk of stroke at ages 59-69. Three British studies (*n* 2,990 [132] to 14,561 [175]) found no strong evidence of an association between childhood BMI and stroke. All studies used objective measures of stroke, namely hospital admission and mortality data from registries.

One small study (n 181), which reported an association between overweight in adolescence and stroke mortality in unadjusted analyses, found that adjusting for adult BMI attenuated this effect to the null, and the association was no longer observed. [204]

Asthma

Two studies reported on self-reported asthma as an outcome. One study from Australia (*n* 753) showed that overweight at age 7 was associated with OR 3.1 (95% CI 1.3, 7.3) for adult-onset asthma in women, [178] while analysis of data from the BCS70 cohort (*n* 6,420) found no strong evidence of an association between BMI category at age 10 and asthma at age 26. [209] A Norwegian study reporting on deaths from diseases of the respiratory system showed an increased risk with higher BMI at age 14-19. [212]

In the Australian study of self-reported asthma and overweight at age 7, the odds ratio was attenuated from 3.1 to 2.13 after adjustment for BMI in adulthood, and the 95% confidence interval was widened to include OR=1 (0.82 to 5.57). [178]

Cancer

Evidence for an association between BMI status in childhood and cancers was mixed. Three studies reported on cancers (not cause-specific) from objective measures (registry or mortality data); one study of 2,347 British men and women showed that cohort members with BMI-SDS in the highest quartile at age 2-14 years had a 40% increase in risk of cancer (morbidity and mortality, up to age 80). [214] In a Norwegian cohort, having a very high BMI at age 14-19 was associated with a 20% increase in risk of cancer mortality among women only. [212] An analysis of data from 78,612 Dutch men showed no association between BMI at age 18 and cancer mortality at ages 18-49. [196] Colorectal cancer mortality was shown to be associated with BMI in adolescence (ages 13-19) in two studies (RR 2.1 to 9.1) [131 212]; this effect was observed among men only in one of the studies. [131] In a Norwegian study (n 227, 221), high BMI at ages 14-19 was associated with kidney cancer among men (RR 2.6 [1.5, 4.7]). [184]

Of four publications that looked at breast cancer outcomes, one study of 117,415 Danish women showed that increased BMI at age 14 years was associated with a reduction in risk of breast cancer in adulthood (RR 0.97, 95% CI 0.96, 0.98). [180] Another study (case-control study of >10,000 women) reported that the risk of pre-menopausal cancer was lower among women who were obese at age 18 (RR 0.6, 0.2 to 0.9), but there was no association with post-menopausal cases. [171] The remaining studies from the UK and Hawaii [172] found no strong evidence of an association between BMI at ages 2-25 years and breast cancer in later life. One study analysing cervical cancer mortality among Norwegian women showed that very high BMI at ages 14-19 was associated with an almost doubling of risk (RR 1.9 [1.1, 3.2]), [212] while another Norwegian study looking at ovarian cancer in 111,883 women showed that high BMI at ages 14-19 was associated with 43-56% increase in risk of ovarian tumour. [187]

The US study which showed that overweight at age 13-18 years was associated with colorectal cancer mortality reported wide confidence intervals for the hazard ratio (HR 9.1, 95% CI 1.1 to

77.5) (*n* 181), which widened to include HR=1 when adjusted for adult BMI. [204] This study also reported on a variety of other morbidity and mortality outcomes, and no associations with adolescent obesity were observed after adjustment for adult BMI. The case-control study of breast cancer [171] assessed outcomes according to weight status at ages 18 and in adulthood, and showed that women who were not overweight in adolescence but overweight in adulthood had an increased risk of pre- and post-menopausal breast cancer compared to those who were not overweight in either period (RR for premenopausal cancer 1.5, 95% CI 1.2 to 1.9); there was no difference in risk for those who were overweight at age 18, regardless of weight status in adulthood.

All-cause mortality

Six of the included studies reported on the relationship between BMI status in early life and all-cause mortality. Two studies from Norway (*n* 226, 678 [185] and 227,003 [188]) one from Sweden (*n* 45,884 men [205]), one from the US (*n* 13,146 [206]) and another from Britain (*n* 2,990) [195] showed that high BMI at ages 2-19 was associated with 40-60% increase in risk of all-cause mortality in adulthood. In a small US cohort (*n* 181), an association was observed among men but not women [204]; when this estimate was adjusted for adult BMI, there was no longer any strong evidence for an association.

Table 3-3: Summary of included studies

Outcome	Number of studies	Summary of evidence	Description
Type 2 diabetes	11	++++++++++?	10 studies [124 174 177 182 191 197 200 203 207 210]: increased BMI/overweight at various ages in childhood and adolescence associated with increased risk of type 2 diabetes in adulthood 1 study: no association [204]
Hypertension	6	++++++	5 studies [135 174 182-183 193 200 202 204 207 210]: increased BMI/overweight at various ages in childhood and adolescence associated with increased risk of hypertension in adulthood
Coronary heart disease	15	++++++++++???? + (♂)	10 studies [173 176 181-182 185 189 192 195-196 210]: increased BMI/overweight at various ages in childhood and adolescence associated with increased risk of CHD (nonfatal and fatal) in adulthood 1 study [204]: Positive association between BMI in adolescence and CHD mortality in men only 4 studies [190 194 199 201]: no association
Stroke	8	+++ –??? + (♂)	2 studies [176 192]: increased BMI/overweight in adolescence associated with increased risk of stroke in adulthood 1 study [185]: higher BMI in adolescence associated with increased risk of death from cerebrovascular diseases 1 study [204]: positive association between BMI in adolescence and stroke mortality in men only 1 study [208]: increased BMI at ages 2 and 7 associated with reduced risk of stroke in adulthood 3 studies [195 199 201]: no association
Asthma	2	? + (♀)	1 study [178]: increased BMI in childhood associated with increased risk of asthma in women only 1 study [209]: no association between BMI at age 10 y and asthma in adulthood
All cancers	3	+? + (♀)	1 study [198]: Higher BMI-SDS in childhood associated with increased odds of cancer (cases and mortality); stronger association with cancers related to smoking 1 study [185]: higher BMI in adolescence associated with increased risk of cancer mortality in women only 1 study [196]: no association between BMI category at age 18 y and cancer mortality
Colon cancer	2	++	2 studies [185 204]: Higher BMI in adolescence associated with increased risk of colorectal cancer mortality

Kidney cancer	1	+ (♂)	1 study [184]: High BMI in adolescence associated with increased risk of renal cancer in boys
Breast cancer	4	–???	1 study [180]: lower BMI at age 14 y associated with increased risk of breast cancer in adulthood 3 studies [171-172 186]: no association
Cervical cancer	1	+	1 study [185]: Higher BMI in adolescence associated with increased risk of cervical cancer mortality
Ovarian cancer	1	+	1 study [187]: High BMI in adolescence associated with increased risk of ovarian cancer
All-cause mortality	6	+++++ + (♂)	5 studies [185 188 195 205-206]: increased BMI in childhood/adolescence associated with increased risk of mortality. 1 study [204]: high BMI in childhood associated with all-cause mortality in men only

+ indicates positive association between BMI/weight status and disease; – indicates negative association; ? indicates no strong evidence of association; ♂=male; ♀=female

Table 3-4: Summary of excluded studies relevant to the review

Study	Outcome(s)	Main result	Main reason for exclusion
Xu et al [137]	Asthma (physician diagnosed)	Obesity at age 14 y associated with doubling of asthma risk (OR 2.09; 95% CI 1.23, 3.57)	BMI from self-reported weight and height at age 14
Baer et al [215]	Pre-menopausal breast cancer	Higher BMI at ages 5, 10 and 20 y associated with lower risk of breast cancer	BMI from recalled weight and height at ages 5, 10, 20
Bardia et al [216]	Post-menopausal breast cancer	Above average weight at age 12 y associated with lower risk of breast cancer (RR 0.85; 95% CI 0.74-0.98)	Recalled weight status at age 15 years
Merten et al [217]	Asthma, diabetes, hypertension	Obesity in adolescence (age 2-19 y) associated with increased risk of hypertension; obesity in adolescence and in adulthood (age 19-26) associated with all outcomes	BMI from self-reported height and weight in adolescence
Sanderson et al [218]	Pre-menopausal breast cancer	No association between perceived weight status at age 15 y and later breast cancer risk	Recalled/perceived weight status at age 15
Ursin et al [219]	Pre-menopausal breast cancer	No association between BMI at age 18 y and later breast cancer risk	BMI from recalled weight and height at age 18
Verla-Tebit et al [220]	Pre-menopausal breast cancer	Larger body build at menarche associated with lower risk of breast cancer (OR 0.69; 95% CI 0.49, 0.96)	Recalled/perceived body build at menarche
Weiderpass et al [221]	Pre-menopausal breast cancer	Heavier build at age 7 and 18 y associated with lower risk of breast cancer	Recalled/perceived body shape in childhood
Lubin et al [222]	Ovarian cancer	Higher BMI at age 18 y associated with increased risk of ovarian cancer	BMI from recalled weight and height at age 18
Ferraro et al [223]	All-cause mortality	Overweight at age 12 y associated with lower risk of mortality) RR 0.68; 95% CI 0.59, 0.80)	Recalled/perceived weight status at age 12
Franks et al [224]	Mortality – all-cause, external and endogenous	BMI $\geq 95^{th}$ centile at mean age 11 y associated with increased risk of death from endogenous causes (incidence rate ratio 1.90; 95% CI 1.37, 2.65)	Participants from select American Indian population
Van Dam et al [134]	All-cause mortality	Overweight and obesity at age 18 y associated with all-cause mortality (HR for obesity 2.79; 95% CI 3.04, 3.81)	BMI from self-reported weight and height at age 18

3.4 Summary and implications

This review has found that there is a consistent body of evidence that shows associations between childhood overweight and cardiovascular outcomes and mortality in adulthood. However, few studies have assessed the effects of childhood overweight on adult disease independent of adult weight status.

The finding that childhood overweight is associated with type 2 diabetes, hypertension, coronary heart disease, and mortality, unadjusted for adult BMI, is in line with a recently updated systematic review of overweight in childhood and mortality and adult morbidity. [17] Evidence for stroke outcomes is mixed, with half of the included studies reporting a positive association with early life BMI, and half reporting the inverse or no association. A systematic review which explored the relationship between childhood obesity and asthma in adolescence concluded that obesity precedes, and is associated with, asthma [97]; however, based on the two studies included in this review, there is no strong evidence for an effect of childhood BMI on adult-onset asthma. There is limited evidence that childhood BMI is associated with increased risk of colorectal and kidney cancers. Three of four studies found no association between overweight in youth and breast cancer; one study showed that higher BMI in adolescence was associated with reduced risk of breast cancer, [180] as has been observed in studies using BMI from recalled height and weight in adolescence. [215-216] These findings are in line with a previous review, which found no consistent evidence of associations between relative weight in childhood or adolescence and breast cancer risk. [225] High BMI in adolescence may be associated with cervical and ovarian cancers; however pooled analysis of data from six cohorts with recalled weight at age 18 or 20 found no association between BMI in early adulthood and ovarian cancer risk. [226] Inspection of a funnel-plot [227] using effect sizes unadjusted for adult BMI revealed asymmetry, indicating the possible presence of publication bias.

This review has expanded on previous reviews [17] by assessing the evidence for the effects of childhood overweight on adult disease, independent of the association with adult BMI. The issue of independent effects is important to understanding the progression of long-term disease risk in overweight children. A handful of studies have examined the independent effects of childhood BMI. These have mostly assessed independent effects by simultaneously adjusting for BMI in adulthood, and most of them showed that effect sizes were attenuated after adjustment for adult BMI. For example, in a study of diabetes (*n* 10,683) the odds ratio for one unit increase in BMI-SDS at age 11 was reduced from 1.78 (95% CI 1.5 to 2.1) to 1.06 (0.8 to 1.3) after adjustment for BMI at age 23 [197]; in a small study of hypertension (*n* 286), adjustment for adult BMI did not lead to a change in the point estimate for the association with childhood overweight, but confidence intervals were wider. [193] In contrast, a study of CHD (*n* 37,674) reported that the hazard ratio for incident CHD for men with BMI in the top decile in

adolescence increased from 5.43 (95% CI 2.77 to 10.62) to 6.85 (3.3 to 14.2) after adjustment for adult BMI. [210]

The results of such analyses are generally interpreted as evidence that observed associations between childhood BMI and adult disease risk can be accounted for by adult BMI, and that childhood BMI has no underlying effect on disease risk. However, adjusting for adult BMI in this way has limitations. In particular, adult BMI is likely to be on the causal path from childhood BMI to later disease; consequently, adjustment for adult BMI can introduce overadjustment biases, which tend to pull effect estimates towards the null.[228] A statistical effect called the 'reversal paradox' has been described, in which adjustment for variables on the causal pathway lead to artifactual associations between exposures and outcomes. [229-230] Furthermore, adjustment for adult BMI does not enable us to differentiate between the effects of early life BMI and change in size (or BMI) over the period between measurements, [231-232] as inclusion of adult BMI in a regression model is effectively adjusting for the change in relative size between periods. [231] It is therefore difficult to conclude that childhood overweight has long-term effects on health based on the results of standard analyses. A number of alternative statistical approaches to studying the effects of early life BMI on later health have been suggested, including structural equation modelling, [233] and random effects models. [234] Another approach has been to use different combinations of exposure to overweight in childhood and later life as the predictor variable, as was used in the pooled analysis of cohort data looking at hypertension and type 2 diabetes. [174] Examination of relative risks in this way allows insight into the effects of exposure to overweight at different developmental periods. The limitations of standard adjustment and alternative methods are discussed in more detail in Chapter 4.3.2.

Given the high and rising prevalence of childhood overweight in all parts of the world, it is increasingly important to know whether childhood obesity has long-term effects on health which may contribute to future health burden. This review has shown that evidence that childhood obesity has effects on long term health, independent of adult BMI, is lacking. Direct effects of obesity in early life on long-term health may not be detected due to limitations in the statistical analyses and study designs that are commonly used. Studies that use alternative approaches to analysis may address some of the issues associated with standard adjustment for adult BMI. If it was found that childhood obesity had a direct effect on long term health, this would place the imperative on prevention and early treatment in childhood, and could provide important insight into the underlying mechanisms of disease progression and potential targets for intervention.

4. METHODOLOGICAL ISSUES AND APPROACHES TO ANALYSIS

In this thesis, data from three British National Birth Cohort studies are analysed to explore the relationships between overweight and obesity in childhood and adolescence and disease outcomes in adulthood; a life course perspective informs the approaches to analysis. The aim of this chapter is to introduce the datasets, and to describe the theoretical grounding, methodological issues and approaches to analysis in this thesis.

4.1 A life course approach

Life course epidemiology has been described by Kuh et al as the study of the long-term effects on health or disease risk of biological, behavioural and psychosocial exposures during gestation, childhood, adolescence, early adulthood or across generations. [235] Much of the recent interest in the effects of early life nutrition on adult health has its roots in the 'foetal origins of adult disease hypothesis', which was developed by David Barker and colleagues, and in its most recent incarnation is known as the Developmental Origins of Health and Disease (DOHaD) hypothesis. [236] In their analyses of historical cohorts, Barker et al showed that small size at birth was a risk factor for coronary heart disease (CHD), stroke, diabetes and associated risk factors. [213 237-238] These findings were interpreted as evidence for long-term effects of undernutrition *in utero*. Further studies have shown that small size at birth (early life undernutrition) followed by catch-up growth (improved postnatal nutrition) may increase disease risk in adulthood. [183 189 239] This effect may be associated with body size over the life course; a systematic review found that early rapid growth was associated with later overweight and obesity. [240]

The focus on the long-term effects of early life size and growth has increasingly informed approaches to the study of childhood overweight and obesity and chronic disease risk. [223] The chronic diseases that are commonly associated with obesity, notably type 2 diabetes and coronary heart disease and stroke, [241] are end stage outcomes of progressive cardio-metabolic changes which have their origins in early life. [242-243] There is also emerging evidence that metabolic abnormalities in early life are associated with asthma risk, [244] and that airway remodelling in children with asthma is associated with continued impaired lung function into adulthood. [245] With the life course approach, the temporal ordering of exposures (overweight and obesity) over the life course is conceptualised and incorporated into analysis. Different conceptual models for the effects of risk factors on disease risk over the life-course have been proposed: [235 246]

1) The 'accumulation-of-risk' model corresponds to a model in which the effects of exposure to overweight over the life-course accumulate to determine overall disease risk. A recent analysis of the Framingham Cohort Study, which included data from adults who had been

followed up every two years for up to 48 years, showed that the number of years of obesity was associated with all-cause, cardiovascular, cancer, and other-cause mortality. [247] These findings are consistent with an accumulation of risk model, in which each year lived with obesity contributes to future risk of mortality.

2) The 'critical period' model represents the case where individuals have increased vulnerability to effects of overweight during specific periods of the life-course, resulting in permanent changes in disease risk. The critical period model is consistent with the foetal origins of adult disease hypothesis, which suggests that undernutrition *in utero* leads to lasting anatomical and metabolic changes that increase risk of chronic diseases such as cardiovascular disease, diabetes and hypertension. However, this model does not necessarily preclude later effect modification. For example, the effects of low birth weight on cardiovascular diseases may appear stronger in individuals who are also obese in later life. [238 248]

3) The 'sensitive period model' represents an overlap between the accumulation of risk and critical period models, and proposes that there are periods when the effects of overweight or obesity have greater impact on later health than exposure at other periods, and that changes may not be permanent or may be reversible outside the sensitive windows. [235] A US study of weight status in adolescence (age 12-19 years) and early adulthood (age 19-26) showed that obesity during adolescence and early adulthood was associated with increased risk of asthma, diabetes, high cholesterol and hypertension in adulthood. [217] Obesity in adolescence only was associated with increased risk of high cholesterol and hypertension, while obesity in adulthood only was associated with increased risk of diabetes, high cholesterol and hypertension, relative to those cohort members who were not obese in both periods. These findings are consistent with an accumulation of risk model for obesity (assuming similar duration of obesity in childhood and adulthood), but also reveal that obesity isolated to a single period can have an effect on disease risk, as in the case of adolescent obesity and hypertension.

4.1.1 Defining life stages

In developmental terms, childhood refers to the period from infancy (ages 0-2 year) to the onset of puberty, and usually encompasses ages 0-12 years. Adolescence describes the transitional period between childhood and adulthood, from the onset of puberty to maturity. [249] During this time, a number of physiological and psychological changes take place which make this life stage biologically and socially distinct. For example, early adolescence is a high-risk time for weight gain due to the effects of metabolic and behavioural changes [250]; furthermore, obese adolescents are more likely to be stigmatised and subject to negative stereotypes than are younger obese children. [112-113] Although the timing and duration of puberty varies among individuals, adolescence is usually considered to include ages 13-19 years.

Figure 4-1: Life stages of interest and approximate ages included in these stages

Adulthood begins once a person has reached full maturity, and in Western industrialised societies can be further subdivided into life stages commonly identified as: early adulthood (ages 20-39.9 years), middle adulthood (ages 40-64.9), and late adulthood (ages 65+). Whilst childhood and adolescence are often marked by significant biological changes and cultural rites of passage, the exact definitions of life stages in adulthood vary according to the conceptual framework that is adopted. For example, ageing may be viewed as both a biological process and a social phenomenon: in women, decline in fertility and menopause may be seen as a biological signal of middle age, while reaching pensionable age might mark entry into late adulthood. Different stages of adulthood are also associated with marked differences in experience of disease, especially the chronic diseases that are of interest in this thesis. For example, results from the 2007 General Household Survey showed that the prevalence of longstanding illnesses of the heart and circulatory system was 1.4% among men and women aged 16-44 years, 12.8% among those aged 45-64 years, and 27.7% among those age 65-74 years. [251] Similar patterns in disease prevalence were observed for problems of the musculoskeletal system (5.7% at age 16-44, 18.2% at age 45-64, and 27.3% at age 65-74), and for endocrine and metabolic disorders (1.6% at age 16-44, 7.7% at age 45-64 and 11.0% at age 65-74).

4.2 The British National Birth Cohorts

Prospective longitudinal studies are ideal for studying life course effects because they present the opportunity to measure exposures that act over the life course. The British National Birth Cohorts from 1946 (MRC National Survey of Health and Development NSHD), 1958 (National Childhood Development Study NCDS) and 1970 (British Cohort Study BCS70) are nationally representative prospective cohorts that have collected data from birth and followed up participants at several points during childhood, adolescence and adulthood. [252-254] The three cohorts have comparable target and sample populations, and data collection at similar life stages (Table 4-1). They have data on anthropometric measurements in childhood and adolescence and health outcomes in adulthood, in addition to numerous other variables such as educational and employment history, relationships, family circumstances, and health-related lifestyle choices. Consequently, these cohorts provide a unique opportunity to study the development of health outcomes over a long period of time.

Table 4-1: Summary of British National Birth Cohorts from 1946, 1958 and 1970

	MRC NSHD 1946 [254]	NCDS 1958 [253]	BCS 1970 [252]
Target population/ inclusion criteria	All singleton babies born to married women in England, Wales and Scotland in one week in March 1946	All babies born alive or dead in England, Wales and Scotland in one week in March 1958	All babies born alive or dead after 24th week of gestation in E&W, Scotland and N Ireland in one week in April 1970
Sample	All births to women with husbands in non-manual or agricultural jobs and ¼ of births to women with husbands in manual jobs	All births; immigrants to Britain born during same week incorporated at 7, 11, 16 years	All births; participants from NI dropped in all subsequent sweeps; immigrants incorporated at 5, 10, 16 years
Sample size at baseline	5,362	17,638	16,567
Participant characteristics	Representative of the national population of similar age. 49% male, 51% female at most recent data collection.	Representative of the national population of similar age. 49% male, 51% female at most recent data collection	Representative of the national population of similar age.
Data collection occasions	22 occasions	9 occasions	8 occasions
Ages for which data available	Birth to 53 years	Birth to 47 years	Birth to 34 years
Sample size at last follow-up	2,948	9,534	9,656
Notes	Stratified-sample design: sample should be weighted to account for this. Pre-NHS; mothers living during World War 2. Data obtained from the Medical Research Council NSHD team at University College London.	Includes stillbirths, non-singleton births and immigrants to Britain. Data downloaded from UK Data Archive, University of Essex [255-260]	Includes stillbirths and non-singleton births. Data obtained from the UK Data Archive.

The oldest of the British National Birth Cohorts is currently approaching late adulthood, and the youngest cohort is entering middle adulthood. The endpoints of interest in this thesis are disease outcomes at ages 34-53 years. As the cohort studies vary in the ages at follow-up, for

each of the life stages (childhood, adolescence, and adulthood), the measurement taken closest to the mid-point age of the defined interval was used (Table 4-2).

Table 4-2: Ages at measurement in British National Birth Cohort Studies that are closest to mid-point age for each life stage of interest

Life stage	Age range (years)	Mid-point age (years)	Age at measurement closest to mid-point age		
			NSHD 1946	NCDS 1958	BCS 1970
Childhood	0-12	6	7	7	10
Adolescence	13-19	16	15	16	16
Adulthood (middle)	40-64	52	53	46	34

4.3 Analysis of longitudinal data

Analysis of data from longitudinal studies raises issues because exposures over the life course tend to be correlated within individuals because of common causal pathways or lifestyles. [233] For example, overweight in childhood tends to persist into later life, [18] while cardiovascular risk factors cluster in childhood [71-72] and track into adulthood. [261] These temporal and causal hierarchies mean that observations on a subject will be more similar to each other than to observations on other subjects, thereby violating any assumption of independence. The presence of collinearity must be accounted for in statistical analyses to ensure that standard errors of parameter estimates and confidence intervals are correctly estimated. [262]

4.3.1 Tracking of overweight and obesity

Tracking refers to the persistence of values or relative positions/ranks of a certain trait over time. Two broad concepts are involved: 1) the relation between early measurements and those later in life (the longitudinal stability of a variable); and 2) the predictive value of early measurements for future values. [118] These concepts can be operationalised using a tracking coefficient and a predictive value or risk measure.

There are a number of approaches to measuring tracking (Table 4-3). For example, the degree of tracking between two measurements at T1 and T2 may be quantified using a correlation coefficient such as Spearman's rank or Pearson's linear correlation coefficient, or by dividing a population into subgroups according to percentile ranking (e.g. into tertiles, quartiles or quintiles) and calculating the proportion of individuals who stay in the same group. With the latter approach, the magnitude of the tracking coefficient depends highly on the way in which the population is divided into subgroups, which can make the assessment of tracking problematic.

In longitudinal studies with two or more time points ($T \geq 2$), Cohen's kappa (κ) can be used. This coefficient counts the number of times that a given individual is in a particular percentile (or other defined) group, and compares this with the value that would be expected if the individuals were randomly assigned to the different groups at each measurement. κ takes values of between 0 and 1, and Landis and Koch suggest the following cut-offs as criteria for agreement: [168] $\kappa < 0.40$ indicates poor agreement (or tracking), $\kappa = 0.41\text{-}0.60$ is moderate agreement, $\kappa = 0.61\text{-}0.80$ is substantial agreement, and $\kappa > 0.81$ indicates excellent agreement. A weighted κ can also be used, in which the movements between percentile groups are weighted according to the distance moved. κ coefficients can be interpreted as intraclass correlation coefficients (ICC). [118] When $T > 2$, Kendall's coefficient of concordance W can be used to describe tracking. Kendall's W is calculated on the basis of changes in individual rankings over time, and is directly related to the average Spearman correlation coefficient. W takes values of between 0 and 1 and indicates the degree of association between rankings at each measurement, but W is not equal to 0 for random numbers and has to be rescaled accordingly for comparison with other coefficients. An alternative approach to describing tracking has been used by Lauer et al, [263] in which each value of the variable of interest is expressed as a percentile rank, and for each individual the average of percentile ranks over time is calculated. A regression line is then calculated for each individual which describes the change of percentiles over time (the trend in rank), and the goodness of fit of the regression line is measured as the residual standard deviation (RSD, which measures variability over time and is inversely related to goodness of fit). Individuals with strong trends and low variability are said to track, and the proportion of individuals who belong to this group is calculated. Lauer's coefficient is based on a different definition of tracking, and is not comparable to the other coefficients described previously.

Table 4-3: Nonparametric tracking coefficients (adapted from Twisk et al *'Mathematical and analytical aspects of tracking'* Epidemiologic Reviews. 1994; 16(2): 165-183 [118])

Coefficient	Range (min. to max.)	Tracking criterion*	Data points†
Spearman's ρ	-1 to 1	Arbitrary	2
% at high risk	0 to 100%	>20% (quintiles) or >25% (quartiles)	2
Lauer's %	0 to 40%	Arbitrary	All
Cohen's κ	0 to 1	>0.75 good >40 moderate	All
Nishio's TI			
Quintiles	1 to 8.3	Arbitrary	2
Quartiles	1 to 4.0		
Kendall's W	0 to 1	Significance	All

*Criterion to decide whether a variable tracks; †Number of data points used to calculate the coefficient

The benefit of Cohen's κ, Kendall's W and Lauer's coefficients for the assessment of tracking is that they can be used with more than two longitudinal measurements, thus making use of all the available data. These coefficients are also relatively simple to compute. As nonparametric approaches, they make fewer assumptions about the distribution of the data than parametric methods, and can be used for categorical variables such as overweight status. The advantage of κ over the other two methods is that it is on a 0-1 scale (0 for no tracking and 1 for perfect tracking) that is easily interpreted and comparable to other measures.

The predictive value of early measurements for those in later life can also be assessed in a number of ways. For T=2, predictive value may be defined as the proportion of individuals in a high risk group at initial measurement that have stayed in that group at the second measurement period. For multiple measurements, various regression analysis methods can be used, in which the value of the last measurement is the outcome variable and values of earlier measurement are the exposure variables. A systematic review of the literature on tracking of childhood overweight into adulthood showed that correlation coefficients, relative risks of overweight and percentages of overweight children who remain overweight in adulthood are commonly reported measures of tracking. [18]

4.3.2 Childhood overweight and outcomes in adulthood: analytical approaches

A standard approach to studying the effects of obesity in early life on later outcomes is to fit measures of adiposity at different ages as the exposures, with adjustment for current obesity or BMI, as described in the studies in the literature review (Chapter 3). However, this approach is problematic for a number of reasons.

One issue is that adult BMI, which is correlated to childhood BMI, is a likely intermediate variable on the causal path from childhood BMI to later disease outcomes; consequently, adjustment for adult BMI is likely to introduce overadjustment biases, which tend to pull effect estimates towards the null.[228] In the context of the foetal origins hypothesis, a statistical effect called the 'reversal paradox' has been described, in which adjustment for variables on the causal pathway lead to artifactual associations between exposures and outcomes. [229-230] In a series of simulations, Tu et al, [230] showed that a genuine positive association between birth weight and adult blood pressure could be attenuated after adjusting for current weight, and even reversed when the correlations between birth weight and current weight and between current weight and blood pressure were increased. These same effects are relevant to the study of childhood overweight and adult disease, particularly given the correlation between childhood and adult BMI. Furthermore, multiple regressions that use several closely spaced BMI measurements are subject to issues of multicollinearity [264]; the interdependence of the BMI measurements reduces the amount of information that they contribute to explaining variance. The result is inflated variance for regression coefficients and less robust parameter estimates.

There are also problems with the interpretation of results from standard analyses [233]; adjustment for adult BMI does not enable us to differentiate between the effects of early life BMI and change in size (or BMI) over the period between measurements. [231-232] For example, the parameter estimate for childhood BMI in a regression model adjusted for adult BMI can be interpreted as the effect of childhood BMI in individuals who all have the same adult BMI; however, inclusion of adult BMI in the model is also effectively adjusting for the change in relative size between time childhood and adulthood, therefore another interpretation can be the effect is associated with the change in adiposity between childhood and adulthood. [231] Since these effects cannot be distinguished, it is difficult to conclude whether childhood BMI has any long-term effects on health based on the findings of standard analyses.

A number of statistical approaches have been suggested to address these issues in studies of life course obesity. One approach is structural equation modelling (SEM), including path analysis, [233 265] which specifies causal and temporal pathways between variables in a model, and uses simultaneous equations to produce estimates of the direct and indirect effects of variables on each other and on the outcomes. This approach requires specification of a model which explicitly details the interrelationships between variables, and assumes that there are no

unmeasured variables that are associated with both the exposure and the outcome; for a given scenario there may be several potential model specifications, and in complex systems the causal relationships may not be well known. [266] This issue may be avoided if information on potential confounders is excluded (or unavailable [265]) but this is likely to result in biased estimates.

Other studies have used multilevel or random effects models in a two-step approach to study the effects of BMI change or growth on later outcomes. In the first step, growth is modelled using multilevel models, which explicitly account for clustering by including one or more random effects which are assumed to have mean zero and to vary randomly between clusters (or individuals, in the case of repeated measures). For example, the model could allow each individual a different random intercept (baseline BMI) and a random slope (linear change in BMI). This model would enable estimation of BMI growth velocity for each individual over a certain time period. In the second step, growth parameters from the growth model (such as the BMI growth velocity) are used as predictors of the outcome of interest in another model. To characterise growth trajectories in detail, multiple measures of weight and height in childhood are required. A study of the Northern Finland Birth Cohort 1966 (NFBC1966), which had data on height and weight measurements on several occasions between birth and age 2 years, fitted polynomial random effects growth curves to the height and weight growth data and used these to derive peak height velocity and peak weight velocity in infancy. [234] These growth parameters were then used as predictors in models with metabolic traits at age 31 years as the outcomes. In a meta-analysis of data from 8 cohorts, growth curves were fitted on BMI in infancy and childhood, and the relationship of growth parameters with variation at the *FTO* locus was explored. [267] Other studies have used splines (linear growth between specified knots) rather than complex polynomials to characterise growth, as complex polynomials are often difficult to interpret. [268] Growth modelling using piecewise linear random coefficients models was used to describe BMI trajectories in the British National Birth Cohorts. [268]

Another approach that has been adopted in previous studies of obesity has been to use different combinations of exposure to obesity over the life course as the predictor variable. [269] In these cases, individuals are categorised according to the life stages at which they were obese. For example, in an analysis of the NFBC1966, odds ratios for abdominal obesity at age 31 years were estimated for cohort members with different combinations of weight status at age 14 years (normal weight or overweight) and at age 31 years (normal, overweight or obese). [270] In a study of adult socioeconomic, educational, social and psychological outcomes associated with childhood obesity by Viner and Cole, [141] individuals from the BCS70 cohort were categorised according to whether they were obese in childhood only, obese in adulthood only, obese in childhood and adulthood; the risks of negative outcomes for each subgroup were then compared to risk in those who were not obese in either period. To test for potential bias due to the categorisation of exposure variables, the authors then entered childhood obesity and adult

obesity as main effects in the model and tested for interaction between these variables. A similar approach was used by Merten in his study of weight status in adolescence (ages 12-19 years) and early adulthood (ages 19-26), and their associations with diagnosis of asthma, diabetes, high cholesterol and high blood pressure in early adulthood. [217] As in the study by Viner and Cole, individuals were categorised according to whether they were obese in adolescence only, obese in adulthood only, obese during adolescence and adulthood, and never obese. These categories were then used as exposures in regression models to examine their association with health outcomes. Wills et al also defined 'overweight trajectories' in this way based on weight status at three ages in adulthood for individuals in the NSHD cohort, [271] and used regression models to estimate mean blood pressure for different trajectories. Similarly, in a recent pooled analysis of data from four cohort studies of cardiovascular risk factors, participants were assigned to one of four groups according to whether they were normal weight or overweight/obese in childhood and adulthood (group 1: normal BMI in childhood and non-obese in adulthood; group 2: overweight/obese in childhood and non-obese in adulthood; group 3: overweight/obese in childhood and adulthood; group 4: normal BMI in childhood and obese in adulthood), and relative risks of cardiovascular outcomes were estimated for each group. [174] The disease outcomes of interest in this thesis are conditions which develop over time, therefore studies that examine their association with exposure to overweight at a single time point ignore the combined effects of exposures that potentially act over longer periods. The advantage of an approach that uses different combinations of overweight as an exposure is that it can provide insight into the contribution of overweight at different stages of the life course to outcomes, with important implications for understanding the progression of disease and approaches to intervention.

4.4 Conceptual framework

In observational studies like the British National Birth Cohort studies, establishing causality is complicated by the presence of biases and confounders, some of which may be hidden or unmeasured. These issues are particularly salient when studying childhood obesity and adult health, as the exposure and outcome are separated by a long time period, and there may be several possible explanations for the data.

Figure 4-2 shows the causal directed acyclic graph (DAG) for the relationships between childhood overweight, chronic disease outcomes and the key covariates of interest that informs the analyses in the following chapters. The key covariates and their relationships with childhood obesity and chronic disease were selected based on a review of the literature and available data for the three cohorts (Table 4-4). The process of selecting the statistical models for analyses in the following chapters was informed by this conceptual framework.

Figure 4-2: Generic causal directed acyclic graph (DAG) for childhood BMI status and adult disease

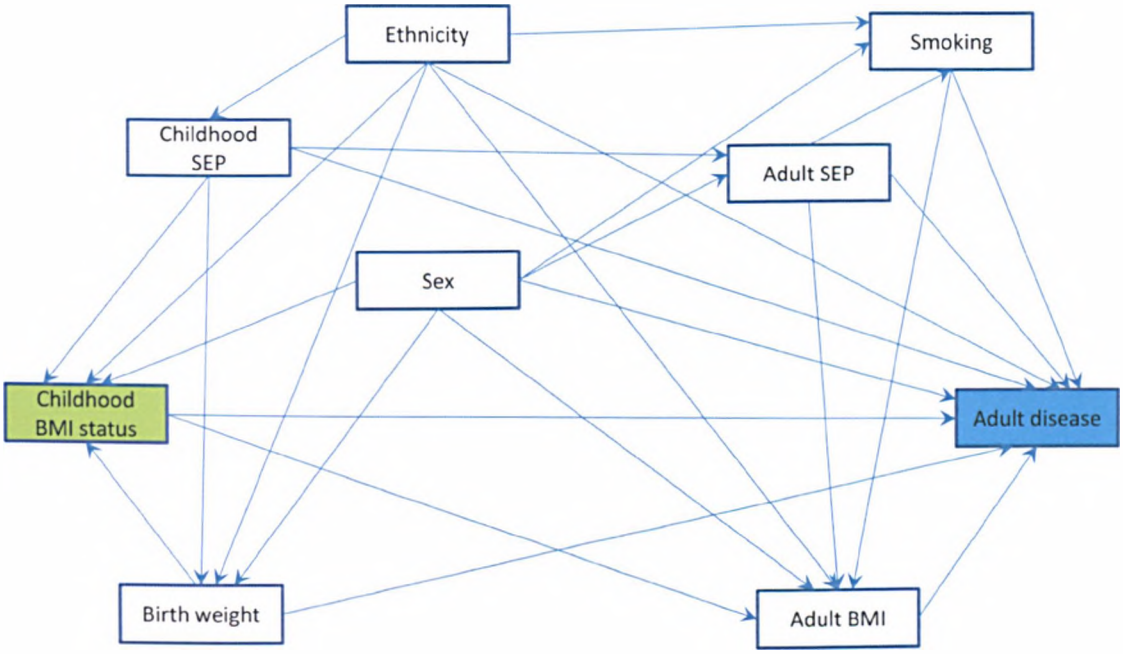


Table 4-4: Key covariates in the relationship between childhood overweight and chronic diseases in adulthood identified in the literature, strength of the evidence and categorisation as *confounders, effect modifiers or mediators*

Covariate	Correlated with the exposure? †	Risk factor for the outcome? ‡	Effect modifier?	On the causal pathway?	Summary
Adult BMI status	Overweight in adulthood is associated with overweight in childhood. [18] [120] (++) RR for being overweight in adulthood (age 19-35) for overweight children aged 9-11 y (BMI ≥ 85th centile) vs. normal weight children = 1.9. [272] RR for being overweight in adulthood (age 18-37) for overweight children aged 2-17 y (BMI ≥ 95th centile) vs. normal weight children = 3.2, RR for being obese in adulthood for overweight children (BMI ≥ 95th centile) vs. normal weight children = 10.1. [273] OR (95% CI) for being obese in adulthood (age 24-54) for overweight adolescents aged 14-19 y (BMI ≥ 85th centile) vs. adolescents with BMI 25th-74th centile males/females = 15 (14-17) / 12 (11-13). [274]	Adult overweight is a risk factor for numerous disease outcomes (++) RR (95% CI) for ischemic stroke for overweight vs. normal weight = 1.22 (1.05-1.41), for obesity vs. normal weight = 1.64 (1.36-1.99). [275] Men: 5 unit increase in BMI is associated with oesophageal adenocarcinoma (RR = 1.52), thyroid cancer (1.33), colon cancer (1.24), and renal cancer (1.24). Women: 5 unit increase in BMI associated with endometrial cancer (1.59), gallbladder cancer (1.59), oesophageal adenocarcinoma (1.51), and renal cancer (1.34). [276] HR (95% CI) for overall mortality with each 5 unit increase in BMI above 22.5-25 kg/m2 = 1.29 (1.27-1.32), for vascular mortality = 1.41 (1.37-1.45), for diabetic mortality = 2.16 (1.89-2.46), for neoplastic mortality = 1.10 (1.06-1.15). [8]	The relationship between childhood BMI and disease outcomes may be modified by adult BMI (+) Pooled analysis of data from four cohorts showed that overweight/obesity in childhood was not associated with increased risk of type 2 diabetes, hypertension and other CV risk factors in those who were non-obese in adulthood, but childhood overweight was associated with these outcomes in those who were obese in adulthood [174](not strictly evidence of effect modification, but accumulation of effects).	Adult BMI status is likely to be on the causal pathway between childhood BMI status and disease outcome. Positive associations between childhood BMI and adult cardiovascular risk factors are generally attenuated after adjustment for adult BMI. [121]	Adult BMI status is positively associated with childhood BMI status and with disease risk, and is likely to be on the causal pathway between childhood BMI status and disease outcome. Adult BMI status may be an effect modifier of the relationship between childhood BMI status and disease outcome, such that being overweight in childhood is more strongly associated with disease in those who are overweight also in adulthood than in those who are not overweight in adulthood.

Sex	Sex is associated with childhood BMI status (++) Among contemporary UK children, prevalence of overweight and obesity is higher among boys than girls (prevalence ov and ob combined: at age 5 24.0% versus 21.1%; at age 11 34.3% versus 30.7%) [54], although the opposite was true for older cohorts, i.e. higher prevalence of overweight among girls than boys. [277]	Sex is a risk factor for numerous disease outcomes (++) The incidence of coronary heart disease morbidity and mortality among men is twice that in women, although the sex differential is reduced among post-menopausal women. [278] Some outcomes are sex-specific (or very rare in the opposite sex), e.g. endometrial cancer, breast cancer, prostate cancer.	Sex is likely to be an effect modifier in the relationship between childhood BMI status and disease outcome (++) A study of mortality and morbidity outcomes at age 73 showed that BMI status at age 13-18 (overweight or lean) was associated with all-cause, cardiovascular and colorectal cancer mortality in men, but was not associated with any of these outcomes in women. [131] Very high BMI at age 14-19 was associated with more than doubling of renal cancer risk among men, but no association was observed in women. [184]	No, child BMI status does not affect sex.	Sex is associated with childhood BMI status and disease risk. It is likely to be an effect modifier of the relationship between childhood BMI and adult disease risk.
Ethnicity	Ethnicity is associated with childhood BMI status; generally children from ethnic minority backgrounds have higher prevalence of obesity than White children (++) In the UK, obesity prevalence (BMI ≥95th centile of UK reference population) among Black (prevalence 26.4%) and Asian	Ethnicity is a risk factor for numerous disease outcomes [279] (++) South Asians have a higher prevalence of coronary heart disease (CHD) and cardiovascular mortality compared with Europeans; African-Americans have higher rates of CHD and stroke; African/Caribbeans in the UK have lower CHD rates and higher stroke rates than British Europeans.	The relationship between childhood BMI and disease outcomes is likely to be modified by ethnicity (+) In adults, people of South Asian descent have a more adverse cardiovascular risk profile than those of European descent at the same BMI. [280] Similarly, South Asian	No, child BMI status does not affect ethnicity	Ethnicity is associated with childhood weight status and adult disease risk. Ethnicity is likely to modify the effect of childhood BMI status, such that the risk of disease outcomes is higher among ethnic minority groups than among White

	(21.5%) children is higher than the national average, and lower among Chinese (13.7%) and White (17.3%) children. [54]	Other non-European groups such as the Chinese and Japanese have high rates of stroke but not CHD; Mexican Americans have a higher prevalence of stroke and CHD; North American native Indians have high rates of CHD.	adolescents are more insulin resistant than white European adolescents. [77] This is due to differences in body composition and fat distribution between ethnic groups at same BMI, e.g. BMI underestimates body fat percentage in Asians compared to Caucasians. [281-282]		groups at same BMI.
Birth weight	Birth weight is positively correlated with childhood BMI status (++) In one US study, each 1 kg increase in birth weight was associated with a 30% increase in odds of overweight (BMI 85th-94th centile) at age 9-14 y and 40% increase in odds of obesity (BMI ≥95th centile) [283]. In a Danish study, each 0.5 kg increment in birth weight was associated an increase in relative risk of overweight at age 6-13 y. [284]	Low birth weight is a risk factor for a number of adverse health outcomes (+) E.g. Birth weight is inversely associated with systolic blood pressure [285-286]. Low birth weight is associated with a 70% increase in odds of chronic kidney disease. [287] A systematic review showed that low birth weight was associated with ischaemic heart disease, [288] but larger size in infancy may be associated with increased risk of insulin-dependent diabetes. [167]	Birth weight may modify the relationship between childhood BMI and disease (+) Given that low birth weight and childhood overweight are associated with disease outcomes, it is expected that those children with low birth weight + childhood overweight are more likely to have adverse outcomes that those with higher birth weight + childhood overweight. One study showed that among males who had the same BMI at age 18 y, those who were of lower birth weight had on average higher blood pressure	No, child BMI status does not affect birth weight	Birth weight is associated with both childhood weight status and adult disease outcome, but is not on the causal pathway between them. There may be effect modification between birth weight and childhood BMI, such that the combination of low birth weight and childhood overweight is associated with a higher risk of disease than higher birth weight and childhood overweight in a non-additive way.

			and increased risk of hypertension. [289]		
Childhood socioeconomic position	Childhood SEP is associated with childhood BMI status (++) In most Western countries, prevalence of overweight is higher among children from less affluent families, whilst the opposite is true in developing countries. [290] In ALSPAC, higher prevalence of overweight was observed among 11 year old boys whose mothers had lower educational attainment; in girls, the same pattern was observed, in addition to an association with lower family income. [53] In a study of London school children, the prevalence of overweight and obesity was highest among those from the most deprived quintile at all ages. [291]	Low childhood SEP is a risk factor for numerous adverse health outcomes in adulthood (++) E.g. childhood SEP is inversely associated with adult cardiovascular outcomes and risk factors. [292] A systematic review of the literature showed that poor socioeconomic conditions in early life were associated with increased risk of mortality. [293] In another study, childhood SEP was a predictor of incident diabetes [294-295].	Childhood SEP may be an effect modifier of the relationship between childhood BMI and disease outcomes. In a Finnish sample, rapid BMI increase in early life was associated with hypertension in adult life; this effect was large among children living in poor social conditions, and small among those living in good living conditions. [183]	No, child BMI status does not affect childhood SEP	Childhood SEP is associated with childhood BMI status and adult disease outcome. There may be effect modification of the association between childhood BMI status and adult disease risk by childhood SEP. The effects of early life SEP are likely to act through many of the other risk factors discussed here, including birthweight and childhood height.
Adult socioeconomic position	Adult SEP is associated with childhood BMI status (- +) Among women, having a BMI >90th centile at age 11 was associated with 3.5% lower income at age 23; this effect was not observed in men. [140]	Adult SEP is associated with most health outcomes [296] (++) Among African American women, incidence of type 2 diabetes was 28% higher among women with ≤12 y education compared to those with ≥17 y education, 57% higher for	There is not much evidence that adult SEP modifies the relationship between childhood BMI and adult disease [183] (- +), but it has been shown that obesity is less likely to persist from childhood into adulthood	Some evidence that childhood BMI status can affect adult SEP among women. In females, there was an inverse relationship between obesity at age	Low SEP in adulthood may be associated with childhood overweight and is a strong risk factor for disease outcomes. In women, adult SEP may be on the causal pathway between childhood BMI

		those with household income <$15,000 compared to >$100,000, and 65% higher among those living in lowest quintile of neighbourhood SES compared to the highest. [297]	among women with a university degree versus elementary degree. [298] It may be expected that an individual who has been overweight in childhood and has low SEP in adulthood may be more likely to have an adverse outcome than an individual who has been overweight in childhood but has a high SEP in adulthood.	16 and earnings at age 23, independent of parental social class and childhood ability test scores; this effect persisted regardless of whether women stayed obese or became lean (this relationship not seen among men). [140] Obesity pre-adolescence does not seem to impact on adult SEP. [141]	status (specifically, in adolescence) and adult disease. There is no direct evidence of effect modification by adult SEP, and an effect independent of adult BMI status seems unlikely. The effect of SEP on disease outcomes may be mediated by health-related behaviours that are more common in low SEP groups (such as smoking).
Adult smoking behaviour	Few studies have explored the association between childhood obesity and adult smoking behaviour (+). However, it is known that children of mothers who smoke are at greater risk of overweight, [299] and that children whose parents are smokers are also more likely to smoke themselves. [300-301] Thus it may be expected that there will be an association between childhood BMI status and adult smoking behaviour.	Smoking is a risk factor for most disease outcomes (++) Smoking is a risk factor for many chronic diseases [302] and mortality. [303] E.g. smoking is a known risk factor for coronary heart disease. [304]	There is no clear evidence that smoking modifies the relationship between childhood BMI status and disease outcomes (--) E.g. No strong evidence that survival is different between adult smokers and non-smokers at same BMI, [305] nor for IHD or stroke. [175]	No direct evidence that childhood BMI status can affect adult smoking behaviour, although potentially being overweight in childhood could lead to psychosocial problems which may make smoking more likely.	It may be expected that childhood overweight is associated with adult smoking, although direct evidence for this was not found. Smoking is a strong risk factor for most chronic diseases, but does not seem to be an effect modifier in the relationship between BMI status and disease. The absence of evidence for effect modification is unexpected, but this may be due in part to issues of statistical power in tests

					for interaction. Furthermore, smoking is associated with low SEP, which is a risk factor for overweight and many disease outcomes.
Child height	BMI is not independent of height (++) Height and BMI at age 9 y showed a linear association among children in the US, with each 1 cm increase in height associated with 0.18 kg/m2 increase in BMI [306]. In the NCDS 1958 British birth cohort, being taller was associated with being overweight at age 11 y in both girls and boys. [140]	Height is a risk factor for some disease outcomes of interest, although few studies have addressed the association between childhood height and adult disease directly (+) In a Scottish study, height was inversely associated with all cause, CHD, stroke, respiratory disease and stomach cancer mortality, but risk of colorectal and prostate cancer mortality increased with height [307]. In a study of US physicians, men in the tallest height category (≥185.4) had a 35% lower risk of MI than men in the shortest height category (≤170.2) [RR 0.65; 95% CI 0.44-0.99]. [308]	Childhood height and childhood BMI may interact to affect adult disease risk (+). E.g. Among overweight children, being taller is associated with higher BMI in young adulthood (which affects risk of disease) [306]	Childhood BMI is associated with height, but the casual relationships between these are unclear.	Childhood height is correlated with childhood BMI, and is also a risk factor for several disease outcomes (height is likely to be an indicator of/proxy for early life exposures, e.g. nutrition). The causal association between these variables is unknown. There may be effect modification between childhood height and BMI, as children who are tall and overweight are more likely to be overweight adults. [306]
Year of birth	Prevalence of childhood overweight and obesity have increased over time [309] and over successive cohorts [277] (++)	Year of birth is a risk factor for many disease outcomes (+) E.g. Age standardised rates of breast cancer and colorectal cancer incidence have increased over the past 4 decades, while stomach and	Year of birth may modify the association between childhood BMI and adult disease risk (+) The prevalence of cardiovascular risk factors, e.g. hypertension, have	No, childhood BMI status does not affect year of birth.	Year of birth is associated with childhood BMI status and is also a risk factor for disease outcomes. The relationship between childhood BMI status and adult disease may be

	cervical cancer have declined. [310]	decreased over time across all BMI groups; the greatest reductions have been observed among overweight/obese groups, such that the risk associated with overweight is lower for those born more recently than for those born earlier. [311]	modified by the year of birth.

† BMI status; ‡ Disease outcomes; -- No strong evidence; -+ Mixed evidence; + Indirect evidence; ++ Direct evidence

4.5 Definition of variables

4.5.1 Main outcome: obesity-related diseases

The main outcomes of interest in the main analyses were determined based on previous reviews of the literature. [45] The comprehensive review conducted for the Foresight Obesities report identified that increasing body fatness was associated with type 2 diabetes, hypertension, coronary heart disease and stroke, respiratory problems, cancers, arthritis and liver and gallbladder disease.

For analysis, these outcomes were defined as binary measures (ever had/never had the condition), based on self-reported questionnaire responses. At each follow-up, an individual was classified as having a disease outcome of interest if they reported ever having had that disease, or treatment for that disease in response to direct questions about the outcome, e.g. "Have you ever had or been told you had asthma?" These responses were combined with information on self-reported long-standing illnesses, reasons for medical supervision or recent hospital admission, which were coded according to ICD-9 or ICD-10 codes. Although blood pressure data were available, cohort members were not classified as having hypertension on the basis of single casual measurements, which can be unreliable as indicators of hypertension. [312] If an individual reported ever having had an outcome at an earlier wave but did not report it at a later wave, they were classified as having had the disease. If an individual provided questionnaire responses at a given wave but had missing data in response to a question about a specific illness, they were classified as not having the disease (unless they reported the outcome in a previous wave). In NSHD, diabetes was classified by a clinician at the MRC Unit for Lifelong Health and Ageing (Dr Mary Pierce), as type 1, type 2, gestational, unknown or unsure, according to use of medication and insulin, and age at diagnosis or diagnosis during pregnancy. For NCDS and BCS70, I classified diabetes cases according to self-report of whether diabetes was insulin or non-insulin dependent, as reported at ages 42 (NCDS) or 30 y (BCS70); additionally, cases of type 2 diabetes were identified from ICD codes for self-reported long-standing illnesses at age 47 or 34 years (Table 4-5).

Table 4-5: International Classification of Diseases (ICD) codes used in generating outcome variables

Outcome	ICD classification	
	ICD-9	ICD-10
Asthma	493	J45
Gallbladder disease	574, 575	K80- K82
Hypertension	401, 402	I10, I11
Type 2 diabetes	250	E11, E14
CHD	410-414	I20-I25
Stroke	430- 432	I61- I64
Arthritis	715	M15-M19, M47
Colorectal cancer	153, 154	C18-C20
Breast cancer	174, 175	C50
Uterine cancer	182	C54, C55
Oesophageal cancer	150	C15
Liver cancer	155	C22
Kidney cancer	189	C64, C65

Individuals with any of the reported disease outcomes before age 20 years were excluded from analysis of that disease to account for pre-existing conditions which could have biased the outcome. Similarly, cohort members that had congenital defects related to the outcome, such as heart defect for coronary heart disease, were excluded from analyses of that outcome. The only exception was in the case of asthma, where cases reported before age 20 were included because the usual age of onset for asthma is in early childhood even though asthma relapse may occur in later life. [313] Data on age at onset were available for varying numbers of respondents. For example, information on age at onset was available for 27.3% of cohort members who ever had hypertension, 409 out of 463 (88.3%) individuals with diabetes, and 168 out of 173 (97.1%) individuals with CHD.

4.5.2 Main exposure: BMI categories

BMI categories (also referred to also as weight categories) were the main exposures of interest. Cohort members' BMI values at each wave were categorised as: normal, overweight, or obese, and treated as ordered categorical data. In childhood and adolescence (age ≤19 years), weight categories were generated by applying IOTF definitions to BMI measurements [31] using the `zbmicat` command in Stata (authors: Vidmar, Carlin, Hesketh and Cole). BMI measurements before age 2 years were not included as exposure variables, as obesity is not typically recognised in this age group. In adulthood, these groups were defined according to BMI cut-off points proposed by the WHO [314]: normal (including underweight) <25 kg/m^2, overweight 25-29.9 kg/m^2, and obese ≥30 kg/m^2. Underweight individuals (BMI <18.5) were not considered as a separate group in these analyses, as the aim was to explore the effects of overweight and obesity on excess or additional disease burden, relative to the rest of the population.

In NSHD, weight in underclothes and standing height without shoes were measured at ages 7 (childhood) and 15 years (adolescence) by the school doctor. At age 43, standing height in centimetres and weight in kilograms were measured in a physical examination. In NCDS, childhood (age 7 y) height without shoes to the nearest inch or centimetre (cm), and weight in underclothes to the nearest pound were measured in a medical examination. Height was measured using a pocket stadiometer, which was issued to schools. Adolescent (age 16 y) height in bare feet was measured to the nearest inch or cm using a steel or wooden measuring rod, or if not available, a steel tape measure; weight in underclothes was recorded to the nearest pound, or in kilograms (kg) to two decimal places using a beam balance or other weighing apparatus, as available. At age 42 years, height and weight were self-reported by respondents in a computer assisted interview. In BCS70, height to the nearest 0.1 cm and weight to the nearest gram were recorded by the school nurse at ages 10 and 16 years. Height was measured using a steel or wooden measuring rod or steel tape measure, or if not available, the stadiometer on the back of a weighing machine. Weight was measured using a beam balance or other weighing apparatus. At age 34, respondents self-reported their weight in either kilograms or stones and pounds, and height in metres and centimetres or feet and inches in a computer assisted interview.

BMI was calculated as weight in kilograms divided by height in metres squared. Height and weight data reported in imperial measurements were converted to metres and kilograms using the conversion factors shown in Table 4-6. Height and weight data were plotted and checked for extreme values.

Table 4-6: Conversion factors for weight and height – imperial to metric measurements

Imperial	Metric
1 foot	0.3048 metres
1 inch	0.0254 metres
1 stone	6.3503 kilograms
1 pound	0.4536 kilograms

4.5.3 Birth weight

Birth weight was included as a potential confounder, as several studies indicated that low birth weight (< 2,500 grams) was a risk factor for a number of adverse health outcomes, including components of the metabolic syndrome [237 315] and coronary heart disease and stroke, [288 316] as well as being correlated with BMI in later life. Birth weights to the nearest ounce were extracted from birth records, and were converted to grams (using conversion factor 28.3495).

4.5.4 Year of birth

The potential effect of calendar time or cohort on the association between BMI/weight category and disease outcomes was assessed by testing for interaction by year of birth (1946, 1958, 1970).

4.5.5 Sex

Sex was extracted from baseline survey data. Sex is a potentially important effect modifier in the relationship between weight status is early life and disease outcome in later life. This effect was assessed by the inclusion of interaction terms.

4.5.6 Exact age at measurement

Exact age at height and weight measurement was calculated using date of birth and the date of measurement. Where these data were unavailable (exact age at measurement could not be calculated for 15.9% of participants), mean age at measurement for other cohort members in the wave was used as the imputed value. Imputation using the group mean can be problematic as this approach can lead to underestimation of the standard deviation, [317] but this approach did not seem unreasonable given that these were birth cohorts with data collection in waves and therefore ages did not vary greatly at any given data collection point.

4.5.7 Multiple births

The NSHD 1946 cohort included only singleton births. Multiple births are more likely to be preterm and of low birthweight than singleton births, [318] and are at increased risk of consequent developmental and health problems. To ensure comparability of analyses across cohorts, those cohort members who were multiples at birth were excluded from analysis of the 1958 and 1970 cohorts.

4.5.8 *Ethnicity*

For these analyses, ethnicity was originally classified into five broad categories: 1) White/European; 2) Black African/Caribbean; 3) Indian/Pakistani/other South Asian; 4) Other; 5) Mixed. Self-identified ethnicity at ages 42 or 33 years was used preferentially over assigned ethnicity (at ages 11 or 16 years) where this information was available. [319] Ethnic minority groups (non-White) were later grouped into a single category and ethnicity treated as a binary variable in the main analyses, due to small numbers in some of the categories. Information on ethnicity was not available for the NSHD cohort, although it can be assumed that <1% of the population would be from ethnic minority groups.[320]

4.5.9 *Socioeconomic position*

Socioeconomic position (SEP) is an important potential confounder of the relationship between early life weight status and later health, [297] as SEP is associated with both the likelihood of being overweight[50 53] and with many of the disease outcomes of interest. Indicators of socioeconomic position include education, housing tenure/conditions/amenities, income, and occupation based measures. [321-322]

The British National Birth Cohorts had data on occupation, education, income and housing characteristics. There were also various derived occupation based measures, including the Registrar General's Social Class (RGSC), Social Class based on occupation (SC), socio-economic group (SEG) and the National Statistics Socio-economic Classification (NS-SEC). For this study, occupation was categorised using the six-category RGSC classifications: i) Professional; ii) Managerial/technical; iiia) Skilled (non-manual); iiib) Skilled (manual); iv) Partly skilled; and v) Unskilled, to ensure comparability across waves. SEP in early life has been shown to predict health outcomes in adulthood. [323-324] Cohort members were assigned a childhood social class based on the occupation of their father (or head of household if not the father) at birth. In cases where this information was missing, father's occupation at the earliest wave available in childhood was used. If there was no information on father's occupation at any age in childhood, mother's occupation was used. Social class in adulthood was categorised using the current/most recent occupation of the respondent.

4.5.10 *Smoking behaviour*

Smoking is a potential confounder of the association between weight status and health outcomes. [302] Current smoking behaviour of each individual was categorised into three groups: 1) Never smoked, 2) Ex-smoker (cohort member previously smoked at least one cigarette per day for 12 months or longer), and 3) Current smoker. Smoking status was defined according to participants' responses to the question, 'Have you ever smoked cigarettes regularly? By regularly, I mean at least one cigarette a day for 12 months or more.' Reported smoking status at

last follow-up (in adulthood) was used. If missing, smoking status at the previous wave was used (last observation carried forward) to maximise the data.

4.5.11 Height

In children, BMI is not independent of height, and it has been suggested that BMI may consequently overestimate overweight and obesity in taller children. As a result, a common approach has been to further adjust for height. [141]

4.5.12 Other considerations

In a small number of cases where the cohort member was unable to participate in an interview or complete a self-administered questionnaire, short proxy interviews were undertaken with a family member or carer. These interviews covered the same general topics as the cohort member interviews, but in less detail. Proxy responses (n=53) were excluded from these analyses as these data were less complete and subject to different biases than self-reported data.

4.6 Missing data

Missing data are commonly encountered in research, but are particularly an issue in longitudinal studies such as the British National Birth Cohorts, which follow participants over time. [325] Missing data present a potential source of bias, as participants who remain in a study may be different to those who drop out with respect to variables that are relevant to the analysis. For example, if overweight participants who suffer from ill health are more likely to drop out of a study than those in good health, an analysis of only those remaining in the study may underestimate the impact of weight status on disease outcomes.

There is no universal method for handling missing data, as the missingness mechanism (the reasons why observations become missing) is usually unknown; analysis of missing data requires additional assumptions to be made, which cannot be tested using the data. The sensitivity of the conclusions to different assumptions therefore needs to be investigated. [326] There are a number of ad-hoc ways to deal with missing data, including complete case analysis, simple mean imputation, regression mean imputation, creating an extra category for missing values and last observation carried forward (LOCF). [317] Other methods for analysis of missing data include multiple imputation and inverse probability weighting, maximum likelihood methods, and probability weighting. [327]

In order to maximise the available data, last observation carried forward was used for socioeconomic position, smoking behaviour, and outcomes in adulthood, as described above. As a sensitivity check, a complete case analysis excluding those individuals with incomplete data was carried out and compared with LOCF results.

4.7 Statistical analysis

Following analysis of each cohort separately, individual level data from the three British National Birth Cohorts (NSHD 1946, NCDS 1958, and BCS70 1970) were pooled for the main analyses. This was considered to be reasonable given the similarities in study design and target populations among these cohorts, as described in Chapter 5, and on inspection of the odds ratios from analysis of individual cohorts. Tests for homogeneity of odds ratios from Mantel-Haenszel estimates controlling for cohort indicated that ORs (for main effects) were not statistically different, except in the case of hypertension and combined disease outcomes. Further inspection of ORs for hypertension showed that these were similar for NCDS (OR 1.74, 95% CI 1.44, 2.11) and BCS70 (2.22, 95% CI 1.54, 3.20), with no association observed in NSHD (OR 0.93, 95% CI 0.75, 1.14). The same pattern was observed for the composite disease outcome; given the smaller sample size of NSHD, it was thought that pooled analyses for these outcomes would not be unreasonable. Variables for the pooled analysis were harmonised across the datasets and these were appended to create the pooled dataset. Data on asthma outcome in adulthood were available only for NCDS and BCS70. Throughout the thesis, I refer to conventional levels of statistical significance as $p<0.05$, although interpretation of results does not necessarily rely on this cut-off. All data management and statistical analyses were performed using Stata SE, version 12.1 (StataCorp, TX, USA).

Data collected at three life stages were used: childhood, adolescence and adulthood (age at adulthood corresponds to the last age for which data were available, and is also referred to as 'current age'). For NSHD, BMI data at ages 7, 15 and 43 years were used, with disease outcomes measured at age 53 years; for NCDS, BMI at ages 7, 16 and 42 years, and disease outcomes measured at age 47 years; for BCS70, BMI at 10, 16 and 34 years, and disease outcomes at age 34 years. A variable for birth cohort was generated and included as an additional key covariate in the analyses. All covariates and their relationships to the key variables were described. Analyses were restricted to singleton births, and in the main analyses modification of the main effects by sex and cohort was assessed by the inclusion of interaction terms. Study participants who experienced the outcome of interest before age 20 (pre-adulthood) were excluded for those analyses, except in the case of asthma, for which individuals who were diagnosed in childhood were included. The weighted sample design in NSHD (sampling of all births to women with husbands in non-manual or agricultural jobs and ¼ of births to women with husbands in manual jobs) was accounted for by applying sampling weights to the dataset, using the `pweight` command in Stata.

For the main analysis, two main approaches to analysis were adopted; the first approach used a series of logistic regression models of increasing complexity to model different life course effects (referred to as the 'stepwise' approach), while the second compared relative risks of

disease for different combinations of overweight over the life course (the 'overweight patterns' approach). Each of these is described in detail below.

4.7.1 The Stepwise approach

In the stepwise approach, logistic regression analyses were carried out to assess the association between weight category (normal, overweight or obese) at different life stages (childhood, adolescence and adulthood) and each disease outcome of interest. A series of models was fitted, with adjustment for potential confounders and effect modifiers in stages (selected *a priori*, see Table 4-4). The approach was based on that proposed by Lucas, Fewtrell and Cole (1999), [231] which seeks to disentangle early and later life effects of body size on adult disease through a series of regression models:

1) Early Model – regression used to relate early size to outcome;
2) Combined Model – adds later size to the early model;
3) Interaction Model – adds the interaction of early and later size to the combined model; and
4) Late Model – regression used to relate later size to outcome, to help interpretation of the relative importance of early and later size independently and in combination.

Adjustment for covariates was in two stages, 'early' and 'late', according to the point in the life course at which they were considered to have an effect. Based on the proposed causal DAG for the relationship between childhood BMI status and generic adult disease, it was shown that a sufficiently adjusted model could be achieved by adjusting for birth weight, childhood SEP, ethnicity and sex. Due to the small proportion of ethnic minority groups (4%) there was no adjustment for ethnicity; analyses were stratified by sex. The goodness-of-fit for each model was assessed using a Hosmer-Lemeshow test adjusted for survey data.[328] The analyses were repeated using BMI instead of weight category, yielding an estimate of the relative risk of each disease outcome associated with a one unit increase in BMI (kg/m^2). In each model, all available cases were used to maximise the data. The main outcome measures were reported as odds ratios with 95% confidence intervals, stratified by sex. The models are described in more detail in Chapter 6.3.

4.7.2 The 'Overweight patterns' approach

The 'Overweight patterns' approach was based on that adopted by Mishra et al, [269] in their analysis of the effects of SEP over the life course on BMI in adulthood in the NSHD cohort, as an alternative approach to standard adjustment. Similar methods have been used by Merten [217] in his study of weight status in adolescence and asthma, diabetes, hypertension and high cholesterol in early adulthood among participants in the US National Longitudinal study of Adolescent Health, and by Viner and Cole in their study of childhood obesity and adult socioeconomic, educational and psychological outcomes in the BCS70 cohort. [141] In these

studies, different combinations of a binary exposure over the life course were treated as the exposure variables, to represent different life-course histories.

A similar categorisation of exposures was used in this thesis in an attempt to determine the effects of different life course exposures and to assess the relative contribution of BMI status at different stages of the life course to disease outcomes. Cohort members were categorised into 8 groups, according to weight status in each of childhood, adolescence and adulthood. Weight status referred to whether cohort members were normal weight or overweight in childhood and adolescence, where overweight included overweight and obesity as defined by IOTF BMI cut-offs, [31] and nonobese or obese in adulthood, as defined by WHO cut-offs. [314] Overweight and obesity in childhood were combined for these analyses because of the low prevalence of obesity in childhood and adolescence in these cohorts. Cohort members were categorised as follows:

Table 4-7: Categorisation of overweight patterns according to overweight/obesity in childhood, adolescence and adulthood

Overweight pattern	Weight status		
	Childhood	Adolescence	Adulthood
Never overweight	0	0	0
Childhood only	1	0	0
Adolescence only	0	1	0
Adulthood only	0	0	1
Childhood + adolescence	1	1	0
Childhood + adulthood	1	0	1
Adolescence + adulthood	0	1	1
Persistent overweight	1	1	1

In childhood and adolescence, 0= normal weight; 1=overweight or obese. In adulthood, 0=nonobese; 1=obese.

For each disease outcome, a logistic regression model was specified to calculate odds ratios of the outcome and 95% confidence intervals for each overweight pattern, with never overweight as the reference category. These models were adjusted for sex, year of birth, exact age at measurement of childhood weight and height, birth weight, SEP at birth, SEP in adulthood, and smoking status in adulthood. Coefficients for different patterns of overweight were compared using an adjusted Wald test.

As an extension of the overweight patterns approach, sensitive period and accumulation of risk models [269] were explored to assess whether overweight or obesity at particular life stages, or the number of life stages exposed to overweight or obesity was associated with disease outcomes. In these analyses, individuals were categorised according to the life stages (sensitive periods) at which they were exposed to overweight or obesity (Table 4-8), and the number of life stages at

which they were overweight (accumulation of risk score). For each sensitive period, logistic regression models were specified to calculate odds ratios of disease outcomes for overweight in the sensitive period and overweight in any other periods, compared to a reference category of never overweight. Coefficients for overweight in each sensitive period and overweight in the other periods were compared using an adjusted Wald test. The accumulation of risk model compared odds of disease for exposure at each number of time points to odds for never overweight. Tests for trend of odds were carried out to assess whether there was a relationship between the increasing exposure and disease outcomes. As above, these analyses were adjusted for sex, year of birth, exact age at measurement of childhood weight and height, birth weight, SEP at birth, SEP in adulthood, and smoking status in adulthood.

Table 4-8: Categorisation of overweight patterns according to sensitive periods of overweight/obesity and accumulation of risk

Life course hypothesis	Overweight patterns	
Sensitive period		
Child	1, 0, 0	Childhood only
	1, 1, 0	Childhood+adolescence
	1, 0, 1	Childhood+adulthood
	1, 1, 1	Persistent overweight
Other periods	0, 1, 0	Adolescence only
(not childhood)	0, 1, 1	Adolescence+adulthood
	0, 0, 1	Adulthood only
Adolescent	0, 1, 0	Adolescence only
	1, 1, 0	Childhood+adolescence
	0, 1, 1	Adolescence+adulthood
	1, 1, 1	Persistent overweight
Other periods	1, 0, 0	Childhood only
(not adolescence)	1, 0, 1	Childhood+adulthood
	0, 0, 1	Adulthood only
Adult	0, 0, 1	Adulthood only
	1, 0, 1	Childhood+adulthood
	0, 1, 1	Adolescence+adulthood
	1, 1, 1	Persistent overweight
Other periods	1, 0, 0	Childhood only
(not adulthood)	0, 1, 0	Adolescence only
	1, 1, 0	Childhood+adolescence
Accumulation of risk		
1 time point	1, 0, 0	Childhood only
	0, 1, 0	Adolescence only
	0, 0, 1	Adulthood only
2 time points	1, 1, 0	Childhood+adolescence
	1, 0, 1	Childhood+adulthood
	0, 1, 1	Adolescence+adulthood
3 time points	1, 1, 1	Persistent overweight

In childhood and adolescence, 0= normal weight; 1=overweight or obese. In adulthood, 0=nonobese; 1=obese.

As a sensitivity check, the analyses were re-run under the following conditions: 1) Excluding ethnic minority groups, 2) Adjusting BMI measurements for self-reported weight and height; the sex- and BMI-specific adjustments in Table 4-9 were used to account for underreporting of weight and overreporting of height, as observed in a sample of men and women aged 35-76 in England, [329] 3) Complete case analysis, including only those cohort members with complete data on all variables, and 4) Survival analysis using Cox regression models for time to event data; time to event results were not treated as the primary outcomes in order to maximise the data.

Table 4-9: Sex- and BMI-specific adjustments used to account for self-reported weight and height in adulthood. Source: Spencer et al (2002) "Validity of self-reported height and weight in 4808 EPIC–Oxford participants" Public Health Nutrition 5(04): 561-565.

BMI category (kg/m^2)	BMI adjustment (kg/m^2)	
	Men	Women
<20	-0.61	-0.19
20-24.9	+0.60	+0.44
25-29.9	+1.02	+0.96
≥30	+1.66	+1.35

4.7.3 Power calculations

Consideration of power issues informed the interpretation of results, and the limitations associated with these are discussed in the following chapters. Power calculations were performed and are presented for selected outcomes in Table 4-10. Calculations were based on methods for logistic regression with binary interaction (between obesity in childhood and obesity in adulthood) as described by Demidenko (2008). [330]

The assumptions in these calculations were based on estimates from analyses of the cohort data:

- Prevalence of obesity in childhood (age 10 years) is 2%
- Prevalence of obesity in mid-adulthood (age 40 years) is 20%
- OR of obesity in adulthood given obesity in childhood is 3
- alpha=0.05
- Minimum detectable OR of interaction effect=1.5

Hypertension

- OR of hypertension associated with childhood obesity is 2 (unadjusted)
- OR of hypertension associated with obesity in adulthood is 4
- Prevalence of hypertension is 17%

Type 2 diabetes

- OR of type 2 diabetes associated with childhood obesity is 4 (unadjusted)
- OR of type 2 diabetes associated with obesity in adulthood is 10
- Prevalence of type 2 diabetes is 2%

Disease (all outcomes combined)

- OR of disease associated with childhood obesity is 1 (unadjusted)
- OR of disease associated with obesity in adulthood is 2.5
- Prevalence of disease is 30%

Table 4-10: Study power for different sample sizes under combined model for hypertension, type 2 diabetes and all disease outcomes combined (unadjusted)

Cohort Size	Power (%)		
	Hypertension	Type 2 diabetes	Disease
5,000	14	10	15
10,000	24	16	26
15,000	34	21	37
20,000	43	27	46
25,000	52	32	55
50,000	81	57	84
90,000	97	81	98

5. DESCRIPTION OF THE BRITISH NATIONAL BIRTH COHORT DATA

In this chapter, the British National Birth Cohort data [252-254] are explained in more detail, and the results of descriptive analyses are reported. Overviews of the patterns of response, data collection, and characteristics of the study cohorts are presented. BMI trajectories over the life-course, patterns of overweight, and key relationships between the variables of interest are explored, and differences in these characteristics between the three cohorts are examined.

5.1 Patterns of response

Of the 5,362 births in NSHD, 4,956 cohort members contributed data at more than one wave (406 cohort members present at baseline were not observed again). All cohort members were singleton births. The patterns of response to 11 waves of the survey (ages 2 to 53 years) are shown in Table 5-1. A fifth of cohort members (20.1%) contributed some data at all 11 waves, but patterns of response were varied. At age 53 years, some data were available for 2,948 cohort members.

Table 5-1: Patterns of response to NSHD 1946 waves 1-11 for cohort members with >1 follow-up; '1' indicates that some data are available at that wave; '0' Indicates that there are no data available

Pattern	Frequency	Percent
11111111111	994	20.06
11111111000	184	3.71
01111111111	167	3.37
11111011111	145	2.93
11111111110	142	2.87
111111.1111	141	2.85
11111110000	139	2.80
11111100000	103	2.08
10000000000	71	1.43
other patterns	2870	57.91
total	**4956**	**100.00**

In NCDS, 18,558 cohort members were observed, of whom 17,638 were present at baseline (additional children born in the same week who immigrated to the UK were recruited to the study in later waves n=920). The patterns of response to the first 8 waves of the NCDS (ages 0-46) are shown in Table 5-2. More than a third of cohort members (37.3%) contributed some

data at all waves. The second most common pattern of response (18.8%) was for cohort members to have data at the first 4 waves, and to be lost to follow-up after age 16 years. At age 46, some data were available for 9,534 cohort members; 1,240 cohort members had died, 1,306 had emigrated, 612 refused to participate, and 4,893 were lost to follow-up. [331] 428 stillbirths, abortions and early neonatal deaths, 590 pre-term births (gestational age <36 weeks), 357 multiple births and 3 cohort members of unknown sex were excluded from the main analyses, for reasons explained in Chapter 4.5.

Table 5-2: Patterns of response to NCDS 1958 waves 0-7 for cohort members with >1 follow-up; '1' indicates that some data are available at that wave; '0' indicates that there are no data available

Pattern	Frequency	Percent
11111111	6924	37.32
11110000	3492	18.82
11111000	1522	8.20
11111110	1382	7.45
11110111	913	4.92
11111100	863	4.65
11111011	638	3.44
11111010	355	1.91
11110110	309	1.67
other patterns	2157	11.62
total	**18555**	**100.00**

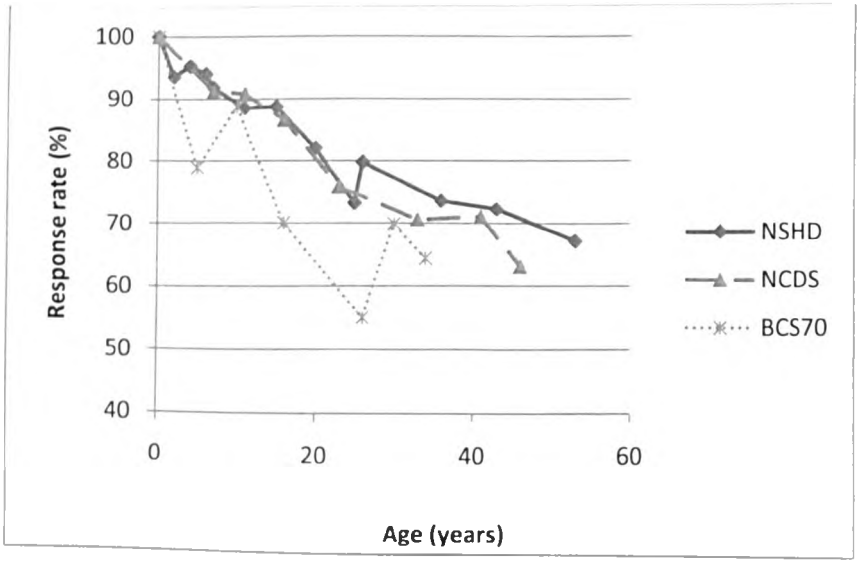
In BCS70 (data downloaded from UK Data Archive, University of Essex [332-338]), 18,126 cohort members were observed, of whom 16,567 were present at baseline. Data at more than one wave were available for 15,832 cohort members. The patterns of response to the 7 waves of BCS70 (ages 0-34) are shown in Table 5-3. More than a quarter of cohort members (26.1%) contributed some data at all 7 waves of the study. The second and third most common patterns of response (8.6% and 6.8% respectively) were to have data missing at wave 4 (age 26), or to be lost to follow-up after age 16 years. At age 34 some data were available for 9,665 cohort members; 800 cohort members had died, 451 had emigrated, 1,393 refused to participate, and 4,962 were lost to follow-up. 223 prenatal and neonatal deaths, 748 pre-term births and 236 multiple births were excluded from analyses.

Table 5-3: Patterns of response in BCS70 waves 0-6, for cohort members with >1 follow-up; '1' indicates that some data are available at that wave; '0' Indicates that there are no data available

Pattern	Frequency	Percent
1111111	4129	26.08
1111011	1363	8.61
1111000	1078	6.81
1110000	930	5.87
1110111	720	4.55
1111110	664	4.19
1111010	510	3.22
1011111	439	2.77
1110011	419	2.65
other patterns	5580	35.25
total	**15832**	**100.00**

Study response rates (as percentage of target sample) in the three cohorts can be seen in Figure 5-1. Response rates in NSHD and NCDS decreased in a relatively regular fashion over time, while in BCS70 they fluctuated, with notably low response rate of 55% at age 26 years. In general, retention rates in NSHD and NCDS were higher than in BCS70 for any given age. For example, at age 15/16 years, the response rates in NSHD and NCDS were 89% and 87% respectively, compared to 70% in BCS70. At the final wave of each study, response rates were 67% for NSHD, 63% for NCDS, and 64% for BCS70. Analysis of the characteristics of non-respondents indicated that males, cohort members from lower socioeconomic positions, and individuals from ethnic minority backgrounds were more likely to be lost to follow-up. [339]

Figure 5-1: Longitudinal response rates by age in NSHD, NCDS and BCS70



5.2 Data collection methods

Data collection methods for the key variables in each cohort are summarised in Table 5-4, Table 5-5 and Table 5-6. In childhood and adolescence, all cohorts used a combination of maternal interview, medical records and health visitor examinations to collect information on weight, height, health and social class. Childhood and adolescent weight and height were measured by a trained assessor (doctor, nurse or health visitor). In adulthood, both self-completed and interviewer-administered (face-to-face or telephone) techniques were used for data collection, resulting in a combination of self-reported and measured variables. Notably, weight and height were self-reported at wave 7 of NCDS (age 41/42 years), and at all ages in adulthood in BCS70. Analyses were rerun using BMI adjusted for self-reported height and weight [329] as a sensitivity check. In NCDS and BCS70, computer-based methods, including computer assisted personal interviewing (CAPI) and computer aided self-interviewing (CASI)[340] were used in recent waves of data collection. Health outcomes in adulthood were self-reported, either using self-completed postal questionnaires (NSHD) or interviewer-administered questionnaires (NCDS and BCS70). The key variables included in the main analyses and the methods used to collect this information are described in the following sections.

Table 5-4: Data collection in MRC NSHD (1946)

Year	Age (y)	Data collection method	N	Weight & height	Disease outcomes	SEP	Smoking
1946	0	MatInt	5,362	bw	N/A	PaOcc (ParInt)	N/A
1948	2	MatInt+ records+ HV assessment	4,689	M	N/A	N/A	N/A
1950	4	MatInt+ records+ HV assessment	4,700	M	N/A	PaOcc (ParInt)	N/A
1952	6	MatInt+ records+ medical exam	4,603	M	N/A	N/A	N/A
1953	7	Medical exam	4,480	M	N/A	N/A	N/A
1957	11	MatInt+ medical exam	4,281	M	N/A	PaOcc (ParInt)	N/A
1961	15	MatInt+ medical exam	4,274	M	N/A	PaOcc (ParInt)	N/A
1966	20	SCQ	3,899	SR	N/A	N/A	Current smoker
1971	25	SCQ	3,307	N/A	N/A	N/A	N/A
1972	26	SCQ	3,604	SR	SCQ	CurrentOcc (SCQ)	N/A
1977	31	SCQ+ physical exam		N/A	SCQ	N/A	Current smoker; ever smoked
1982	36	SCQ+ physical exam	3,322	M	SCQ	CurrentOcc (SCQ)	Current smoker; ever smoked
1989	43	SCQ+ physical exam	3,262	M	SCQ	CurrentOcc (SCQ)	Current smoker; ever smoked
1999	53	SCQ+ physical exam	3,035	M	SCQ		Current smoker; ever smoked

MatInt = Maternal interview; SCQ = self-completed questionnaire; bw = birth weight; M = measured; SR = self-reported; PaOcc = father's (or male Head of Household's) occupation; CurrentOcc = current occupation; HV = health visitor

Table 5-5: Data collection in NCDS (1958)

Year	Age (y)	Data collection method	N	Weight & height	Disease outcomes	SEP	Ethnicity	Smoking
1958	0	MatInt + records	17,415	bw	N/A	PaOcc (ParInt)	N/A	N/A
1965	7	ParInt + medical exam	15,051	M	Medical history and examination	PaOcc (ParInt)	N/A	N/A
1969	11	ParInt + medical exam	14,757	M	Medical history and examination	PaOcc (ParInt)	N/A	N/A
1974	16	ParInt + medical exam	13,917	M	Medical history and examination	PaOcc (ParInt)	N/A	Current smoker, ever smoked
1981	23	CMInt	12,044	SR	CMInt	CurrentOcc (CMInt)	N/A	Current smoker, ever smoked regularly*
1991	33	CMInt + SCQ	10,986	M	CMInt	CurrentOcc (CMInt)	CMInt	Current smoker, ever smoked regularly
1999/ 2000	41/ 42	CAPI + CASI	10,979	SR	CAPI	CurrentOcc (CAPI)	SR	Current smoker, ever smoked regularly
2004/ 2005	46/ 47	CATI	9,534	M	CATI	CurrentOcc (CATI)	N/A	Current smoker, ever smoked

MatInt = Maternal interview; ParInt = Parental interview; CMInt = cohort member interview; SCQ = self-completed questionnaire; CAPI = computer assisted personal interviewing; CASI = computer aided self-interviewing; CATI = computer assisted telephone interviewing; bw = birth weight; M = measured; SR = self-reported; PaOcc = father's (or male Head of Household's) occupation; CurrentOcc = current occupation; * Regular smoking defined as smoking at least one cigarette a day for 12 months or longer

Table 5-6: Data collection in BCS70 (1970)

Year	Age (y)	Data collection method	N	Weight & height	Disease outcomes	SEP	Ethnicity	Smoking
1970	0	MatInt + medical records	16,571	bw	N/A	PaOcc (ParInt)	N/A	N/A
1975	5	MSQ + ParInt + health records	12,981	N/A	ParInt	PaOcc (ParInt)	ParInt	N/A
1980	10	MSQ + ParInt + medical exam	14,350	M	ParInt and examination	PaOcc (ParInt)	ParInt	N/A
1986	16	MSQ + ParInt + SCQ + medical exam	11,206	M	ParInt, SCQ and examination	PaOcc (ParInt)	ParInt	N/A
1996	26	SCQ	8,654	SR	SCQ	CurrentOcc (SCQ)	N/A	Current smoker, ever smoked
1999/ 2000	30	CAPI + CASI	10,833	SR	CAPI	CurrentOcc (CAPI)	SR	Current smoker, ever smoked regularly*
2004/ 2005	34	CAPI	9,665	SR	CAPI	CurrentOcc (CAPI)	SR	

MatInt = Maternal interview; MSQ = maternal self-completed questionnaire; ParInt = Parental interview; CMInt = cohort member interview; SCQ = self-completed questionnaire; CAPI = computer assisted personal interviewing; CASI = computer aided self-interviewing; CATI = computer assisted telephone interviewing; bw = birth weight; M = measured; SR = self-reported; PaOcc = father's (or male Head of Household's) occupation; CurrentOcc = current occupation; * Regular smoking defined as smoking at least one cigarette a day for 12 months or longer

5.3 BMI from height and weight measures

BMI data were available for 3,977 cohort members at age 7 in NSHD and 2,948 cohort members at age 53 (Table 5-8). In NCDS, BMI data were available for 12,985 cohort members at age 7 and 11,086 cohort members at age 42. In BCS70, BMI data were available for 11,283 individuals at age 10 and 8,799 at age 34, with only 5,365 cohort members contributing data at age 16.

5.3.1 BMI distributions

Visualisation of BMI distributions using histograms showed that the distribution at each wave of NSHD was positively skewed. The variance and skewness of the BMI distribution increased with age (Figure 5-2). Similar patterns were observed in NCDS and BCS70 (Figure 5-3 and

Figure 5-4), although more extreme values at the upper end of the distribution were observed in adulthood in these cohorts (Figure 5-5).

Figure 5-2: BMI distribution at ages 7, 11, 15, 26, 36 and 53 in MRC NSHD

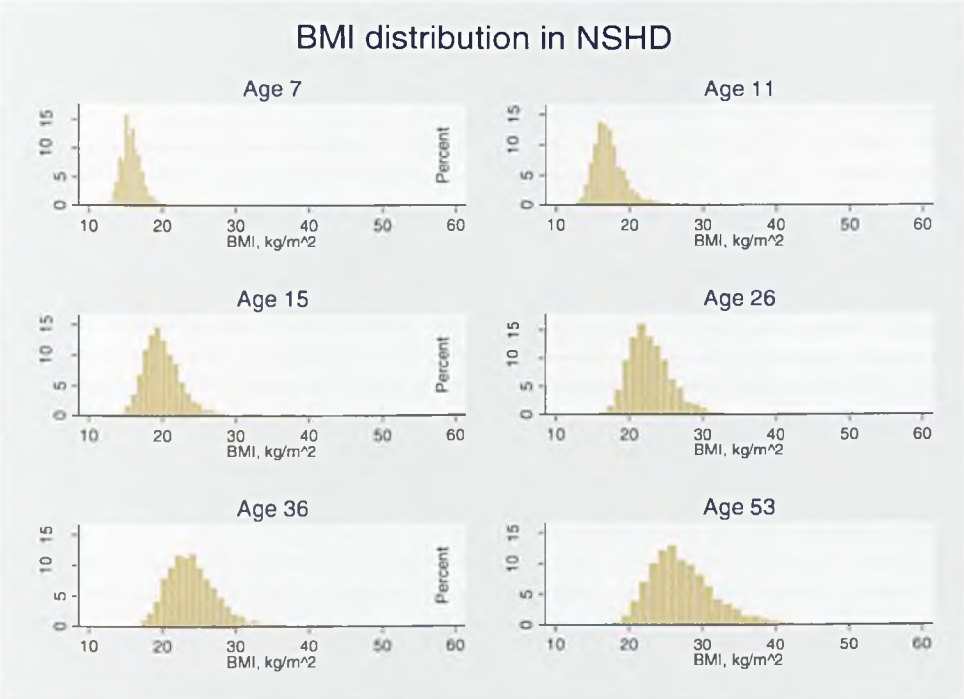


Figure 5-3: BMI distribution at ages 7, 11, 16, 23, 33 and 45 in NCDS

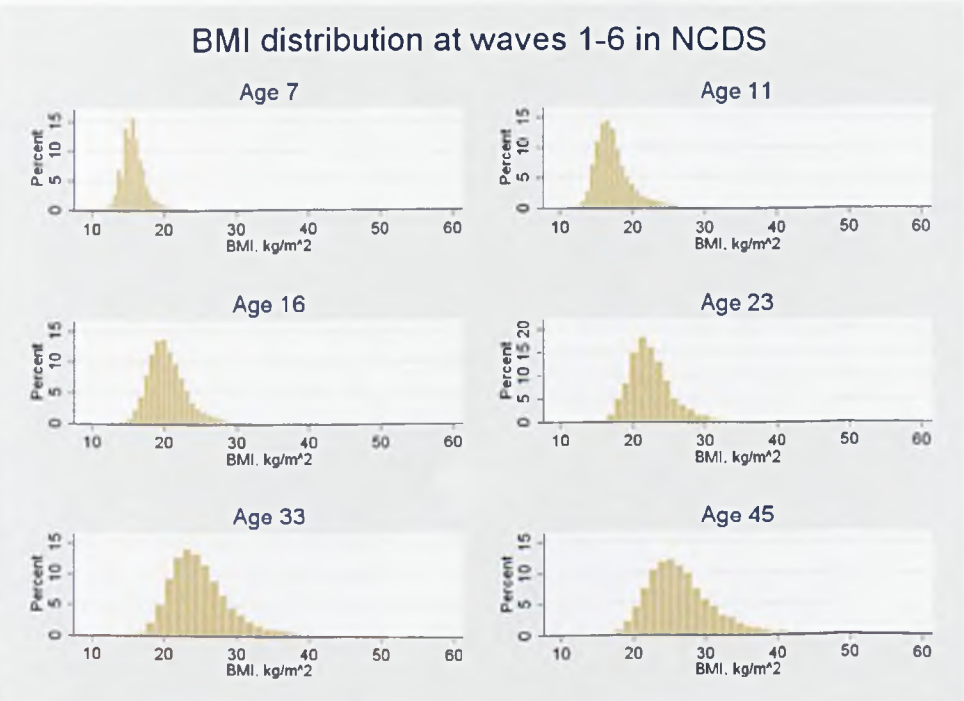


Figure 5-4: BMI distribution at ages 10, 16, 26, 30 and 34 in BCS70

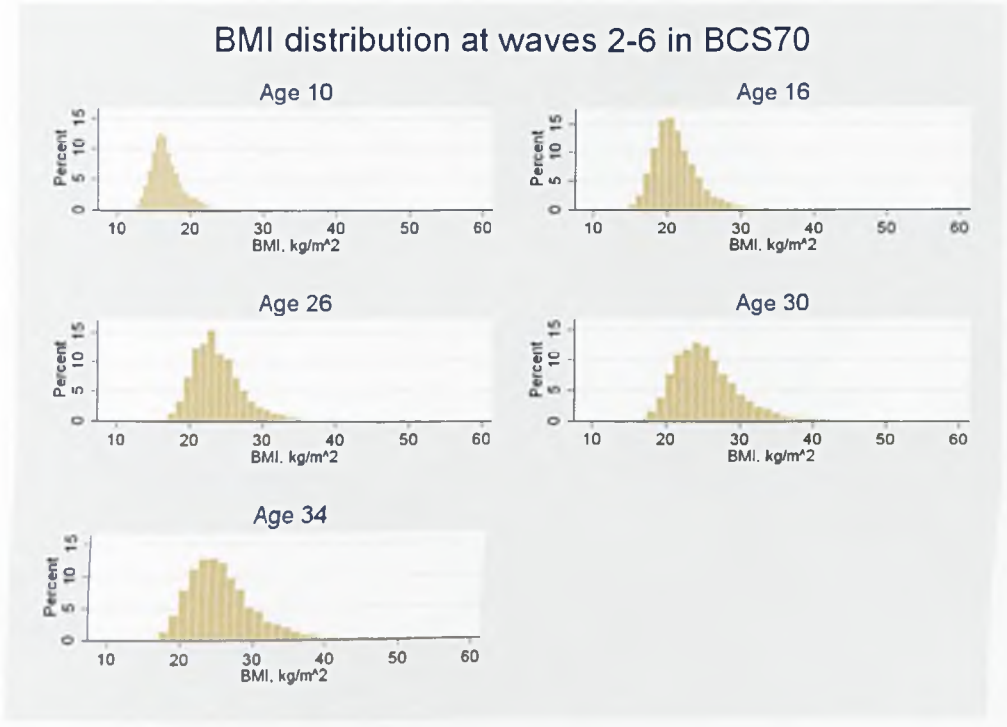
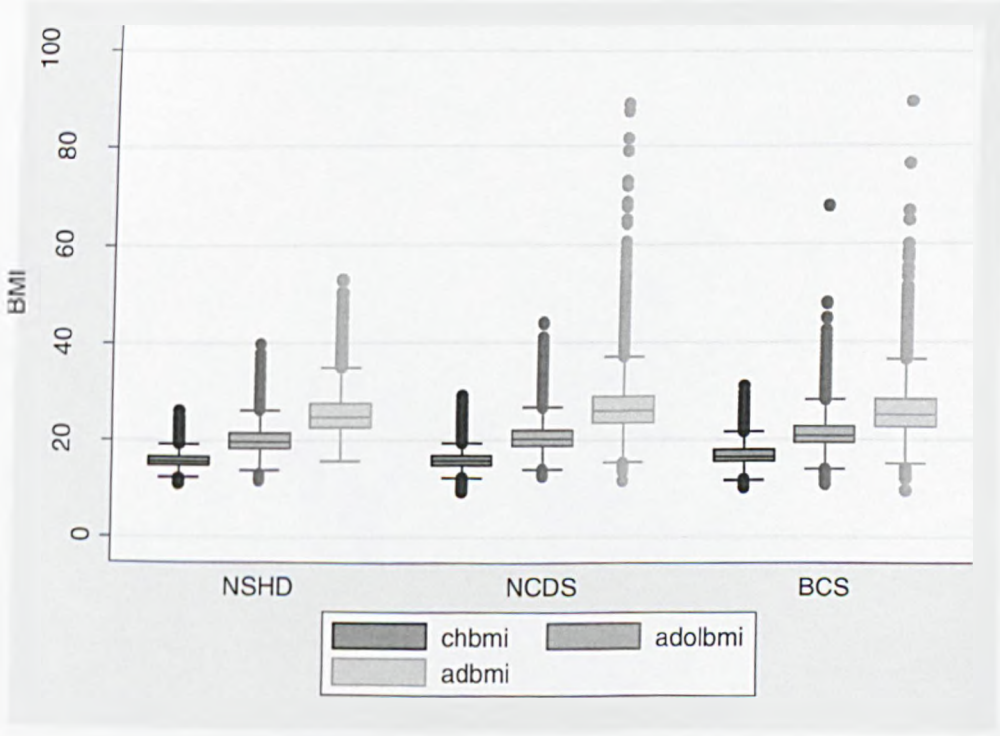


Figure 5-5: Box and whisker plot of BMI distribution in childhood, adolescence and adulthood for NSHD, NCDS and BCS70 cohorts.



Box represents interquartile range (IQR); whiskers represent upper and lower adjacent values (±1.5 x IQR). chbmi=BMI in childhood, adolbmi=BMI in adolescence, adbmi=BMI in adulthood.

5.3.2 *BMI trajectories*

Piecewise linear random coefficients models were applied to analyse the repeated measures of BMI for each cohort, and the coefficients from these models were examined to assess differences between BMI trajectories. Models were specified to start from age 7 years to avoid the adiposity rebound which usually occurs at around age 6 years, [341] prior to which many non-linear changes in adiposity occur (illustrated in Figure 5-6 using data from the 1946 NSHD cohort). Knots were selected at 16 years, and were used for all cohorts to ensure comparability. Models were tested for random effects and non-linearity.

Figure 5-6: Mean BMI for male cohort members from age 2 to 53 years in 1946 NSHD cohort

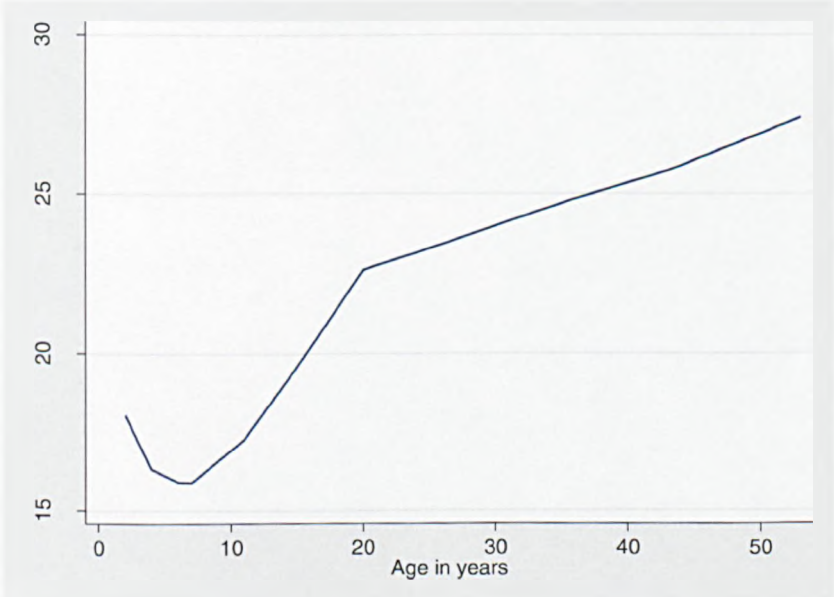


Figure 5-7 and Figure 5-8 show the observed means and estimated trajectories of BMI in the three cohorts, among males and females respectively. These plots show that BMI increase was faster in childhood (age <16 years) than in adulthood in all cohorts ($p<0.01$) (Table 5-7). Likelihood ratio tests indicated a linear trend in BMI gain in childhood, and in adulthood among females in NCDS, but a quadratic trend in adulthood for males in all three cohorts, and females in NSHD and BCS70. These results illustrate that mean BMI at any given age in adulthood increased with successive cohorts, but this trend was not apparent in childhood. Comparison of the estimated BMI trajectories also revealed that the rate of BMI increase in adulthood increased with successive cohorts in both sexes, e.g. among females, BMI gain was at 0.083 kg/m^2 per year in NSHD, 0.211 in NCDS, and 0.337 in BCS70 (although slowing down with age, as indicated by the negative coefficient for the quadratic term) (Table 5-7).

Figure 5-7: Estimated BMI trajectories and observed mean BMI at various ages for male cohort members in 1946 NSHD, 1958 NCDS and 1970 BCS70. Knots are at 16 years.

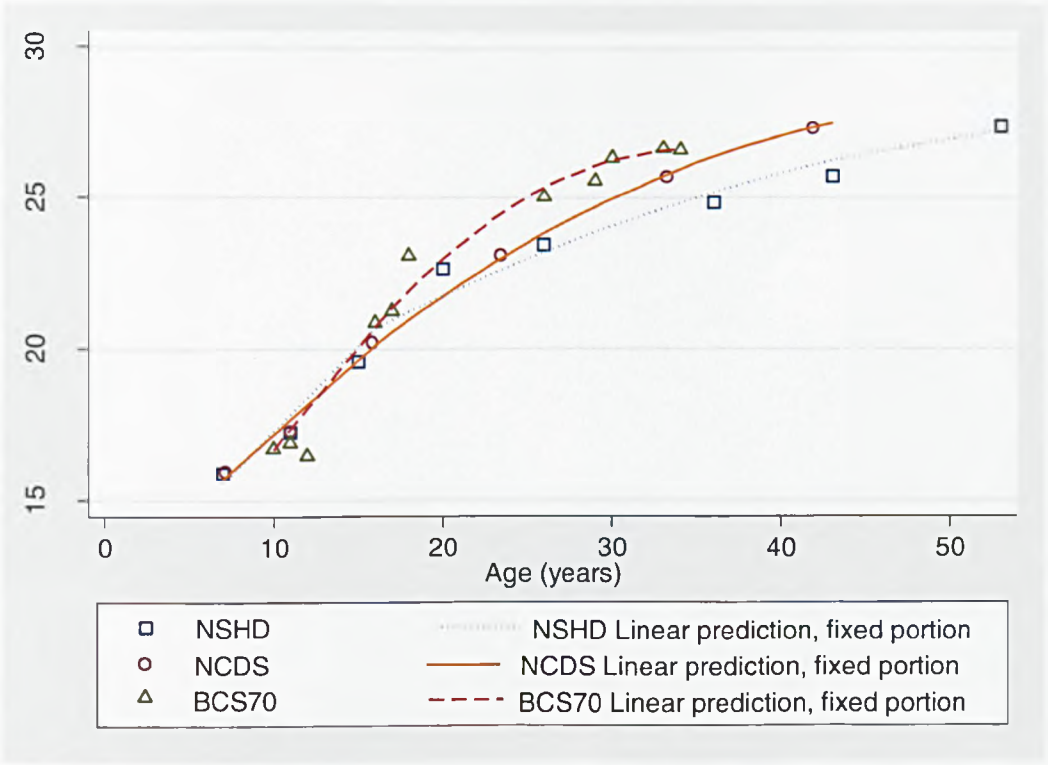


Figure 5-8: Estimated BMI trajectories and observed mean BMI at various ages for female cohort members in 1946 NSHD, 1958 NCDS and 1970 BCS70. Knots are at 16 years.

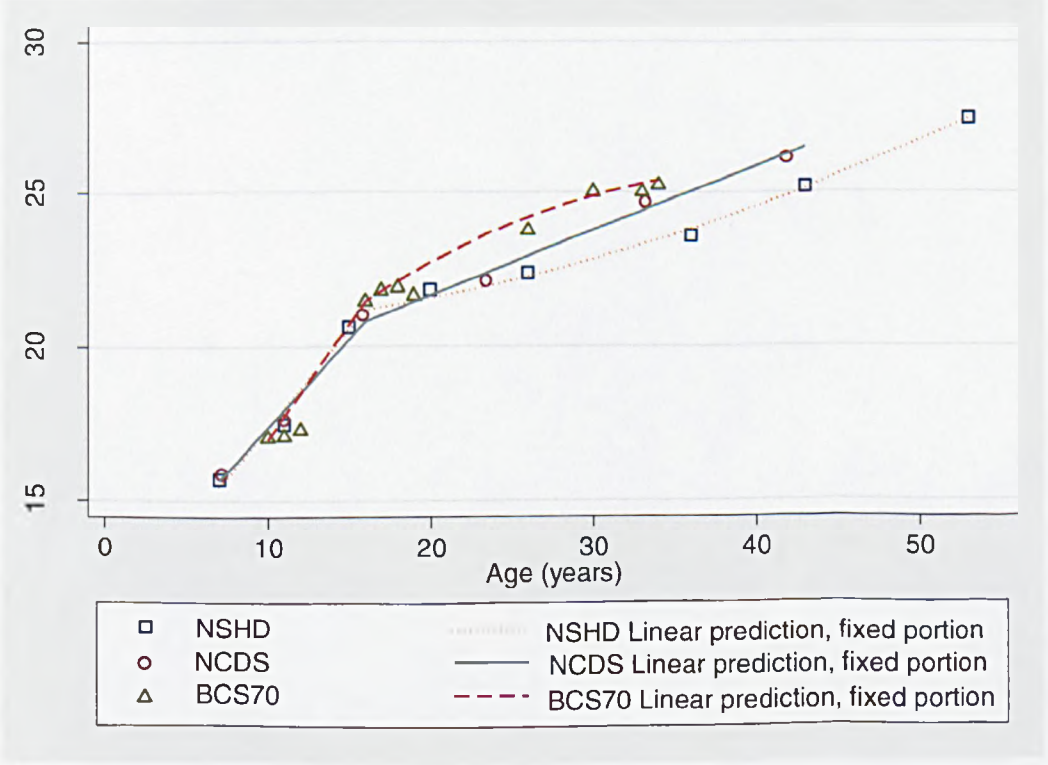


Table 5-7: Parameter estimates for 1946 NSHD, 1958 NCDS and 1970 BCS70 cohorts from piecewise linear model. Knot at 16 years.

Parameter effects	MRC NSHD		NCDS		BCS70	
(fixed effects)	Coefficient	95% CI	Coefficient	95% CI	Coefficient	95% CI
Males						
Intercept	11.59	11.46, 11.71	12.25	12.15, 12.34	9.93	9.74, 10.12
Age (childhood*)	0.568	0.556, 0.579	0.493	0.484, 0.501	0.675	0.658, 0.692
Age (adult)	0.280	0.270, 0.290	0.424	0.414, 0.434	0.627	0.607, 0.648
Age^2 (adult)	-0.003	-0.003, -0.002	-0.006	-0.006, -0.005	-0.017	-0.018, -0.016
Females						
Intercept	10.99	10.85, 11.13	11.68	11.58, 11.78	9.54	9.34, 9.74
Age (childhood*)	0.637	0.623, 0.651	0.570	0.561, 0.579	0.745	0.727, 0.762
Age (adult)	0.083	0.072, 0.094	0.211	0.206, 0.216	0.337	0.318, 0.357
Age^2 (adult)	0.002	0.002, 0.003	-	-	-0.007	-0.008, -0.006

* Childhood <16 years, adulthood ≥ 16 years

5.3.3 Overweight and obesity prevalence

The prevalence of overweight and obesity in each cohort increased substantially between childhood and adulthood. In NSHD, 6.5% of male and 8.8% of female cohort members were overweight or obese at age 7, compared to 74.6% and 62.9% overweight or obese at age 53 (Table 5-8). In NCDS, 7.9% of male and 10.9% of female cohort members were overweight or obese at age 7; at age 42, 70.2% of men and 49.2% of women were overweight or obese (these figures were based on BMI calculated from self-reported height and weight). In BCS70, 6.5% of boys and 10.7% of girls were overweight or obese at age 10, and these figures had risen to 60.6% and 40.5% at age 34, although again this was based on self-reported measures of weight and height. There is indication of a cohort effect on obesity prevalence from adolescence onwards; younger cohorts appear to have higher prevalence of obesity at a given age, an effect which becomes more apparent at older ages. For example, among males, 0.6% in NSHD were classified as obese at age 15, compared to 1.5% of boys in NCDS at age 16, and 2.0% in BCS70. In contrast, 0.5% in NSHD were obese at age 7, 1.3% in NCDS at the same age, and 0.3% in BCS70 at age 10. Compared to contemporary populations with childhood obesity

prevalence of 7-10%, [45] obesity prevalence in childhood and adolescence was low in these cohorts, ranging from 0.5- 2.4%.

5.3.4 Overweight over the life course

Analysis of the relationships between overweight and obesity in childhood, adolescence and adulthood revealed positive associations between overweight over the life course. Table 5-9 shows that cohort members in NSHD and NCDS who were overweight or obese in childhood (age 7 years) had more than double the odds of overweight or obesity in adulthood compared to those who were normal weight, while those that were obese in childhood had more than six times the odds of obesity in adulthood (NSHD: OR 6.55; 95% CI 2.21, 19.83, NCDS: OR 6.35; 95% CI 4.52, 8.93). In BCS70, those who were overweight in childhood had more than four times the odds of overweight or obesity in adulthood (OR 4.52; 95% CI 3.66, 5.57), and a similar effect size was observed for obesity (OR 4.00; 95% CI 1.68, 9.53). However, cross-tabulations of weight status in childhood and in adulthood revealed that a sizable proportion of overweight children did become normal weight adults in these cohorts, and vice versa. For example, in NSHD, 20% of cohort members who were overweight at age 7 were normal weight at age 53, while 65% of those who were normal weight at age 7 became overweight or obese in adulthood; in NCDS, 24% of those who were overweight and 12% of those who were obese at age 7 were normal weight at age 42, and 58% of those who were normal weight in childhood were overweight or obese in adulthood.

The associations between weight status in adolescence (age 15-16) and adulthood (age 34-43 years) were stronger than those between childhood and adulthood (Table 5-10). In all three cohorts, there was strong evidence that overweight/obesity in adolescence was associated with overweight/obesity in adulthood, and effect sizes were larger in younger cohorts, which had a shorter period of time between measurements (NSHD: OR 5.92; 95% CI 3.81, 9.21, NCDS: OR 6.83; 95% CI 5.43, 8.61, BCS70: OR 8.01; 95% CI 6.13, 10.45). Obesity in adolescence was associated with very large increases in odds of obesity in adulthood, and in contrast to overweight, effect sizes were smaller in younger cohorts (NSHD: OR 41.18; 95% CI 10.66, 159.04, NCDS: OR 13.65; 95% CI 9.04, 20.61, BCS70: OR 10.36; 95% CI 6.45, 16.65). This stronger association was reflected in cross-tabulations, which showed that few cohort members that were overweight or obese in adolescence became normal weight adults; 13% of overweight and 0% of obese adolescents in NSHD, and 12% of overweight and 3% of obese adolescents in NCDS were normal weight in adulthood.

Table 5-8: Mean BMI and prevalence of overweight and obesity at each age in NSHD, NCDS and BCS70 cohorts, by sex

Cohort,		BMI, kg/m^2				Prevalence of overweight + obesity [a b]				Prevalence of obesity [b]			
Age at measurement		Male		Female		Male		Female		Male		Female	
‡		Mean (SD)	n	Mean (SD)	n	%	n	%	n	%	n	%	n
NSHD 1946 †	7	15.9 (1.4)	2,057	15.7 (1.8)	1,920	6.5	2,057	8.8	1,920	0.5	2,057	1.3	1,920
	11	17.2 (2.3)	2,050	17.5 (3.0)	1,887	6.4	2,050	10.2	1,887	1.0	2,050	1.8	1,887
	15	19.6 (3.0)	1,881	20.7 (3.7)	1,700	6.8	1,881	12.1	1,700	0.6	1,881	1.9	1,700
	26	23.6 (3.4)*	1,822	22.6 (3.8)*	1,782	27.9*	1,822	17.8*	1,782	2.7*	1,822	3.3*	1,782
	36	25.0 (3.6)	1,632	23.8 (4.9)	1,648	47.0	1,632	28.3	1,648	6.4	1,632	7.2	1,648
	42	25.9 (4.0)	1,617	25.4 (6.0)	1,608	58.7	1,617	42.3	1,608	10.8	1,617	14.8	1,608
	53	27.6 (4.6)	1,452	27.7 (6.6)	1,496	74.6	1,452	62.9	1,496	23.1	1,452	27.0	1,496
NCDS 1958	7	15.9 (1.6)	6,717	15.9 (1.9)	6,268	7.9	6,717	10.9	6,268	1.3	6,717	2.2	6,268
	11	17.3 (2.4)	6,382	17.6 (2.7)	6,117	8.7	6,382	11.9	6,117	1.6	6,382	1.7	6,117
	16	20.3 (2.7)	5,611	21.0 (2.7)	5,249	9.0	5,611	12.6	5,249	1.5	5,611	1.9	5,249
	23	23.1 (2.9)*	6,127	22.2 (3.3)*	6,148	19.9*	6,127	14.4*	6,148	2.3*	6,127	3.0*	6,148
	33	25.7 (4.7)	5,428	24.6 (5.5)	5,609	51.3	5,428	35.7	5,609	11.2	5,428	12.1	5,609

	42	27.3 (4.6)*	5,493	26.1 (5.3)*	5,593	70.2*	5,493	49.2*	5,593	19.9*	5,493	18.3*	5,593
BCS70 1970	**10**	16.8 (1.9)	5,756	17.1 (2.3)	5,527	6.5	5,756	10.7	5,527	0.3	5,756	0.5	5,527
	16	20.8 (3.2)	2,591	21.4 (3.3)	2,774	11.8	2,591	14.9	2,774	2.0	2,591	2.4	2,774
	30	26.3 (4.2)*	4,992	24.9 (5.0)*	5,271	59.6*	4,992	38.4*	5,271	14.9*	4,992	13.4*	5,271
	34	26.5 (4.5)*	4,253	25.5 (5.2)*	4,546	60.6*	4,253	40.5*	4,546	17.7*	4,253	15.5*	4,546

[a] Overweight according to IOTF definitions in childhood and adolescence, and as BMI $\geq 25 kg/m^2$ for adults
[b] Obesity according to IOTF definitions in childhood and adolescence, and as BMI $\geq 30 kg/m^2$ for adults
* Self-reported
† Adjusted for weighted sample; SD estimated from standard error
‡To ensure comparability of measurements across the studies, measures of BMI in childhood were centred at ages using predictions from linear regression models assuming a linear trend with age over short periods of time.

Table 5-9: Association between 1) overweight+obesity and 2) obesity in adulthood and childhood

	Overweight (inc obesity)		Obesity (kg/m^2)	
	OR† (95% CI)	P-value	OR‡ (95% CI)	P-value
NSHD 1946	2.54 (1.76, 3.68)	<0.001	6.55 (2.21, 19.38)	0.001
NCDS 1958	2.64 (2.21, 3.16)	<0.001	6.35 (4.52, 8.93)	<0.001
BCS70 1970	4.52 (3.66, 5.57)	<0.001	4.00 (1.68, 9.53)	0.002

†OR of overweight +obesity in adulthood for overweight+obesity in childhood; ‡OR of obesity in adulthood for obesity in childhood; adjusted for weighted sample in NSHD. NB. Weight status in adulthood calculated from self-reported weight and height for NCDS and BCS70.

Table 5-10: Association between 1) overweight+obesity and 2) obesity in adulthood and adolescence

	Overweight (inc obesity)		Obesity (kg/m^2)	
	OR† (95% CI)	P-value	OR‡ (95% CI)	P-value
NSHD 1946	5.92 (3.81, 9.21)	<0.001	41.18 (10.66, 159.04)	<0.001
NCDS 1958	6.83 (5.43, 8.61)	<0.001	13.65 (9.04, 20.61)	<0.001
BCS70 1970	8.01 (6.13, 10.45)	<0.001	10.36 (6.45, 16.65)	<0.001

†OR of overweight +obesity in adulthood for overweight+obesity in adolescence; ‡OR of obesity in adulthood for obesity in adolescence; adjusted for weighted sample in NSHD. NB. Weight status in adulthood calculated from self-reported weight and height for NCDS and BCS70.

Table 5-11: Association between 1) overweight+obesity and 2) obesity in adolescence and childhood

	Overweight (inc obesity)		Obesity (kg/m^2)	
	OR† (95% CI)	P-value	OR‡ (95% CI)	P-value
NSHD 1946	11.72 (8.26, 16.62)	<0.001	200.40 (66.82, 601.06)	<0.001
NCDS 1958	10.24 (8.64, 12.13)	<0.001	38.40 (24.93, 59.14)	<0.001
BCS70 1970	12.86 (10.14, 16.31)	<0.001	27.30 (8.04, 92.66)	<0.001

†OR of overweight +obesity in adolescence for overweight+obesity in childhood; ‡OR of obesity in adolescence for obesity in childhood; adjusted for weighted sample in NSHD

5.4 Diseases in adulthood

In all three cohorts, respondents were asked at each wave in adulthood if they suffered from any of a list of common health problems. Conditions covered included asthma/wheezing, hay fever, bronchitis, back problems, skin problems, arthritis/painful joints, diabetes, epilepsy, bladder/kidney problems, migraine, stomach problems, cancer and problems with teeth/gums. Cohort members were asked whether they had ever experienced these conditions and about health problems in the last 12 months. Respondents also reported other longstanding illnesses or health problems that required regular medical supervision, and these were coded using the International Classification of Diseases (ICD) 3 digit classification. For this study, self-report of

ever having had any of: hypertension, gall bladder disease, coronary heart disease, stroke, arthritis or cancers (colorectal, breast, uterine, oesophageal, liver and kidney), were the outcomes of interest. The frequencies of these outcomes are described for each cohort below.

In NSHD, hypertension was the most common outcome, reported by 60% of men and 49% of women by age 53, followed by arthritis which was reported by 20.1% of women and 13.5% of men; 5.6% of men and 3.3% of women reported coronary heart disease (Table 5-12). Other outcomes were less common, with 3.1% of cohort members reporting gall bladder disease (1.4% of men versus 4.7% of women), 1.9% reporting type 2 diabetes (2.1% of men versus 1.6% of women), and 1.4% reporting any of the cancers of interest (0.3% of men versus 2.4% of women). When all outcomes were combined, 61.9% of respondents had experienced at least one of the disease outcomes of interest; 64.5% of men reported ever suffering from any of the diseases of interest, compared to 59.3% of women.

Some disease outcome data at age 47 years were available for 9,198 cohort members in NCDS (Table 5-13). Asthma was the most common morbidity, reported by 15.8% of men and 19.5% of women. 12.7% of men and 14.9% of women reported ever having had hypertension. As in NSHD, other outcomes were less common, with 2.7% reporting gall bladder disease (1.0% of men versus 4.4% of women), 2.8% reporting type 2 diabetes (3.4% of men versus 2.2% of women), and <1% reporting CHD (0.5% of men versus 0.2% of women), stroke (0.3% among men and women), arthritis (0.6% of men versus 1.3% of women), and each cancer type. There were no reported cases of oesophageal cancer. When all disease outcomes were combined, it was shown that almost a third of respondents (32.5%) had experienced at least one of these outcomes. With the exception of type 2 diabetes, coronary heart disease (CHD), colorectal cancer and kidney cancer, disease outcomes were more commonly reported among women than men at age 47 years (35% of women versus 29% of men).

In BCS70, disease outcome data at age 34 years were available for 8,530 cohort members (Table 5-14). As in NCDS, asthma was the most commonly reported morbidity, affecting 10.3% of men and 11.6% of women. Hypertension was reported by 4.7% of men and 5.6% of women. 1.2% of cohort members reported type 2 diabetes (1.4% of men versus 1.0% of women), while all other disease outcomes were reported by <0.2% of respondents. There were no reported cases of oesophageal cancer, liver cancer or kidney cancer. When all disease outcomes were combined in a single variable, it was shown that 16.7% of cohort members had ever experienced at least one of the morbidities of interest (15.6% of men versus 17.7% of women).

Table 5-12: Frequency of self-reported disease outcomes (ever had) in NSHD (age 53 years), by sex

	Number of self-reported cases n (%)		
	Men	**Women**	**Total**
Hypertension	1,103 (59.5)	894 (49.0)	1,997 (54.3)
Gall bladder disease	21 (1.4)	72 (4.7)	93 (3.1)
Type 2 diabetes	38 (2.1)	30 (1.6)	68 (1.9)
Coronary heart disease	82 (5.6)	51 (3.3)	133 (4.4)
Stroke	12 (0.8)	14 (0.9)	26 (0.9)
Arthritis	221 (13.5)	327 (20.1)	548 (16.8)
Colorectal cancer	5 (0.3)	3 (0.2)	8 (0.3)
Breast cancer	N/A	32 (2.1)	N/A
Uterine cancer	N/A	2 (0.1)	N/A
Oesophageal cancer	N/A	N/A	N/A
Liver cancer	N/A	N/A	N/A
Kidney cancer	N/A	N/A	N/A
Female cancers* combined	N/A	34 (2.2)	N/A
Cancers combined**	5 (0.3)	37 (2.4)	42 (1.4)
All diseases combined†	1,196 (64.5)	1,082 (59.3)	2,278 (61.9)

*Breast and uterine cancers; **Colorectal, breast, uterine, oesophageal, liver and kidney cancers; † All diseases listed in table

Table 5-13: Frequency of self-reported disease outcomes (ever had) at wave 7 of NCDS (age 47 years), by sex

	Number of self-reported cases n (%)		
	Men	**Women**	**Total**
Hypertension	562 (12.7)	700 (14.9)	1,321 (14.0)
Asthma	708 (15.8)	922 (19.5)	1,676 (17.6)
Gall bladder disease	43 (1.0)	205 (4.4)	255 (2.7)
Type 2 diabetes	152 (3.4)	105 (2.2)	266 (2.8)
Coronary heart disease	22 (0.5)	10 (0.2)	35 (0.4)
Stroke	11 (0.3)	12 (0.3)	23 (0.2)
Arthritis	25 (0.6)	61 (1.3)	86 (0.9)
Colorectal cancer	3 (0.07)	1 (0.02)	4 (0.04)
Breast cancer	N/A	51 (1.0)	N/A
Uterine cancer	N/A	20 (0.4)	N/A
Oesophageal cancer	0	0	0
Liver cancer	0	2 (0.04)	2 (0.02)
Kidney cancer	1 (0.02)	0	1 (0.01)
Female cancers combined*	N/A	71 (1.4)	N/A
Cancers combined**	4 (0.1)	74 (1.5)	78 (0.8)
All diseases combined†	1,312 (29.3)	1,673 (35.4)	3,090 (32.4)

*Breast and uterine cancers; **Colorectal, breast, uterine, oesophageal, liver and kidney cancers; † All diseases listed in table

Table 5-14: Frequency of self-reported disease outcomes (ever had) at wave 6 of BCS70 (age 34 years), by sex

	Number of self-reported cases n (%)		
	Men	**Women**	**Total**
Hypertension	189 (4.7)	250 (5.6)	482 (5.1)
Asthma	416 (10.3)	521 (11.6)	1,037 (10.9)
Gall bladder disease	1 (0.02)	7 (0.2)	8 (0.1)
Type 2 diabetes	56 (1.4)	46 (1.0)	113 (1.2)
Coronary heart disease	3 (0.07)	1 (0.02)	4 (0.05)
Stroke	3 (0.07)	5 (0.1)	8 (0.1)
Arthritis	3 (0.07)	9 (0.2)	13 (0.1)
Colorectal cancer	0	2 (0.04)	2 (0.02)
Breast cancer	N/A	3 (0.07)	N/A
Uterine cancer	N/A	4 (0.09)	N/A
Oesophageal cancer	0	0	0
Liver cancer	0	0	0
Kidney cancer	0	0	0
All female cancers combined*	N/A	7 (0.2)	N/A
All cancers combined**	0	9 (0.2)	9 (0.1)
All diseases combined†	630 (15.6)	794 (17.7)	1,570 (16.6)

*Breast and uterine cancers; **Colorectal, breast, uterine, oesophageal, liver and kidney cancers; † All diseases listed in table

5.5 Cohort characteristics: covariates of interest

The distribution of the covariates of interest within each cohort can be seen in Table 5-15.

5.5.1 Sex

The distribution of sex was similar across all three cohorts, with men making up just over half of the study population at baseline.

5.5.2 Ethnicity

Information on ethnicity was not available for the NSHD cohort, although as previously discussed, it can be assumed that a small minority (<1%) of the population would be from ethnic minority groups.[320] In NCDS, ethnic minority groups made up 3.1% of the population, compared to 4.5% in BCS70.

5.5.3 Social class based on occupation

In childhood, the pattern of social class distribution was similar for all three cohorts, with the majority of participants born into manual social class III (skilled manual worker) households (46% in NSHD, 51% in NCDS, 46% in BCS70). Social class I (higher managerial, administrative or professional) made up the smallest proportion of study participants (3.0% in NSHD, 4.6% in NCDS, 5.6% in BCS70). 12-19% of study participants were from social classes II (intermediate managerial, administrative or professional) and IV (semi- and unskilled manual workers), and 6-10% were from social class V (casual or lowest grade workers, and those who depend on the state for income). In adulthood, the distribution of social class was shifted towards non-manual skilled occupations, with the majority of cohort members belonging to social class II (29.3% in NSHD, 41.4% in NCDS, 40.1% in BCS70), and with smaller proportions in skilled manual, semi- and unskilled and casual or lowest grade occupations, compared to in childhood. There were also expected trends across cohorts, with social class I growing and social class V shrinking over successive cohorts.

5.5.4 Smoking status

The distribution of smoking status was largely similar across cohorts, with nearly half of the cohort members being never smokers (40% in NSHD, 45% in NCDS, 44% in BCS70). There was evidence for different patterns of current and previous smoking according to cohort age; there was a higher proportion of ex-smokers in NSHD (34%) than in NCDS (27%) and BCS70 (22%), while a larger proportion of BCS70 were current smokers compared to NSHD and NCDS (χ^2 $p<0.001$). This may reflect people giving up smoking at older ages, as other studies have shown decreasing smoking prevalence with age. [342]

Table 5-15: Characteristics of NSHD, NCDS and BCS70

	Cohort %		
	NSHD†	NCDS	BCS70
Sex (at baseline)	**5,362**	**17,611**	**14,325**
Male	52.6	51.7	51.5
Female	47.4	48.3	48.5
Ethnic group	**-**	**15,923**	**15,628**
White/European	-	96.9	95.5
Ethnic minority group	-	3.1	4.5
Childhood social class	**4,673**	**15,581**	**14,032**
i	3.0	4.6	5.6
ii	13.7	13.0	11.5
iii non-manual	9.0	9.7	13.7
iii manual	46.2	50.7	46.0
iv	18.9	12.1	16.9
v	9.1	9.9	6.3
Adult social class	**4,159**	**8,264**	**7,802**
i	4.9	6.0	6.9
ii	29.3	41.4	40.1
iii non-manual	23.6	20.4	21.0
iii manual	22.5	18.9	18.8
iv	14.9	11.0	11.0
v	4.8	2.3	2.2
Smoking status (adult)	**2,988**	**11,845**	**11,633**
Never smoked	40.3	45.2	43.9
Ex-smoker	34.1	26.5	22.3
Current smoker	25.6	28.3	33.8

† Adjusted for weighted sample

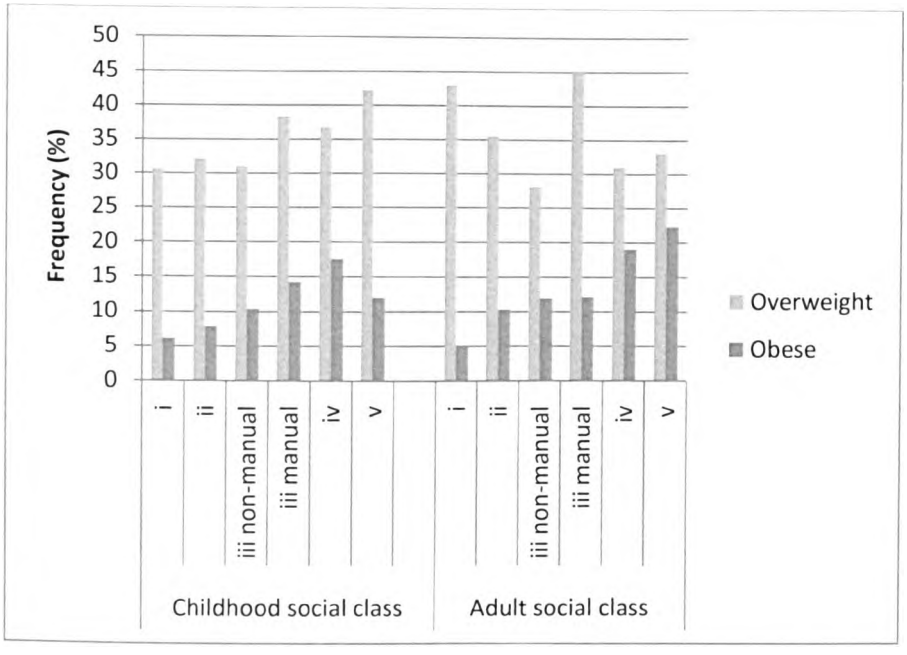
5.6 BMI status by cohort characteristics

Table 5-16 shows the distribution of BMI status at age 43 in NSHD by the covariates of interest. The proportion of cohort members classified as obese was higher among women than men

(13.9% of women obese versus 10.6% of men), but more men were overweight (44.8% versus 25.9%), and fewer men fell in the normal weight category (44.7% of men versus 60.2% of women normal weight) (p from chi-squared test <0.001). A social gradient in BMI status can be seen, with higher proportion of obesity among lower social classes, for both childhood and adult social class (p<0.001); 4.9% of those in adult social class I (higher managerial, administrative or professional) were obese, compared to 22.3% of those in social class V (casual or lowest grade workers, and those who depend on the state for income). The patterning of overweight was more complex, with higher prevalence of adult overweight among cohort members who were in the lowest social classes in childhood, but high levels of overweight among cohort members in social class I in adulthood. However, overall, a higher proportion of overweight+obesity is seen among lower social classes, with more participants in higher social classes being classified as normal weight (52.2% normal weight in social class I, versus 44.6% in social class V). By smoking status, the highest prevalence of obesity was observed among ex-smokers (13.9% obese), and the lowest among current smokers (9.9%). A smaller proportion of ex-smokers fell into the normal weight category (48.7%) compared to never smokers (54.9%) and current smokers (56.2%) (p<0.001).

In NCDS (Table 5-17), higher levels of overweight and obesity in adulthood were observed among men than women at age 42; 50.5% of men versus 31.0% of women were overweight, while 19.9% of men versus 18.3% of women were obese (p<0.001). There was no strong evidence for differences in the prevalence of overweight and obesity by ethnicity (p=0.324). The social patterning of obesity was similar to that observed in NSHD, with the highest levels of obesity in social class V and lowest levels in social class I (p<0.001); 20.8% of adults who were in social class V in childhood were obese, compared to 13.0% of those who had been in social class I, while 23.4% of adults currently in social class V were obese, compared to 15.4% of those in social class I. As in NSHD, overweight in adulthood showed different gradients for childhood social class compared to adult social class. Those who had been in lower social classes in childhood were more likely to be overweight than those who had been in higher social classes, whilst those in the highest social classes in adulthood were more likely to be overweight than those in social classes IV or V. Patterns of overweight and obesity by smoking status were similar to those in NSHD; the highest prevalence of obesity was observed among ex-smokers (21.1%) and the lowest in current smokers (17.8%) (p<0.001). A higher proportion of ex-smokers were also overweight (42.6%) compared to never smokers (40.6%) and current smokers (38.4%).

Figure 5-9: Distribution of weight status in adulthood within social class strata in NSHD



In BCS70, the prevalence of overweight and obesity in adulthood was higher among men than women ($p<0.001$); 17.9% of men were obese at age 34 compared to 15.4% of women, and 42.9% of men compared to 25.0% of women were overweight. Among ethnic minority groups, 18.7% were obese, compared to 16.5% of the white/European population; however, the prevalence of overweight was lower (28.7% versus 34.0%) and overall evidence for ethnic differences was weak ($p=0.143$). However, it is important to note that the BMI cut-offs used to define weight status were not ethnicity-specific, and may underestimate overweight and obesity in some groups, particularly South Asian populations. As in the two earlier cohorts, prevalence of obesity tended to be higher among lower social classes ($p<0.001$); 11.3% of cohort members who were born to social class I fathers were obese at age 34, compared to 21.1% and 20.4% of those in social classes IV and V, respectively. 11.9% of those in social class I in adulthood were obese, compared to 20.5% in social class V. As in previous cohorts, patterns of overweight by social class were more variable, with higher proportion of overweight among those in the lowest social classes at birth compared to those in higher social classes, but those in the highest social classes in adulthood having similar levels of overweight than those in lower social classes. Patterns of weight status by smoking status showed the highest levels of obesity among ex-smokers (18.1%), and the lowest among current smokers (14.6%), but prevalence of overweight was higher among current smokers (34.6%) than ex-smokers (33.9%) or never smokers (33.2%) ($p=0.010$).

Table 5-16: BMI status in NSHD by covariates of interest; adjusted for weighted sampling (estimated n)

	BMI status at age 43			
	Normal n (%)	Overweight n (%)	Obese n (%)	Total n (%)
Sex				
Male	722 (44.7)	724 (44.8)	171 (10.6)	1,617 (100)
Female	968 (60.2)	416 (25.9)	224 (13.9)	1,608 (100)
Childhood social class				
i	124 (63.3)	60 (30.6)	12 (6.1)	196 (100)
ii	363 (60.1)	194 (32.1)	47 (7.8)	604 (100)
iii non-manual	293 (58.6)	155 (31.0)	52 (10.4)	500 (100)
iii manual	474 (47.6)	381 (38.3)	141 (14.2)	996 (100)
iv	262 (45.6)	211 (36.8)	101 (17.6)	574 (100)
v	88 (45.8)	81 (42.2)	23 (12.0)	192 (100)
Adult social class				
i	107 (52.2)	88 (42.9)	10 (4.9)	205 (100)
ii	639 (54.1)	421 (35.6)	122 (10.3)	1,182 (100)
iii non-manual	444 (60.0)	208 (28.1)	88 (11.9)	740 (100)
iii manual	244 (42.7)	258 (45.2)	69 (12.1)	571 (100)
iv	190 (50.0)	118 (31.1)	72 (19.0)	380 (100)
v	54 (44.6)	40 (33.1)	27 (22.3)	121 (100)
Smoking status				
Never smoked	649 (54.9)	392 (33.1)	142 (12.0)	1,183 (100)
Ex-smoker	474 (48.7)	365 (37.5)	135 (13.9)	974 (100)
Current smoker	347 (56.2)	210 (34.0)	61 (9.9)	618 (100)

Table 5-17: BMI status in NCDS by covariates of interest

	BMI status at age 42			
	Normal	**Overweight**	**Obese**	**Total**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Sex				
Male	1,564 (29.6)	2,664 (50.5)	1,051 (19.9)	5,279 (100)
Female	2,733 (50.7)	1,669 (31.0)	986 (18.3)	5,388 (100)
Ethnic group				
White/European	4,397 (40.5)	4,391 (40.5)	2,064 (19.0)	10,852 (100)
Ethnic minority group	84 (36.0)	98 (42.1)	51 (21.9)	233 (100)
Childhood social class				
i	222 (49.5)	168 (37.5)	58 (13.0)	448 (100)
ii	641 (47.5)	520 (38.6)	187 (13.9)	1,348 (100)
iii non-manual	447 (44.7)	402 (40.2)	150 (15.0)	999 (100)
iii manual	1,863 (38.6)	1,956 (40.5)	1,008 (20.9)	4,827 (100)
iv	395 (33.9)	510 (43.8)	259 (22.3)	1,164 (100)
v	319 (37.9)	348 (41.3)	175 (20.8)	842 (100)
Adult social class				
i	173 (37.5)	217 (47.1)	71 (15.4)	461 (100)
ii	1,354 (42.0)	1,322 (41.1)	543 (16.9)	3,219 (100)
iii non-manual	750 (47.2)	584 (36.8)	255 (16.0)	1,589 (100)
iii manual	433 (30.2)	695 (48.6)	303 (21.2)	1,431 (100)
iv	349 (41.8)	330 (39.5)	156 (18.7)	835 (100)
v	60 (35.9)	68 (40.7)	39 (23.4)	167 (100)
Smoking status				
Never smoked	2,044 (40.7)	2,037 (40.6)	938 (18.7)	5,019 (100)
Ex-smoker	1,072 (36.3)	1,256 (42.6)	622 (21.1)	2,950 (100)
Current smoker	1,365 (43.8)	1,196 (38.4)	555 (17.8)	3,116 (100)

Table 5-18: BMI status in BCS70 by covariates of interest

	BMI status at age 34*			
	Normal	Overweight	Obese	Total
	n (%)	n (%)	n (%)	n (%)
Sex				
Male	1,560 (39.2)	1,708 (42.9)	711 (17.9)	3,979 (100)
Female	2,557 (59.6)	1,070 (25.0)	662 (15.4)	4,289 (100)
Ethnic group				
White/European	4,390 (49.5)	3,013 (34.0)	1,466 (16.5)	8,869 (100)
Ethnic minority group	163 (52.6)	89 (28.7)	58 (18.7)	310 (100)
Childhood social class				
i	313 (61.0)	142 (27.7)	58 (11.3)	513 (100)
ii	569 (54.9)	351 (33.9)	116 (11.2)	1,036 (100)
iii non-manual	663 (53.8)	399 (32.4)	170 (13.8)	1,232 (100)
iii manual	1,763 (47.7)	1,273 (34.5)	658 (17.8)	3,694 (100)
iv	560 (45.7)	407 (33.2)	259 (21.1)	1,226 (100)
v	168 (41.8)	152 (37.8)	82 (20.4)	402 (100)
Adult social class				
i	287 (55.0)	173 (33.1)	62 (11.9)	522 (100)
ii	1,571 (51.6)	1.018 (33.5)	453 (14.9)	3,042 (100)
iii non-manual	831 (52.3)	486 (30.6)	271 (17.1)	1,588 (100)
iii manual	569 (39.1)	599 (41.2)	287 (19.7)	1,455 (100)
iv	379 (45.7)	307 (37.0)	143 (17.3)	829 (100)
v	79 (47.6)	53 (31.9)	34 (20.5)	166 (100)
Smoking status				
Never smoked	2,056 (49.6)	1,377 (33.2)	712 (17.2)	4,145 (100)
Ex-smoker	1,039 (48.0)	732 (33.9)	392 (18.1)	2,163 (100)
Current smoker	1,458 (50.8)	993 (34.6)	420 (14.6)	2,871 (100)

*Note: Height and weight were self-reported

Table 5-19 shows correlations between child, adolescent and adult BMI and key covariates for the three British National Birth Cohorts combined. Lower birth weight was correlated with lower social class in both childhood and adulthood. Birth weight was positively associated with childhood height, and BMI at all stages of life, although the correlation was highest with childhood BMI (0.13; $p<0.001$) and lowest with adult BMI (0.06; $p<0.001$). Lower social class in childhood was associated with smaller height in childhood, lower social class in adulthood, and being a smoker. Lower childhood social class was also associated with increased BMI at all stages of life, although this effect was weakest in childhood (0.01; $p=0.048$) and strongest in adulthood (0.12; $p<0.001$). Smaller height in childhood was associated with lower social class in both childhood (-0.08; $p<0.001$) and adulthood (-0.09; $p<0.001$). Height in childhood was positively correlated with BMI in childhood (0.25; $p<0.001$) and adolescence (0.19; $p<0.001$); as with birth weight, the correlation was strongest in childhood. Lower social class in adulthood was associated with smoking; there was no strong evidence of correlation between social class in adulthood and childhood BMI, but lower social class was correlated with BMI in adulthood (0.07; $p<0.001$). Smoking in adulthood was positively correlated with BMI in childhood (0.03; $p<0.001$) and adolescence (0.03; $p<0.001$), but negatively correlated with BMI in adulthood (-0.01; $p=0.024$). There were moderately high positive correlations between BMI in childhood and BMI in adolescence (0.55; $p<0.001$), between childhood BMI and adult BMI (0.31; $p<0.001$) and adolescent BMI and adult BMI (0.44; $p<0.001$); the magnitude of observed correlations was inversely related to the length of time between measurements. Tests for multicollinearity among study variable (using the `-collin-` command in Stata) indicated that multicollinearity was not a problem (variance inflation factor values were <10).[343]

Table 5-19: Correlation matrix of key study variables for NSHD, NCDS and BCS70 cohorts combined, gives Spearman rank correlation coefficient and n in each cell; birth weight, childhood height, and BMIs treated as continuous variables, social class and smoking status treated as ordinal variables

	Birth weight	Childhood social class	Childhood height	Adult social class	Smoking status	Childhood BMI	Adolescent BMI	Adult BMI
Birth weight	1 35,608							
Childhood social class	-0.0650 ** 33,768	1 34,294						
Childhood height	0.1088 ** 27,707	-0.0809 ** 27,218	1 29,790					
Adult social class	-0.0557 ** 18,541	0.2635 ** 18,133	-0.0944 ** 16,717	1 20,225				
Smoking status	0.0203 * 23,904	0.0738 ** 23,382	0.0106 21,532	0.1490 ** 18,984	1 26,466			
Childhood BMI	0.1339 ** 26,745	0.0122 † 26,271	0.2539 ** 28,741	-0.0084 16,140	0.0317 ** 20,777	1 28,741		
Adolescent BMI	0.0773 ** 18,268	0.0336 ** 17,944	0.1920 ** 17,056	0.0014 12,424	0.0277 ** 15,222	0.5452 ** 16,501	1 20,030	
Adult BMI	0.0631 ** 21,279	0.1176 ** 20,793	-0.0042 19,242	0.0692 ** 18,503	-0.0149 † 23,039	0.3121 ** 18,593	0.4421 ** 14,036	1 23,489

†<0.05; *<0.01; **<0.001

5.7 Changes in social patterning of overweight and obesity over successive cohorts

Changes in the social patterning of overweight and obesity over successive cohorts were explored in further detail, as SEP is a key potential confounder of the relationship between overweight and disease outcomes, and the social patterning of overweight was considered to be an important way in which the three cohorts could differ. Table 5-20 shows that there was no strong evidence for an association between social class at birth and the odds of overweight/obesity in childhood (ages 7years) in NSHD or NCDS, but odds of overweight/obesity was higher with lower social class in BCS70. Similarly, there was no association with BMI treated as a continuous outcome for the NSHD and NCDS cohorts. For BCS70, there was evidence that lower social class at birth was associated with increased BMI at age 10 (coefficient 0.053; 95% CI 0.020, 0.085).

An association between social class at birth and overweight in adolescence was evident for the NCDS and BCS70 cohorts (Table 5-21); each unit change from highest social class I to lowest social class V at birth was associated with a 14-16% increase in the odds of overweight+ obesity at age 16 years (NCDS: OR 1.16; 95% CI 1.10, 1.23, BCS70: 1.14; 95% CI 1.06, 1.22). Similarly, lower social class was associated with increased BMI in these two cohorts. In the NSHD cohort, there was no association between social class at birth and overweight or BMI in adolescence.

Social class at birth was strongly associated with overweight and BMI in adulthood (ages 34-43 years) for all three cohorts (Table 5-22), with lower social class at birth predicting increased odds of overweight in adulthood. In NSHD, each unit change in social class (moving from highest to lowest) was associated with a 17% increase in odds of overweight+obesity (OR 1.17; 95% CI 1.10, 1.25); in NCDS there was 15% increase in the odds of overweight+obesity (OR 1.15; 95% CI 1.11, 1.19); and in BCS70 there was a 16% increase in the odds of overweight+obesity (OR 1.16; 95% CI 1.12, 1.21). Each unit change in social class was also associated with an increase in BMI. Effect sizes were similar in all three cohorts.

Table 5-23 shows the associations between social class, and overweight and BMI in adulthood (ages 34-43 years). It can be seen that lower social class was associated with an increased odds of concurrent overweight in all three cohorts, although the effect sizes were smaller than for social class at birth; each unit change in social class was associated with a 9% increase in the odds of overweight+obesity in NSHD (OR 1.09; 95% CI 1.03, 1.17), a 7% increase in NCDS (1.07; 1.03, 1.11), and a 13% increase in BCS70 (1.13; 1.09, 1.17). As with social class in childhood, effects sizes were similar across cohorts.

Table 5-20: Association between 1) overweight+obesity and 2) BMI in childhood and social class of father at birth in three British National Birth Cohorts

	Overweight (inc obesity)		BMI (kg/m^2)	
	OR† (95% CI)	P-value	Coefficient (95% CI)	P-value
NSHD 1946	0.96 (0.86, 1.07)	0.464	-0.003 (-0.048, 0.042)	0.890
NCDS 1958	0.99 (0.94, 1.04)	0.614	0.003 (-0.023, 0.029)	0.816
BCS70 1970	**1.08** (1.02, 1.14)	0.007	**0.053** (0.020, 0.085)	0.001

†OR of overweight for each unit change in social class at birth (from social class I to V; I being the highest and V being the lowest social class)

Table 5-21: Association between 1) overweight+obesity and 2) BMI in adolescence and social class of father at birth in three British National Birth Cohorts

	Overweight (inc obesity)		BMI (kg/m^2)	
	OR† (95% CI)	P-value	Coefficient (95% CI)	P-value
NSHD 1946	1.06 (0.94, 1.18)	0.336	0.016 (-0.072, 0.104)	0.722
NCDS 1958	**1.16** (1.10, 1.23)	<0.001	**0.107** (0.062, 0.152)	<0.001
BCS70 1970	**1.14** (1.06, 1.22)	<0.001	**0.139** (0.066, 0.212)	<0.001

†OR of overweight for each unit change in social class at birth (from social class I to V; I being the highest and V being the lowest social class)

Table 5-22: Association between 1) overweight+obesity and 2) BMI in adulthood and social class of father at birth in three British National Birth Cohorts

	Overweight (inc obesity)		BMI (kg/m^2)	
	OR† (95% CI)	P-value	Coefficient (95% CI)	P-value
NSHD 1946	**1.17** (1.10, 1.25)	<0.001	**0.382** (0.251, 0.513)	<0.001
NCDS 1958	**1.15** (1.11, 1.19)	<0.001	**0.376** (0.299, 0.454)	<0.001
BCS70 1970	**1.16** (1.12, 1.21)	<0.001	**0.412** (0.322, 0.503)	<0.001

†OR of overweight for each unit change in social class at birth (from social class I to V; I being the highest and V being the lowest social class)

Table 5-23: Association between 1) overweight+obesity and 2) BMI in adulthood and current social class in three British National Birth Cohorts

	Overweight (inc obesity)		BMI (kg/m^2)	
	OR† (95% CI)	P-value	Coefficient (95% CI)	P-value
NSHD 1946	**1.09** (1.03, 1.17)	0.006	**0.381** (0.229, 0.533)	<0.001
NCDS 1958	**1.07** (1.03, 1.11)	0.001	**0.171** (0.084, 0.259)	<0.001
BCS70 1970	**1.13** (1.09, 1.17)	<0.001	**0.271** (0.182, 0.360)	<0.001

†OR of overweight for each unit change in social class in adulthood (from social class I to V; I being the highest and V being the lowest social class)

5.8 Missing data

Table 5-24 shows the frequency of missing data in the three cohorts for key variables in adulthood. While information on ethnicity, smoking status and adult BMI were relatively complete, more than 20% of participants had missing data on BMI in childhood or adolescence. In the case of BCS70, more than half of participants were missing data on BMI in adolescence. Overall, data in NSHD were more complete than in the two more recent cohorts, particularly for birth weight and social class variables.

Table 5-24: Frequency of missing data in adulthood for key variables, by cohort. % as percentage of all respondents in adulthood.

	Cohort n (%)		
	NSHD (n=2,948)	**NCDS (n=9,534)**	**BCS70 (n=9,665)**
Sex (at baseline)	0	0	0
Birth weight	10 (0.3)	1,080 (11.3)	955 (10.1)
Ethnic group	n/a	51 (0.5)	1 (0.01)
Childhood social class	155 (5.3)	1,189 (12.5)	1,118 (11.8)
Adult social class	65 (2.2)	1,270 (13.3)	1,684 (17.8)
Smoking status (adult)	0	4 (0.04)	31 (0.3)
Childhood BMI	506 (17.2)	2,027 (21.3)	2,015 (21.2)
Adolescent BMI	688 (23.3)	2,805 (29.4)	5,453 (57.5)
Adult BMI	200 (6.8)	683 (7.2)	307 (3.2)

5.9 Summary and implications

This chapter has described the datasets and variables that are used in the rest of the thesis, and has examined the relationships between key variables. Analysis of the patterns of response in the three cohort datasets indicated substantial attrition and loss to follow-up over time. Response rates also varied across the cohorts, with lowest response in the youngest cohort, BCS70. Previous analyses of the British National Birth Cohorts have shown that non-responders were more likely to be male, from lower socioeconomic positions, and from ethnic minority groups. [339] In order to maximise data, last observation carried forward was used for some variables with missing data. To assess the effects of missing data, complete case analyses were carried out as a sensitivity check.

Data on both directly measured and self-reported height and weight in adulthood were used in the main analyses. Self-reported weight and height data are subject to bias, which can vary systematically according to socio-demographic characteristics. Most validation studies report underestimation of BMI and prevalence of overweight when self-reported data are used, which is due to a combination of underestimation of weight and overestimation of height. [344-347] Factors such as gender, age, level of education, BMI and social desirability can influence reporting of weight and height. For example, population-based studies show that women tend to underestimate their weight whilst men do not,[345-346] and that older adults (ages 60+) are more likely to misreport weight and height than younger adults. [346 348] Additionally, increasing level of overweight is associated with greater underreporting of weight. [346] The consequent differential misclassification of overweight status can bias risk estimates for disease outcomes, and may account for discrepancies in study findings. [345 349] To assess the potential effect of misclassification due to self-reporting, sensitivity analyses using an adjustment factor for self-reported BMI were carried out. The adjustment factors for BMI from self-reported weight and height were based on a validation study of self-reported height and weight in 4,808 middle-aged participants in the Oxford cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford).[329] The implications of data collection methods and measurement bias are discussed.

Weights and heights in childhood and adolescence were directly measured (as opposed to self-reported or reported by parents). As expected, examination of BMI data revealed that the prevalence of obesity in childhood and adolescence was low in these cohorts relative to current levels (obesity prevalence in childhood ranged from 0.3 to 2.4%). These levels are comparable with those observed in contemporaneous studies.[2] Power calculations in Chapter 4.7.3 showed that large sample sizes are required to identify clinically relevant differences in disease risk when studying the effects of childhood obesity at these prevalences. In an attempt to increase study power, in the main analyses of overweight patterns, overweight and obesity in childhood and adolescence were combined to create a single category. Furthermore, the inclusion of BMI as a continuous exposure was explored.

Disease outcomes were self-reported. The validity of self-reported health data varies for different conditions and according to how these are defined. For example, in a US study of 2,037 middle-aged men and woman, [350] responses to a self-administered questionnaire were compared with medical records. Kappa scores for chronic disorders (diabetes, hypertension), and acute-onset diseases (myocardial infarction MI and stroke) indicated substantial agreement (κ ranged 0.71 to 0.80). However, there was differential misclassification, with younger age, being female, and being more educated being predictors of greater accuracy of reporting. The validity of self-reported cancer was assessed in the Malmö Diet and Cancer Study (MDCS), a population-based prospective cohort study in Sweden. [351] On comparison with information

from the Swedish Cancer Registry (SCR), sensitivity of questionnaire information for malignant tumours was 82%, and specificity was 98%. A κ score of 0.72 indicated substantial agreement. Among men, under-reporting was associated with older age and obesity (obese men were 70-94% more likely to under-report cancer than normal weight men). Most of the health outcomes data in the three British national birth cohorts were collected using interviewer-administered questionnaires, which are considered to be more reliable and valid instruments for assessing medical history than self-administered questionnaires. [352]

In NSHD, the prevalence of hypertension was higher than would be expected given the age of the study population; in the Health Survey for England (HSE) 2009, 33% of men and 25% of women aged 45-54 were hypertensive, including current cases of controlled hypertension and untreated hypertension.[342] Furthermore, comparison of self-reported doctor-diagnosed with survey-defined hypertension in HSE showed that prevalence of hypertension based on survey measurements of blood pressure was higher than self-reported hypertension. However, the measure of hypertension used in this thesis (report of ever having had hypertension) is not directly comparable to cross-sectional prevalence, as the thesis measure would include individuals who were diagnosed as hypertensive previously but managed their condition without medication (these cases would not be picked up in the survey). In addition, changing definitions of high blood pressure over time [353] may have picked up individuals as 'hypertensive' in the past who would not be diagnosed today; although the general trend has been towards lower blood pressure thresholds over time (and therefore would expect fewer diagnoses of hypertension historically), thresholds as low as 130/80 mm Hg have been recommended for individuals with co-morbidities such as diabetes in previous reports.[354] Type 2 diabetes was lower in NSHD than in NCDS despite the more advanced age of the former, but the observed number of cases in NSHD was consistent with a previous analysis of self-reported outcomes in this cohort, [355] and contemporary assessments of prevalence, for example, in 1998, the prevalence of diabetes was 1.6% among men and 0.9% among women aged 35-54.[342]

Some of the *a priori* outcomes of interest, notably stroke and cancers, were rarely observed in these cohorts, which can be attributed to the late-onset nature of these outcomes (for example, the average age at first stroke in the UK is 71 years among men, and 77 years among women [356]), and the relatively young ages of cohort members at last follow-up. Given the small number of cases for these diseases, stroke and cancers were omitted from the main analyses and discussion; results for hypertension, asthma, gallbladder disease, type diabetes, coronary heart disease, and combined diseases are presented.

Comparison of key variables of interest across the three cohorts indicated the presence of cohort effects, notably increasing prevalence of overweight and obesity at comparable ages in adulthood. Such trends over time have been noted elsewhere.[357-358] However, there were also

many similarities among the three cohorts, such as the patterning of overweight by social class in adulthood and smoking status, and associations between overweight in early and later life. Given the similarities in target populations (all babies born in Great Britain in a given week), and the comparability of key variables, pooling these data to maximise study power, with adjustment for cohort and age effects, seemed a reasonable approach.

Analyses indicated the presence of moderate correlations between BMI in early life and in adulthood. These correlations were not high enough to be considered an issue with regards to multicollinearity, but may be sufficient to introduce effects akin to the reversal paradox (as discussed in Chapter 4.3.2). In order to address this, two approaches were adopted for the main analyses: one approach used a series of regression models with stepwise adjustment for covariates, and the other considered different combinations of overweight and obesity across the life stages and their relationships with disease outcomes. The results from these analyses are presented in the next chapter.

6. THE CONTRIBUTION OF CHILDHOOD & ADOLESCENT WEIGHT STATUS TO DISEASE OUTCOMES IN ADULTHOOD

6.1 Introduction

As the literature review in Chapter 3 showed, our understanding of the contribution of overweight and obesity at different stages of the life-course to long-term health outcomes is incomplete. This is in part due to limitations of standard approaches to studying early life effects. Although some studies have indicated that contemporaneous obesity rather than exposure to overweight in earlier life explains most of the observed disease risk in adulthood, [174] others have shown that obesity isolated to a single period in youth may affect later health [217]; it remains unclear whether childhood obesity has long-term effects on health.

In these analyses, data from the three British National Birth Cohorts have been pooled to explore the relationships between overweight at different stages of the life course and morbidity in later life. These three datasets have not previously been analysed together in this way. Pooling of these data increased the study power to explore the relationship between childhood and adolescent weight status and disease in adulthood. A life course approach [235] was adopted in analysing these relationships, and potential sensitive period and accumulation of risk effects were considered.

Findings for selected analyses have been presented at a conference (Park M H, Sovio U, Viner R M, Hardy R and Kinra, S. 'Overweight in childhood, adolescence and adulthood and morbidity in later life'. Poster presentation, ECO 2012 The 19th European Congress on Obesity 9-12 May 2012, Lyon, France). Selected results have also been written up and submitted for publication in a peer-reviewed journal.

6.2 Research questions

1. Are overweight and obesity in childhood and adolescence associated with increased morbidity in later life?

2. Do overweight and obesity in childhood and adolescence contribute to excess risk of disease outcomes in obese adults?

6.3 Methods

The general methods have been described in Chapter 4.7. Pooled data from the three British National Birth Cohorts were analysed, firstly using a series of regression models relating BMI status at each life stage (childhood, adolescence and adulthood) to disease outcomes (the Stepwise approach). In the next stage, associations between different combinations of

overweight at each life stage and outcomes were examined (the 'Overweight patterns' approach). The statistical models used for each approach are described below. The effects of severity of overweight on disease risk were examined by adjusting models for adult BMI, and also by repeating the analyses using obesity in childhood instead of overweight and obesity as a combined category.

The following sensitivity analyses were conducted: 1) Excluding ethnic minority groups – due to the small proportion of ethnic minority groups, analyses were not stratified by ethnicity, and this assumption was checked by excluding ethnic minority (non-White) groups in a sensitivity analysis; 2) Adjusting BMI measurement for self-reported weight and height, using adjustments described previously; 3) Complete case analyses, including only cohort members with complete data on all variables; 4) Survival analysis for time to event data.

STATISTICAL MODELS USED IN THE STEPWISE APPROACH TO ANALYSIS

- Exposure: Childhood BMI status (BMI1); Adolescent BMI status (BMI2); Adult BMI status (BMI3), with normal weight category as the reference group
- Outcome: Disease outcome (DISEASE)

EARLY MODEL– REGRESSION TO RELATE CHILDHOOD BMI STATUS TO DISEASE OUTCOME (SUFFICIENTLY ADJUSTED MODEL)

Log odds(DISEASE) = $\alpha + \beta_1 *$ BMI1

- Stratified by sex
- Adjustment in stages:
  1. Adjusted for key covariates (year of birth [equivalent to cohort], exact age at BMI measurement)
  2. Adjusted for key covariates plus early life variables (birth weight, childhood SEP at birth, childhood height at BMI measurement)

COMBINED MODEL – INCLUDES CHILDHOOD AND ADULT BMI STATUS

Log odds(DISEASE) = $\alpha + \beta_1 *$ BMI1 + $\beta_2 *$BMI3

- Stratified by sex
- Adjustment in stages:
  1. Adjusted for key covariates (year of birth, exact age at BMI1 measurement)
  2. Adjusted for key covariates plus early life variables (birth weight, childhood SEP at birth, childhood height at BMI1 measurement)

3. Adjusted for key covariates, early life variables, and current variables (adult SEP, adult smoking status)

INTERACTION (EFFECT MODIFICATION) MODEL – ADDS INTERACTION OF CHILDHOOD AND ADULT BMI STATUS IN COMBINED MODEL

Log odds(DISEASE) = $\alpha + \beta_1$* BMI1+ β_2* BMI3+ β_3* BMI1* BMI3

- Stratified by sex
- Adjustment in stages:
  1. Adjusted for key covariates (year of birth, exact age at BMI1 measurement)
  2. Adjusted for key covariates plus early life variables (birth weight, childhood SEP at birth, childhood height at BMI1 measurement)
  3. Adjusted for key covariates, early life variables, and current variables (adult SEP, adult smoking status)

LATE MODEL – ADULT BMI STATUS RELATED TO THE OUTCOME

Log odds(DISEASE) = $\alpha + \beta_1$* BMI3

- Stratified by sex
- Adjustment in stages:
  1. Adjusted for key covariates (year of birth)
  2. Adjusted for key covariates plus early life variables (birth weight, childhood SEP at birth, childhood height at BMI1 measurement)
  3. Adjusted for key covariates, early life variables, and current variables (adult SEP, adult smoking status)

THESE ANALYSES WERE REPEATED:

1. with adolescent BMI status (BMI2) as the exposure, and
2. using BMI (kg/m^2) as a continuous exposure

STATISTICAL MODELS USED IN THE OVERWEIGHT PATTERNS APPROACH TO ANALYSIS

Main analysis

Exposure: Patterns of overweight (PATTERN), see Table 4-7, with pattern 1 (never overweight) as the reference group

Outcome: Disease outcome (DISEASE)

Log odds(DISEASE) = $\alpha + \beta_1 *$ PATTERN

1. Adjusted for sex, year of birth, birth weight, childhood SEP at birth, childhood height, adult SEP, adult smoking status
2. Inclusion of interaction terms for sex and cohort (PATTERN*sex and PATTERN*cohort)
3. Adjusted for variables above and adult BMI
4. Repeated using obesity in childhood and adolescence (instead of overweight and obesity) to define patterns of overweight

Sensitive period analysis

Exposure: Sensitive period variables. Childhood - SENS1, with three categories: never overweight, overweight in childhood, overweight in other periods; Adolescence – SENS2, with three categories: never overweight, overweight in adolescence, overweight in other periods; Adulthood – SENS3, with three categories: never overweight, overweight in adulthood, overweight in other periods, with never overweight as the reference group

Outcome: Disease outcome (DISEASE)

Sensitive period in childhood

Log odds(DISEASE) = $\alpha + \beta_1 *$ SENS1

Adjusted for sex, year of birth, birth weight, childhood SEP at birth, childhood height, adult SEP, adult smoking status

Sensitive period in adolescence

Log odds(DISEASE) = $\alpha + \beta_1 *$ SENS2

Adjusted for sex, year of birth, birth weight, childhood SEP at birth, childhood height, adult SEP, adult smoking status

Sensitive period in adulthood

Log odds(DISEASE) = $\alpha + \beta_1 *$ SENS3

Adjusted for sex, year of birth, birth weight, childhood SEP at birth, childhood height, adult SEP, adult smoking status

Accumulation of risk analysis

Exposure: Accumulation of risk score (ACCUM, with four categories: never overweight, overweight at one time point, overweight at two time points, and overweight and three time points), with never overweight as the reference group

Outcome: Disease outcome (DISEASE)

Log odds(DISEASE) = $\alpha + \beta_1 *$ ACCUM

Adjusted for sex, year of birth, birth weight, childhood SEP at birth, childhood height, adult SEP, adult smoking status

6.4 Results

The frequency of each disease outcome by weight status in childhood, adolescence and adulthood is shown in Table 6-1. Hypertension, type 2 diabetes, and gallbladder disease increased with overweight and obesity at all ages. For example, 16.3% of participants who were normal weight in childhood experienced hypertension in adulthood, compared to 18.2% of those who were overweight and 19.6% of those who were obese; 1.7% of participants who were normal weight in adolescence reported type 2 diabetes, compared to 3.9% of those who were overweight, and 15.6% of those who were obese. Asthma was reported more frequently in those who were overweight or obese in childhood and adulthood, but there was no pattern with weight status in adolescence. There were no clear patterns of coronary heart disease, stroke, arthritis or cancers by weight status in childhood or adolescence. For all diseases combined, there was a clear pattern of increasing frequency with overweight and obesity at all ages; 46.6% of those obese in childhood had any disease, compared to 33.2% of those who were overweight and 29.2% of those who were normal weight in childhood.

Table 6-1: Frequency of each disease outcome in adulthood, by weight status in childhood, adolescence and adulthood, for 1946, 1958 and 1970 cohorts combined

Life stage at which BMI measured	N	Self reported cases in weight category % (n)			
		Normal weight	Overweight	Obese	Total
Asthma					
Childhood	14,246	14.3 (1,856)	15.9 (178)	18.1 (24)	14.5 (2,058)
Adolescence	10,423	15.3 (1,405)	14.0 (143)	17.8 (35)	15.2 (1,583)
Adulthood	18,030	12.8 (1,043)	14.3 (960)	18.1 (569)	14.3 (2,572)
Gallbladder disease					
Childhood	16,638	1.6 (238)	2.5 (32)	5.4 (8)	1.7 (278)
Adolescence	12,636	1.9 (216)	3.3 (40)	5.6 (12)	2.1 (268)
Adulthood	20,804	1.1 (102)	1.5 (118)	3.3 (114)	1.6 (334)
Hypertension					
Childhood	18,138	16.3 (2,706)	18.2 (252)	29.6 (48)	16.6 (3,006)
Adolescence	13,936	18.27 (2,266)	22.1 (288)	25.8 (60)	18.8 (2,614)
Adulthood	21,254	13.5 (1,333)	17.2 (1,351)	24.6 (871)	16.7 (3,555)
Type 2 diabetes					
Childhood	17,275	1.9 (297)	4.4 (58)	8.3 (13)	2.1 (368)
Adolescence	13,214	1.7 (202)	3.9 (49)	15.6 (35)	2.2 (286)
Adulthood	21,254	0.8 (77)	1.5 (117)	6.0 (213)	1.9 (407)
CHD					
Childhood	16,732	0.8 (117)	1.6 (20)	0.7 (1)	0.8 (138)
Adolescence	12,711	1.0 (109)	1.8 (22)	0	1.0 (131)
Adulthood	20,813	0.5 (52)	0.8 (60)	1.5 (51)	0.8 (163)
Arthritis					
Childhood	16,948	3.1 (480)	3.5 (46)	3.3 (5)	3.1 (531)
Adolescence	12,906	3.7 (425)	4.8 (58)	4.6 (10)	3.8 (493)
Adulthood	21,255	3.1 (301)	2.7 (215)	3.2 (112)	3.0 (628)
All diseases					
Childhood	18,227	29.2 (4,869)	33.2 (462)	46.6 (76)	29.7 (5,407)
Adolescence	14,005	31.6 (3,942)	37.1 (485)	42.3 (99)	32.3 (4,526)
Adulthood	21,255	26.4 (2,602)	31.0 (2,434)	41.9 (1,484)	30.7 (6,520)

6.4.1 Results from the Stepwise approach

Table 6-2 shows the results from the stepwise regression models for the relationship between childhood overweight, obesity and BMI, and disease outcomes in adulthood. Results from the interaction model are not presented as the numbers were too low in certain combinations of categories for the model to converge. Among males, there was evidence for increased odds of type 2 diabetes with overweight and obesity. However, these associations were attenuated towards the null after adjustment for adult weight status, which also resulted in an improvement in model fit ($p<0.05$ from adjusted Wald test). An association between overweight (but not obesity) and CHD risk was observed, which was also attenuated after adjustment for adult weight status. Among female cohort members, overweight was associated with increased odds of asthma, hypertension, and all disease outcomes, after adjustment for early life covariates. Odds ratios for obesity were also in the same direction for these outcomes, but these estimates were not statistically robust (wider confidence intervals, including 1), which is likely to be a power issue given the low prevalence of obesity in childhood. Both overweight and obesity were associated with increased odds of type 2 diabetes; overweight was associated with a more than doubling of odds (OR 2.62, 95% CI 1.59, 4.29) and obesity was associated with an almost seven-fold increase, although confidence intervals were wide (OR 6.70, 95% CI 2.63, 17.06). After adjustment for weight status in adulthood and later life covariates, weight status in childhood was not associated with any of the outcomes.

The relationships between weight status in adolescence and disease outcomes are presented in Table 6-3. Among male cohort members, overweight was associated with increased odds of hypertension, CHD and combined diseases, after adjustment for early life covariates. Associations between these outcomes and obesity were in the same direction, but confidence intervals were wider. After adjustment for later life covariates and adult weight status, associations were attenuated towards the null. Overweight and obesity in adolescence were associated with increased odds of type 2 diabetes, with increasing odds with greater degree of overweight. After adjustment for adult weight status, an association with obesity remained, although the effect size was smaller (OR 4.43 in the combined model, compared to OR 13.4 in the early model). Among female cohort members, hypertension, CHD, arthritis and combined diseases were associated with overweight but not obesity in adolescence. These effects were attenuated towards the null after adjustment for later life covariates. Overweight and obesity in adolescence were associated with gallbladder disease and type 2 diabetes, and odds for both outcomes increased with the degree of overweight (gallbladder disease: OR for overweight 2.04, OR for obesity 3.88; type 2 diabetes: OR for overweight 2.31, OR for obesity 13.46). After adjustment for adult weight status, an association with gallbladder disease was no longer

observed; in the case of type 2 diabetes, as with male cohort members, the association with overweight was attenuated, but an association with obesity remained (OR 2.83, 95% CI 1.00, 7.96).

Table 6-4 shows that overweight and obesity in adulthood were associated with most of the outcomes of interest, in both sexes. In men, obesity was associated with increased odds of asthma, gallbladder disease, hypertension, type 2 diabetes, CHD, and combined disease outcomes. These associations were generally unchanged after adjustment for early life exposures; examination of goodness-of-fit estimates showed improved fit with the inclusion of early life covariates, except in the case of asthma. Associations with overweight were in the same direction but weaker, and in the cases of asthma, gallbladder disease, type 2 diabetes and CHD, confidence intervals included 1. Among women, obesity in adulthood was associated with asthma, gallbladder disease, hypertension, type 2 diabetes, CHD, arthritis, and combined diseases. Associations with overweight were also observed for gallbladder disease, hypertension, and combined outcomes. As with men, these associations did not change greatly after adjustment for early life covariates.

Table 6-2: Odds ratios of adult disease outcomes for overweight and obesity in childhood (reference category: normal weight in childhood) under different models in the stepwise approach to analysis, by sex.

	Male			Female		
	Model 1	**Model 2**	**Model 3**	**Model 1**	**Model 2**	**Model 3**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Asthma	**n=6,852**	**n=6,454**	**n=5,708**	**n=7,394**	**n=6,962**	**n=5,206**
Overweight	0.75 (0.54, 1.04)	0.82 (0.59, 1.14)	0.71 (0.49, 1.02)	**1.38**** (1.13, 1.68)	**1.43**** (1.16, 1.76)	1.01 (0.77, 1.32)
Obese	0.76 (0.30, 1.94)	0.95 (0.37, 2.46)	0.84 (0.28, 2.50)	1.23 (0.74, 2.05)	1.21 (0.72, 2.04)	0.96 (0.52, 1.77)
Gallbladder disease	**n=9,584**	**n=9,159**	**n=8,239**	**n=10,294**	**n=9,821**	**n=7,883**
Overweight	2.29 (0.72, 7.30)	2.38 (0.77, 7.39)	1.94 (0.60, 6.24)	1.41 (0.86, 2.32)	1.41 (0.84, 2.37)	0.90 (0.49, 1.65)
Obese	2.27 (0.30, 17.26)	2.34 (0.28, 19.92)	2.12 (0.22, 20.75)	1.72 (0.77, 3.84)	1.75 (0.78, 3.93)	1.02 (0.38, 2.71)
Hypertension	**n=11,596**	**n=11,138**	**n=8,238**	**n=11,912**	**n=11,406**	**n=7,858**
Overweight	0.97 (0.71, 1.34)	0.99 (0.71, 1.37)	0.91 (0.60, 1.38)	1.26 (0.97, 1.62)	**1.32*** (1.02, 1.72)	1.05 (0.75, 1.46)
Obese	1.31 (0.50, 3.39)	1.13 (0.41, 3.15)	0.77 (0.18, 3.27)	1.28 (0.69, 2.36)	1.45 (0.76, 2.72)	1.52 (0.65, 3.58)
T2DM	**n=10,336**	**n=9,884**	**n=8,226**	**n=10,938**	**n=10,441**	**n=7,881**
Overweight	**1.77*** (1.12, 2.78)	**1.89****(1.18, 3.02)	0.97 (0.53, 1.79)	**2.65**** (1.67, 4.22)	**2.62****(1.59, 4.29)	1.19 (0.59, 2.39)
Obese	2.60 (0.89, 7.63)	**3.03*** (1.01, 9.09)	2.97 (0.97, 9.08)	**6.99**** (2.73, 17.88)	**6.70**** (2.63, 17.06)	2.06 (0.64, 6.67)
CHD	**n=9,636**	**n=9,200**	**n=8,236**	**n=10,202**	**n=9,730**	**n=7,775**
Overweight	**2.37*** (1.09, 5.14)	**2.55*** (1.17, 5.52)	1.64 (0.62, 4.32)	1.43 (0.49, 4.17)	1.60 (0.49, 5.18)	1.44 (0.31, 6.76)
Obese	1.15 (0.14, 9.64)	1.35 (0.16, 11.48)	1.44 (0.21, 9.77)	omitted	omitted	omitted
Arthritis	**n=9,916**	**n=9,477**	**n=8,208**	**n=10,483**	**n=10,001**	**N=7,842**
Overweight	1.37 (0.66, 2.82)	1.17 (0.55, 2.50)	1.13 (0.44, 2.91)	1.26 (0.75, 2.12)	1.37 (0.81, 2.32)	1.58 (0.89, 2.79)
Obese	2.21 (0.35, 13.86)	1.92 (0.28, 13.27)	3.35 (0.29, 38.79)	0.81 (0.15, 4.44)	0.88 (0.16, 4.82)	1.09 (0.20, 6.00)

Disease	n=11,662	n=11,192	n=8,248	n=11,989	n=11,480	n=7,892
Overweight	0.93 (0.72, 1.20)	0.93 (0.72, 1.21)	0.81 (0.60, 1.10)	**1.31**** (1.08, 1.58)	**1.33**** (1.10, 1.62)	0.98 (0.76, 1.25)
Obese	1.35 (0.63, 2.88)	1.36 (0.60, 3.09)	1.23 (0.40, 3.80)	1.33 (0.81, 2.18)	1.50 (0.90, 2.48)	1.38 (0.76, 2.51)

Model 1: odds ratios of risk of the outcome for overweight and obese compared to normal weight reference category in childhood, adjusted for current age; Model 2: Early Model, adjusted for cohort and current age, early life covariates (birth weight, childhood social class, childhood height, and age at BMI measurement); Model 3: Combined Model, adjusted for cohort and current age, early life covariates (birth weight, childhood social class, childhood height, and age at BMI measurement), late life covariates (adult social class, and adult smoking status), and adult weight category; all analyses adjusted for weighted sample in NSHD, n=effective population size from weighted analysis. CHD=coronary heart disease. T2DM=type 2 diabetes. * $p<0.05$ ** $p<0.01$

Table 6-3: Odds ratios of adult disease outcomes for overweight and obesity in adolescence (reference category: normal weight in adolescence) under different models in the stepwise approach to analysis, by sex.

	Male			Female		
	Model 1	**Model 2**	**Model 3**	**Model 1**	**Model 2**	**Model 3**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Asthma	**n=4,931**	**n=3,947**	**n=3,487**	**n=5,382**	**n=4,357**	**n=3,339**
Overweight	0.78 (0.56, 1.10)	0.76 (0.51, 1.12)	0.65 (0.42, 1.02)	1.00 (0.79, 1.26)	0.98 (0.76, 1.27)	0.75 (0.54, 1.05)
Obese	0.74 (0.37, 1.49)	1.02 (0.50, 2.07)	0.96 (0.45, 2.04)	**1.69*** (1.05, 2.71)	1.31 (0.75, 2.30)	0.46 (0.19, 1.11)
Gallbladder disease	**n=7,514**	**n=6,323**	**n=5,733**	**n=8,043**	**n=6,828**	**n=5,642**
Overweight	0.62 (0.19, 2.06)	0.48 (0.11, 2.14)	0.33 (0.07, 1.50)	**1.87**** (1.18, 2.96)	**2.04**** (1.24, 3.36)	1.28 (0.72, 2.26)
Obese	1.49 (0.20, 11.07)	2.03 (0.26, 15.70)	1.95 (0.23, 16.85)	**2.91**** (1.38, 6.15)	**3.88**** (1.81, 8.37)	0.95 (0.30, 3.04)
Hypertension	**n=9,305**	**n=7,927**	**n=5,735**	**n=9,375**	**n=8,062**	**n=5,620**
Overweight	**1.62**** (1.19, 2.21)	**1.62**** (1.16, 2.26)	0.99 (0.62, 1.58)	**1.37*** (1.06, 1.77)	**1.43*** (1.08, 1.88)	0.94 (0.65, 1.35)
Obese	**2.20*** (1.06, 4.56)	1.94 (0.88, 4.29)	1.76 (0.91, 3.40)	0.80 (0.42, 1.52)	0.82 (0.41, 1.64)	0.62 (0.16, 2.47)
T2DM	**n=8,246**	**n=6,960**	**n=5,727**	**n=8,601**	**n=7,348**	**5,638**
Overweight	**2.35**** (1.48, 3.73)	**2.62**** (1.57, 4.36)	1.10 (0.58, 2.09)	**2.43**** (1.32, 4.50)	**2.31*** (1.19, 4.51)	1.08 (0.47, 2.46)
Obese	**11.83****(6.54, 21.40)	**13.40****(6.86, 26.17)	**4.43**** (1.72, 11.39)	**15.14**** (7.32, 31.31)	**13.46*** (6.20, 29.2)	**2.83*** (1.00, 7.96)
CHD	**n=7,466**	**n=6,284**	**n=5,668**	**n=7,913**	**n=6,724**	**n=5,543**
Overweight	**2.28*** (1.09, 4.78)	**2.58*** (1.16, 5.74)	1.65 (0.61, 4.47)	2.24 (0.86, 5.82)	**3.00*** (1.05, 8.63)	1.84 (0.54, 6.22)
Obese	omitted	omitted	omitted	omitted	omitted	omitted
Arthritis	***n=7,856***	**n=6,617**	**n=5,654**	**n=8,167**	**n=6,941**	**n=5,600**
Overweight	1.23 (0.61, 2.49)	1.22 (0.59, 2.50)	1.18 (0.52, 2.68)	**1.92**** (1.23, 3.00)	**1.87*** (1.15, 3.06)	1.62 (0.87, 2.99)
Obese	0.61 (0.06, 6.40)	0.95 (0.08, 11.23)	omitted	1.64 (0.57, 4.66)	1.41 (0.49, 4.07)	0.83 (0.20, 3.40)

Disease	n=9,357	n=7,966	n=5,742	n=9,434	n=8,117	n=5,647
Overweight	**1.43**** (1.12, 1.83)	**1.45**** (1.10, 1.90)	0.93 (0.66, 1.30)	**1.37**** (1.13, 1.68)	**1.36**** (1.10, 1.69)	0.94 (0.71, 1.25)
Obese	1.53 (0.89, 2.64)	1.60 (0.88, 2.90)	1.29 (0.75, 2.23)	1.23 (0.74, 2.03)	1.11 (0.64, 1.92)	0.50 (0.21, 1.19)

Model 1: odds ratios of risk of the outcome for overweight and obese compared to normal weight reference category in adolescence, adjusted for current age; Model 2: Early Model, adjusted for cohort and current age, early life covariates (birth weight, childhood social class, childhood height, and age at BMI measurement); Model 3: Combined Model, adjusted for cohort and current age, early life covariates (birth weight, childhood social class, childhood height, and age at BMI measurement), late life covariates (adult social class, and adult smoking status), and adult weight category; all analyses adjusted for weighted sample in NSHD, n=effective population size from weighted analysis. CHD=coronary heart disease. T2DM=type 2 diabetes. * $p<0.05$ ** $p<0.01$

Table 6-4: Odds ratios of adult disease outcomes for overweight and obesity in adulthood (reference category: normal weight in adulthood) under different models in the stepwise approach to analysis, by sex.

	Male			Female		
	Model 1	**Model 2**	**Model 3**	**Model 1**	**Model 2**	**Model 3**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Asthma	**n=8,129**	**n=5,903**	**n=5,708**	**n=8,681**	**n=5,384**	**n=5,206**
Overweight	1.02 (0.88, 1.18)	1.06 (0.89, 1.27)	1.08(0.90, 1.29)	**1.23**** (1.07, 1.41)	1.14 (0.96, 1.36)	1.14 (0.95, 1.36)
Obese	**1.20*** (1.00, 1.44)	**1.41**** (1.13, 1.75)	**1.49**** (1.19, 1.87)	**1.75**** (1.51, 2.04)	**1.73**** (1.41, 2.11)	**1.73**** (1.40, 2.14)
Gallbladder disease	**n=11,218**	**n=8,525**	**n=8,239**	**n=11,903**	**n=8,172**	**n=7,883**
Overweight	1.54 (0.72, 3.29)	1.66 (0.71, 3.87)	1.57 (0.67, 3.67)	**2.00**** (1.37, 2.93)	**2.21*** (1.37, 3.58)	**2.26*** (1.39, 3.69)
Obese	**2.75*** (1.20, 6.31)	**2.89*** (1.16, 7.18)	**2.64*** (1.03, 6.76)	**3.99**** (2.76, 5.76)	**4.11*** (2.46, 6.87)	**3.70*** (2.18, 6.28)
Hypertension	**n=11,843**	**n=8,524**	**n=8,238**	**n=12,292**	**n=8,147**	**n=7,858**
Overweight	**1.57**** (1.31, 1.88)	**1.87**** (1.47, 2.37)	**1.85**** (1.45, 2.36)	**1.55**** (1.31, 1.83)	**1.54**** (1.25, 1.91)	**1.59**** (1.28, 1.98)
Obese	**3.38**** (2.68, 4.26)	**4.27**** (3.21, 5.69)	**4.34**** (3.23, 5.83)	**2.56**** (2.09, 3.12)	**2.58**** (1.97, 3.37)	**2.63**** (1.99, 3.48)
T2DM	**n=11,820**	**n=8,512**	**n=8,226**	**n=12,328**	**n=8169**	**n=7,881**
Overweight	1.26 (0.75, 2.12)	**2.02*** (1.02, 4.00)	1.85 (0.93, 9.08)	1.13 (0.60, 2.11)	1.18 (0.51, 2.73)	1.20 (0.51, 2.82)
Obese	**5.74**** (3.53, 9.33)	**7.44**** (3.85, 14.40)	**7.32**** (3.73, 14.36)	**9.05**** (5.55, 14.77)	**10.46**** (5.22, 20.9)	**10.30**** (5.09, 20.8)
CHD	**n=11,221**	**n=8,522**	**n=8,236**	**n=11,880**	**n=8,150**	**n=7,775**
Overweight	1.79 (0.97, 3.29)	1.41 (0.73, 2.74)	1.41 (0.71, 2.83)	1.39 (0.60, 3.24)	0.87 (0.27, 2.87)	0.86 (0.25, 2.98)
Obese	**4.13**** (2.07, 8.28)	**3.78**** (1.72, 8.33)	**3.82**** (1.68, 8.66)	**5.56**** (2.63, 11.78)	**6.44**** (2.68, 15.5)	**6.34**** (2.52, 15.9)
Arthritis	**n=11,800**	**n=8,494**	**n=8,208**	**n=12,280**	**n=8,131**	**n=7,842**
Overweight	1.23 (0.85, 1.77)	1.21 (0.78, 1.89)	1.16 (0.73, 1.82)	0.96 (0.69, 1.33)	1.01 (0.68, 1.51)	1.01 (0.68, 1.53)
Obese	1.43 (0.83, 2.47)	1.39 (0.72, 2.67)	1.41 (0.71, 2.81)	**1.74**** (1.20, 2.51)	**1.91**** (1.21, 3.01)	**1.84*** (1.15, 2.95)

Disease	n=11,855	n=8,534	n=8,248	n=12,347	n=8,181	n=7,892
Overweight	**1.33**** (1.17, 1.52)	**1.46**** (1.24, 1.73)	**1.46**** (1.24, 1.73)	**1.42**** (1.26, 1.61)	**1.37**** (1.17, 1.60)	**1.40**** (1.19, 1.65)
Obese	**2.36**** (2.01, 2.77)	**2.78**** (2.30, 3.35)	**2.88**** (2.37, 3.51)	**2.52**** (2.18, 2.90)	**2.62**** (2.18, 3.15)	**2.68**** (2.21, 3.25)

Model 1: odds ratios of risk of the outcome for overweight and obese compared to normal weight reference category in adulthood, adjusted for current age; Model 2: Late Model, adjusted for cohort and current age, late life covariates (adult social class, and adult smoking status); Model 3: Combined Model, adjusted for cohort and current age, early life covariates (birth weight, childhood social class, childhood height, and age at BMI measurement), late life covariates (adult social class, and adult smoking status), and child weight category; all analyses adjusted for weighted sample in NSHD, n=effective population size from weighted analysis. CHD=coronary heart disease. T2DM=type 2 diabetes. * $p<0.05$ ** $p<0.01$

6.4.2 Results from the Overweight Patterns approach

Table 6-5 shows the frequency of different overweight patterns through childhood, adolescence and adulthood. Patterns of overweight were similar in males and females. The majority of cohort members (75%) were never overweight (not overweight in childhood and adolescence and not obese in adulthood). Upwards movement in weight categories was relatively common: 10% of cohort members were normal weight in childhood and adolescence and became obese as adults, and 3.4% became overweight in adolescence and remained obese in adulthood. 2.3% were persistently overweight or obese at all three life stages. It was uncommon for cohort members who had been overweight in childhood and in adolescence to become non-obese in adulthood (1.4%), but 6.8% were overweight in childhood or adolescence only and normal weight/non-obese thereafter.

Table 6-5: Frequency of different overweight patterns through childhood, adolescence and in adulthood, by sex

Overweight pattern	n (%)		
	Male	Female	Total
Never overweight	4,259 (76.0)	4,328 (74.1)	8,587 (75.0)
Childhood only	150 (2.68)	224 (3.8)	374 (3.3)
Adolescence only	161 (2.9)	236 (4.0)	397 (3.5)
Adulthood only	630 (11.2)	514 (8.8)	1,144 (10.0)
Childhood + adolescence	47 (0.8)	114 (2.0)	161 (1.4)
Childhood + adulthood	67 (1.2)	63 (1.1)	130 (1.1)
Adolescence + adulthood	180 (3.2)	208 (3.6)	388 (3.4)
Persistent overweight	111 (2.0)	155 (2.7)	266 (2.3)
Total	5,605 (100)	5,842 (100)	11,447 (100)

Associations between overweight patterns and disease outcomes

Associations between different patterns of overweight and disease outcomes are presented in Table 6-6. Comparison of odds ratios from analyses stratified by sex and by cohort indicated similar effect sizes; interaction terms for sex and cohort were not significant at conventional levels, therefore results for all cohort members combined are presented. Compared to those who were never overweight, cohort members who were obese in adulthood had increased odds of all outcomes (asthma, gallbladder disease, hypertension, type 2 diabetes, coronary heart disease, arthritis, and combined disease outcome). Those who were also overweight in

childhood or adolescence (in addition to being obese in adulthood) had increased odds of gallbladder disease, hypertension, type 2 diabetes, CHD, and combined outcomes. Overweight in childhood only, and overweight in childhood plus adolescence, were not associated with any of the outcomes, although examination of point estimates indicated increasing CHD risk with overweight in adolescence and overweight in childhood plus adolescence (ORs 1.63 and 3.43, respectively). Examination of odds ratios for type 2 diabetes and CHD indicated that point estimates were higher for persistent overweight compared to overweight in adulthood only (type 2 diabetes: OR for persistent overweight=12.60, OR for obesity in adulthood only=5.5; CHD: OR for persistent overweight=6.6, OR for obesity in adulthood only=3.8) (Figure 6-1). Comparison of the coefficients for adult obesity versus persistent overweight patterns indicated that these were different for type 2 diabetes (p-value from adjusted Wald test=0.015) but not for CHD (p=0.41).

Sensitive period and accumulation of risk models

Results from analysis of the effects of overweight and obesity at different sensitive periods (childhood, adolescence and adulthood) are presented in Table 6-7. Childhood and adolescence did not appear to be a sensitive periods for any outcome: comparison of coefficients for exposure in sensitive periods compared to exposure in other periods using an adjusted Wald test indicated no difference in effect. There was evidence for adulthood as a sensitive period for asthma, gallbladder disease, hypertension, type 2 diabetes, and combined diseases, but not CHD or arthritis.

Analysis of the accumulation of risk model showed that there may be an accumulation of risk effect for cardiovascular outcomes (Table 6-7). Compared to never overweight, overweight at one, two or three time periods in the life course was associated with increased risk of hypertension, type 2 diabetes, CHD and combined diseases. Visual examination of the ORs (Figure 6-3) indicated that overweight at an increasing number of life stages may be associated with increased risk for these outcomes. A test for trend of odds indicated a trend for overweight at an increasing number of life stages for type 2 diabetes (p=0.018), but no such trend for hypertension (p=0.13) or CHD (p=0.15).

Effects of severity of overweight

Cohort members who were overweight at more time periods had higher BMI in adulthood. Those who were overweight at one life stage had mean BMI 30.3 kg/m^2 (SD ±5.36), compared to 32.8 kg/m^2 (±5.51) among those overweight at two stages, and 36.4 kg/m^2 (±4.82) among those overweight at all three. To investigate the possibility that the associations between

sensitive period and accumulation effects and type 2 diabetes may be confounded by the severity of obesity, BMI in adulthood was included in the logistic regression models, and its effect was assessed using an adjusted Wald test. The coefficient for adult BMI in sensitive period models was significant at conventional levels of statistical significance ($p<0.0001$); associations of type 2 diabetes with overweight in childhood and adolescence were in the same direction, but confidence intervals included 1 (OR for exposure in childhood=1.47, 95% CI 0.89, 2.45, p=0.13; OR for exposure in adolescence=1.47, 95% CI 0.91, 2.39, p=0.11).

Under the accumulation of risk model, the coefficient for adult BMI was associated with the outcome ($p<0.001$), but the number of life stages exposed to overweight remained a predictor of type 2 diabetes. OR for overweight at one life stage was 1.99 (95% CI 1.20, 3.31), for overweight at two stages was 2.28 (95% CI 1.24, 4.18), and for overweight at three stages was 4.00 (95% CI 1.74, 9.19). Comparison of coefficients indicated that odds for overweight at three life stages may be different to those for overweight at one life stage (p=0.05), but there was no difference between overweight at two life stages versus three (p=0.14).

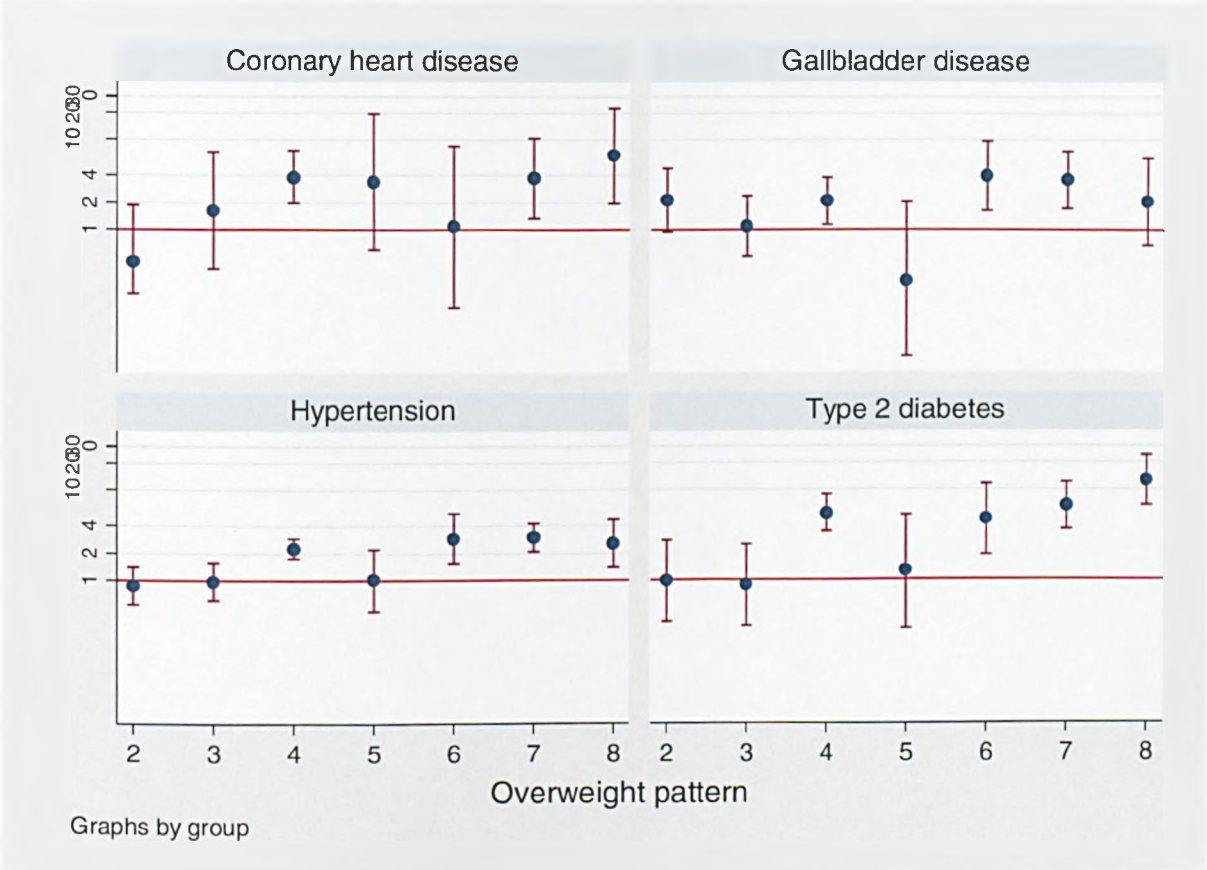
To assess whether combining overweight and obesity as a single exposure category in childhood and adolescence may have masked the effects of more extreme overweight in early life, the effect of using obesity as the exposure in childhood and adolescence (instead of overweight plus obesity) was explored for hypertension and type 2 diabetes, two outcomes with different associations with overweight patterns (Table 6-8). For hypertension, using more severe overweight in early life as the exposure amplified the effect sizes associated with childhood only and adolescence only, but evidence for these effects was weak; there was no strong evidence for an effect of obesity in childhood or adolescence on hypertension risk in obese adults (OR for persistent obesity 2.83; 95% CI 0.35, 22.65, compared to OR 2.47; 95% CI 2.00, 3.05 for obesity in adulthood only). In contrast, for type 2 diabetes the use of obesity as the exposure in early life amplified effect sizes for all patterns that included exposure in childhood or adolescence, and the cumulative effect of obesity over the life course was apparent. Compared to never being obese, obesity in childhood plus adulthood was associated with more than seven times the odds of type 2 diabetes (OR 7.64; 95% CI 1.66, 35.15); obesity in adolescence plus adulthood was associated with a twenty-fold increase in odds of type 2 diabetes (OR 19.45; 95% CI 8.73, 43.33), while persistent obesity was associated an even larger effect (OR 36.79; 95% CI 10.42, 129.9). Comparison of odds ratios indicated that the effect size for obesity in adolescence plus adulthood was larger than the effect size for obesity in adulthood only (p=0.003), as was the effect size for persistent obesity (p=0.004).

Table 6-6: Odds ratio of disease for different overweight patterns through childhood, adolescence and in adulthood

Overweight Pattern	Asthma	GBD	Hypertension	Type 2 diabetes	CHD	Arthritis	Disease
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Never overweight	1	1	1	1	1	1	1
Childhood only	1.01	2.12	0.87	0.99	0.44	1.19	0.99
	(0.68, 1.52)	(0.94, 4.76)	(0.54, 1.40)	(0.35, 2.80)	(0.20, 1.89)	(0.56, 2.55)	(0.68, 1.45)
Adolescence only	**0.53***	1.09	0.97	0.88	1.63	1.67	1.03
	(0.33, 0.87)	(0.50, 2.37)	(0.61, 1.55)	(0.31, 2.50)	(0.37, 7.19)	(0.86, 3.25)	(0.73, 1,46)
Adulthood only	**1.68****	**2.07***	**2.28****	**5.47****	**3.83****	**1.79***	**2.33****
	(1.36, 2.06)	(1.14, 3.76)	(1.76, 2.95)	(3.39, 8.82)	(1.98, 7.42)	(1.15, 2.79)	(1.94, 2.79)
Childhood + adolescence	1.09	0.27	1.01	1.24	3.43	1.68	0.92
	(0.61, 1.94)	(0.04, 2.01)	(0.46, 2.21)	(0.29, 5.25)	(0.60, 19.64)	(0.6, 4.34)	(0.49, 1.74)
Childhood + adulthood	0.82	**3.94****	**2.91****	**4.70****	1.10	2.77	**2.10****
	(0.42, 1.58)	(1.63, 9.63)	(1.54, 5.49)	(1.89, 11.67)	(0.14, 8.48)	(0.78, 9.81)	(1.28, 3.44)
Adolescence + adulthood	1.17	**3.58****	**3.01****	**6.61****	**3.74***	1.29	**2.51****
	(0.79, 1.72)	(1.72, 7.46)	(2.11, 4.29)	(3.61, 12.09)	(1.35, 10.35)	(0.54, 3.05)	(1.91, 3.30)
Persistent overweight	1.14	2.04	**2.56****	**12.60****	**6.62****	1.39	**1.94****
	(0.79, 1.72)	(0.66, 6.34)	(1.40, 4.68)	(6.61, 23.98)	(1.94, 22.65)	(0.50, 3.92)	(1.28, 2.94)

OR is for odds of disease outcome compared to never overweight category; Adjusted for sex, year of birth, exact age and height at childhood BMI measurement, birth weight, SEP at birth SEP in adulthood, and smoking status in adulthood; adjusted for weighted sampling in NSHD; * $p<0.05$; ** $p<0.01$

Figure 6-1: Odds ratio of selected disease outcomes for different overweight patterns through childhood, adolescence and in adulthood (reference group: never overweight)



Reference=Trajectory 1, never overweight. Trajectory: 2= childhood only, 3= adolescence only, 4=adulthood only, 5=childhood+ adolescence, 6=childhood+adulthood, 7=adolescence+adulthood, 8=persistent overweight

Table 6-7: Odds ratios of disease for overweight under different sensitive period models (childhood, adolescence and adulthood) and accumulation of risk model

Outcome	Sensitive period model, OR (95% CI)						Accumulation of risk model, OR (95% CI)		
	Childhood		Adolescence		Adulthood				
	Sensitive period	Other periods	Sensitive period	Other periods	Sensitive period	Other periods	1	2	3
Asthma	1.03	**1.31****	0.92	**1.44****	**1.36 ****	0.69	**1.28****	1.07	1.15
	(0.80, 1.34)	(1.10, 1.57)	(0.73, 1.17)	(1.20, 1.73)	(1.16, 1.61)	(0.47, 0.99)	(1.07, 1.53)	(0.79, 1.44)	(0.73, 1.80)
Gallbladder disease	**1.87***	**2.10 ****	**1.80***	**2.20****	**2.39****	0.81	**1.85***	**2.53****	2.04
	(1.06, 3.31)	(1.32, 3.33)	(1.06, 3.05)	(1.36, 3.55)	(1.57, 3.65)	(0.39, 1.70)	(1.15, 2.97)	(1.41, 4.57)	(0.66, 6.33)
Hypertension	1.38	**1.97****	**1.65****	**1.85****	**2.07****	0.98	**1.58****	**2.23****	**2.51****
	(0.99, 1.92)	(1.59, 2.44)	(1.24, 2.18)	(1.48, 2.32)	(1.69, 2.53)	(0.65, 1.47)	(1.26, 1.96)	(1.59, 3.11)	(1.39, 4.56)
Type 2 diabetes	**4.28****	**4.62****	**4.76****	**4.36****	**5.43****	0.97	**3.63****	**4.93****	**12.65****
	(2.59, 7.06)	(3.04, 7.02)	(3.02, 7.51)	(2.79, 6.80)	(3.69, 7.99)	(0.40, 2.31)	(2.32, 5.69)	(2.92, 8.32)	(6.63, 24.15)
CHD	2.24	**3.25****	**3.22****	**2.78****	**3.21****	2.05	**2.60****	**3.25***	**6.60****
	(0.92, 5.45)	(1.83, 5.78)	(1.56, 6.64)	(1.49, 5.18)	(1.86, 5.55)	(0.63, 6.64)	(1.42, 4.76)	(1.33, 7.91)	(1.92, 22.62)
Arthritis	1.47	**1.66****	1.51	**1.67****	**1.58***	1.68	**1.63****	1.58	1.39
	(0.90, 2.42)	(1.16, 2.39)	(0.97, 2.35)	(1.14, 2.46)	(1.11, 2.24)	(0.96, 2.93)	(1.14, 2.33)	(0.88, 2.84)	(0.50, 3.91)
Disease	**1.30***	**1.97****	**1.51****	**1.90****	**1.99****	1.00	**1.66****	**1.87****	**1.93****
	(1.02, 1.66)	(1.69, 2.30)	(1.23, 1.85)	(1.61, 2.24)	(1.72, 2.31)	(0.74, 1.36)	(1.42, 1.95)	(1.45, 2.41)	(1.27, 2.92)

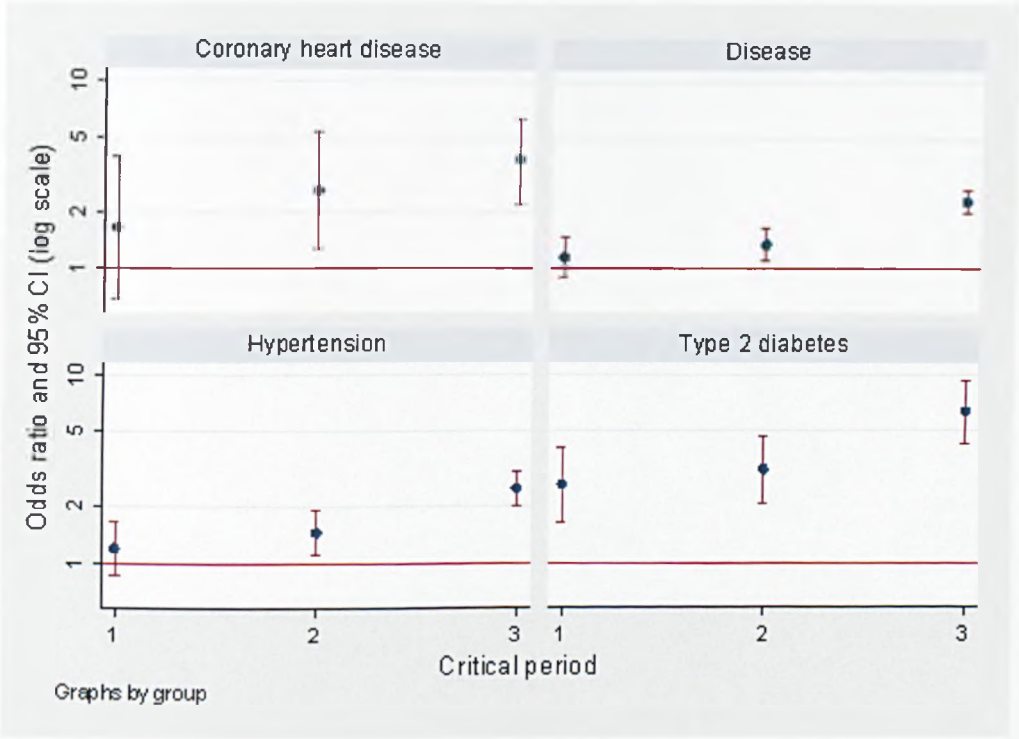
OR is for odds of disease outcome compared to never overweight category; Adjusted for sex, year of birth, exact age and height at childhood BMI measurement, birth weight, SEP at birth SEP in adulthood, and smoking status in adulthood; adjusted for weighted sampling in NSHD; * p<0.05; ** p<0.01

Table 6-8: Odds ratio of hypertension and type 2 diabetes for different overweight patterns through childhood, adolescence and in adulthood using different cut-offs for overweight in early life

Overweight Pattern	Hypertension		Type 2 diabetes	
	Overweight†	Obesity‡	Overweight†	Obesity‡
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Never overweight (or never obese)	1	1	1	1
Childhood only	0.87	1.99	0.99	2.95
	(0.54, 1.40)	(0.38, 10.50)	(0.35, 2.80)	(0.37, 23.31)
Adolescence only	0.97	2.38	0.88	Omitted
	(0.61, 1.55)	(0.78, 7.24)	(0.31, 2.50)	
Adulthood only	**2.28****	**2.47****	**5.47****	**5.67****
	(1.76, 2.95)	(2.00, 3.05)	(3.39, 8.82)	(3.77, 8.52)
Childhood + adolescence	1.01	0.64	1.24	Omitted
	(0.46, 2.21)	(0.04, 11.16)	(0.29, 5.25)	
Childhood + adulthood	**2.91****	**5.00****	**4.70****	**7.64****
	(1.54, 5.49)	(1.82, 13.76)	(1.89, 11.67)	(1.66, 35.15)
Adolescence + adulthood	**3.01****	2.48	**6.61****	**19.45****
	(2.11, 4.29)	(0.72, 8.49)	(3.61, 12.09)	(8.73, 43.33)
Persistent overweight (or persistent obesity)	**2.56****	2.83	**12.60****	**36.79****
	(1.40, 4.68)	(0.35, 22.65)	(6.61, 23.98)	(10.42, 129.9)

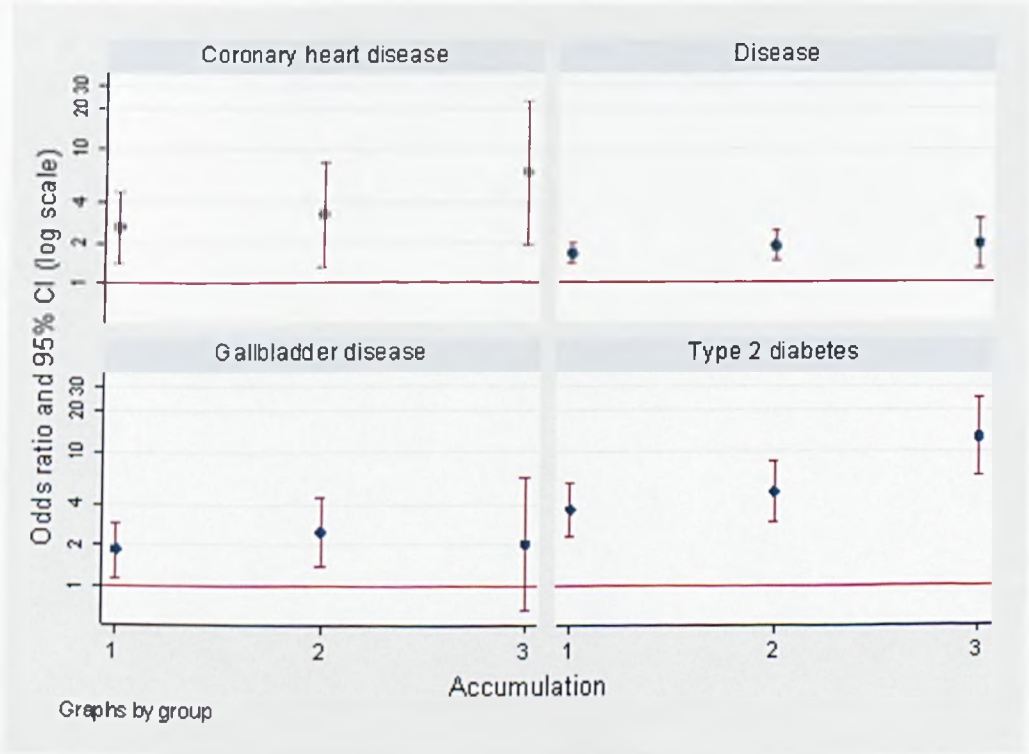
†Overweight patterns refer to overweight defined using IOTF criteria in childhood and adolescence, and obesity in adulthood; ‡Overweight patterns refer to obesity defined using IOTF criteria in childhood and adolescence, and obesity in adulthood. OR is for odds of disease outcome compared to never overweight category; Adjusted for sex, year of birth, exact age and height at childhood BMI measurement, birth weight, SEP at birth SEP in adulthood, and smoking status in adulthood; adjusted for weighted sampling in NSHD; * $p<0.05$; ** $p<0.01$

Figure 6-2: Odds ratio of selected disease outcomes for different sensitive period models (reference group: never overweight)



Sensitive period: 1=childhood, 2=adolescence, 3=adulthood

Figure 6-3: Odds ratio of selected disease outcomes for accumulation of risk models (reference group: never overweight)



Accumulation: 1=exposure at one time point, 2=exposure at two time points, 3=exposure at 3 time point

Sensitivity analyses

Analyses of associations of raw BMI at each life stage with outcomes showed that childhood BMI was positively associated with asthma, hypertension and type 2 diabetes, while BMI in adolescence was positively associated with gallbladder disease, hypertension, type 2 diabetes, and combined diseases. These associations were attenuated to the null after adjustment for BMI in later life. BMI in adulthood was positively associated with all outcomes, and these effects remained after adjusting for early life BMI.

Exclusion of ethnic minority groups from analyses did not appreciably affect the results. For illustration, comparisons of odds ratios for type 2 diabetes from stepwise analyses are presented in Table 6-9. Adjustment for self-reported weight and height in adulthood in NCDS and BCS70 increased the estimated prevalence of overweight and obesity. In NCDS, obesity prevalence among men increased from 19.9% to 27.5%, while overweight and obesity combined increased from 70.2% and 77.0%. Among women, the prevalence of obesity increased from 18.3% to 22.0%, and the prevalence of overweight plus obesity increased from 49.2% to 53.5%. The pattern in BCS70 was the same, with obesity prevalence increasing from 17.7% to 23.3% among males (overweight plus obesity increased from 60.6 to 68.2%), and from 15.5% to 18.0% among female cohort members (overweight plus obesity increased from 40.5% to 44.1%). The results from sensitivity analyses adjusting for self-reported weight and height did not show a substantive change in the direction or magnitude of coefficients. Complete-case analyses resulted in associations in the same direction, but larger effects sizes for childhood obesity were observed. Comparison of hazard ratios from survival analysis with odds ratios from the original pooled analyses indicated similar patterns of association between overweight and obesity at each life stage and disease outcomes.

Table 6-9: Results from sensitivity analyses for type 2 diabetes using Stepwise approach, 1) OR from pooled analyses of all male cohort members, 2) OR from analyses excluding ethnic minority groups, 3) OR from analyses using adjustment for BMI from self-reported height and weight, 4) OR from complete case analysis, and 5) hazard ratio from survival analysis. * p<0.05; ** p<0.01.

Type 2 diabetes		All males OR (95% CI)	Excluding ethnic m. groups, OR (95% CI)	Adjusted for self-reported BMI, OR (95% CI)	Analysis of complete cases, OR (95% CI)	Survival analysis HR (95% CI)
Model 1	Child	n=10,336	n=10,212	n=10,336	n=5,540	n=9,297
	Obese	2.60 (0.89, 7.63)	2.66 (0.90, 7.82)	2.60 (0.89, 7.63)	4.88* (1.28, 18.65)	3.45** (1.39, 8.52)
	Adolescent	n=8,246	n=8,143	n=8,246	n=5,540	n=6,792
	Obese	11.83** (6.54, 21.40)	11.64** (6.33, 21.4)	11.83** (6.54, 21.40)	9.99** (4.27, 23.35)	9.01** (5.30, 15.32)
	Adult	n=11,820	n=11,644	n=11,820	n=5,540	n=9,717
	Obese	5.74** (3.53, 9.33)	6.05** (3.67, 10.0)	5.14** (3.06, 8.62)	6.89** (3.18, 14.96)	5.81** (3.61, 9.37)
Model 2	Child	n=9,884	n=9,778	n=9,884	n=5,540	n=8,468
	Obese	3.03* (1.01, 9.09)	3.03* (1.01, 9.09)	3.02* (1.01, 9.08)	5.41* (1.43, 20.47)	4.01** (1.61, 10.02)
	Adolescent	n=6,960	n=6,905	n=6,960	n=5,540	n=5,657
	Obese	13.40** (6.86, 26.17)	13.56** (6.94, 26.5)	13.30** (6.86, 26.14)	10.46** (4.42, 24.72)	9.92** (5.60, 17.60)
	Adult	n=8,512	n=8,427	n=8,512	n=5,540	n=7,036
	Obese	7.44** (3.85, 14.40)	7.76** (3.96, 15.2)	6.84** (3.44, 13.63)	7.37** (3.34, 16.25)	5.87** (3.25, 10.61)
Model 3	Child	n=8,226	n=8,145	n=8,226	n=5,540	n=6,795
	Obese	2.97 (0.97, 9.08)	2.97 (0.97, 9.11)	3.32* (1.08, 10.19)	3.11 (0.86, 11.21)	3.48** (1.38, 8.80)
	Adolescent	n=5,727	n=5,681	n=5,727	n=5,540	n=4,444
	Obese	4.43** (1.72, 11.39)	4.45** (1.72, 11.6)	4.68** (1.85, 11.85)	4.20** (1.58, 11.21)	3.57** (1.54, 8.27)
	Adult	n=8,226	n=8,145	n=8,226	n=5,540	n=6,795
	Obese	7.32** (3.73, 14.36)	7.62** (3.83, 15.2)	6.60** (3.27, 13.34)	7.27** (3.24, 16.30)	5.75** (3.13, 10.56)

6.5 Summary and implications

Stepwise analyses using standard adjustment for BMI at different periods showed that there were associations between overweight in early life and cardiovascular outcomes, which were attenuated after adjustment for BMI in adulthood, as observed in the systematic review of the literature in Chapter 3. However, results from a life-course approach to analysis indicated that overweight in childhood and adolescence increased type 2 diabetes risk in obese adults, and may have contributed to CHD risk. An effect of overweight in childhood and adolescence was not observed for other outcomes, including hypertension. Based on these results, a series of interpretations can be proposed which help to build a picture of pathways from overweight in early life to the different outcomes, notably cardiovascular outcomes (type 2 diabetes, hypertension and CHD) which have been consistently shown to be associated with childhood overweight.

Analyses of overweight patterns showed that persistent overweight through childhood, adolescence and adulthood was associated with higher odds of type 2 diabetes compared to obesity in adulthood only. This finding was in contrast to those of a previous study, which found no difference in the relative risks of type 2 diabetes between those with persistent overweight through childhood and adulthood, and those with obesity isolated to adulthood [174]; however, the outcomes in this previous study were reported at a younger age than in the present analyses and there were fewer cases of type 2 diabetes, which may have reduced the power to detect a difference. The analyses in this chapter showed evidence of increasing type 2 diabetes risk with overweight at more life stages, a trend which was more apparent when obesity rather than overweight was treated as the exposure in childhood and adolescence. However, an effect of overweight or obesity in childhood and adolescence was not observed in cohort members that were not obese in adulthood; childhood and adolescence therefore did not appear to be critical periods for exposure. This finding is supported by studies which have shown that reduction in overweight in childhood or adulthood can lead to improvement in metabolic parameters [359-360] and reversion from impaired to normal glucose tolerance. [88] Adjustment for adult BMI indicated that the severity of overweight in later life associated with persistent overweight (which may also act as an indicator of cumulative exposure to overweight in adulthood[271]) did not account for all of the excess risk. Although the inclusion of adult BMI in the model is subject to overadjustment issues similar to those discussed in Chapter 4.3.2, this result lends support to a model of type 2 diabetes progression in which risk is affected by the duration or accumulation of exposures over the life-course rather than to the severity of overweight in adulthood. These collective observations would be consistent with a conceptualisation of type 2 diabetes progression in which overweight contributes to (or is a marker of) increasing insulin resistance and gradual loss of beta cell function over time,[361] eventually leading to type 2

diabetes.[362] Individuals that are exposed to overweight in childhood and become non-obese in adulthood may have increased levels of insulin resistance and glucose, which do not reach the threshold for a diagnosis of type 2 diabetes when levels of overweight in adulthood are reduced. A further consideration is that persistent overweight may indicate some underlying genetic predisposition to overweight and metabolic complications. [363]

In contrast to the findings for type 2 diabetes, exposure to overweight in early life did not appear to increase the risk of hypertension in obese adults; this was also the case when more extreme overweight in childhood and adolescence (obesity) was considered as the exposure. These associations are more consistent with a model in which obesity in adulthood accounts predominantly for hypertension risk, rather than longer term effects associated with overweight in childhood and adolescence. This is different to the findings of a previous study, which showed that overweight in childhood and adolescence was associated with additional hypertension risk compared to obesity in adulthood alone.[174] However, other studies have shown that lower BMI in childhood in combination with overweight in adulthood is associated with the highest risk of hypertension, [121] indicating that rapid growth over the life-course may be an important determinant of hypertension risk. [223] Alternative explanations are that obesity has more immediate and temporary effects on blood pressure, or that obesity in adulthood is a marker for other risk factors which may either act over the life-course or more contemoraneously in adulthood, to determine hypertension risk. For example, body size in adulthood may be linked to lifestyle behaviours that are associated with hypertension, such as salt consumption,[364] or to factors that act on hypertension risk through psychosocial pathways, such as anxiety and depression. [365-366] The mechanisms by which obesity leads to hypertension are not well understood, and there may be multiple pathways to elevated blood pressure[367]; further examination of the relative contributions of overweight and other risk factors to hypertension risk may identify where intervention efforts should be focused in order to reduce the burden of hypertension.

Point estimates for CHD indicated a possible trend for higher risk associated with overweight at more life stages. The relatively young ages at measurement of outcomes in these cohorts, which explained the small number of CHD cases, meant that the analyses had limited power to detect a difference. Elevated blood glucose levels and blood pressure are risk factors for cardiovascular disease. [368-369] Consequently, the relationship between overweight and CHD may have been driven in part by the associations of overweight with type 2 diabetes and hypertension. For example, a large study of data from 58 prospective studies indicated that BMI in adulthood did not improve prediction of CVD risk when information on systolic blood pressure, diabetes history and serum lipids was available.[370] The contrasting relationships of type 2 diabetes and hypertension with overweight over the life-course may explain the intermediate effect on CHD that was observed in this chapter, with overweight acting on type 2 diabetes risk from early life

and on hypertension risk at later ages. The effects of adjusting CHD models for type 2 diabetes and hypertension were examined (results presented as supplementary table in Appendix 3); adjustment for hypertension had little impact, while adjustment for type 2 diabetes led to attenuation of effect sizes, indicating that the associations of CHD with overweight patterns may be partly explained by the relationship between overweight and type 2 diabetes. Bringing together the findings for the different cardiovascular outcomes included in this analysis, a theoretical model may be proposed as a framework for understanding cardiovascular risk: childhood and adolescent overweight may contribute to high blood glucose levels (possibly leading to type 2 diabetes) and atherosclerosis, which in addition to high blood pressure and obesity in later life lead to further atherosclerosis and increased CHD risk. Disentanglement of the relationships between overweight and other cardiovascular risk factors, and their contributions to type 2 diabetes, hypertension and CHD over the life-course will be key for understanding the mechanisms to cardiovascular disease, and this will have important implications for approaches to interventions to reduce cardiovascular burden.

In these analyses, overweight in childhood and adolescence did not appear to contribute to asthma, gallbladder disease or arthritis risk; obesity in adulthood was associated with each of these outcomes, but there was no indication of a cumulative effect of overweight from childhood. As the review in Chapter 3 demonstrated, evidence for a relationship between childhood overweight and non-cardiovascular outcomes is relatively limited. One interpretation of these findings is that obesity in adulthood has the largest effect on these outcomes, while overweight and obesity in earlier life have little effect on long-term risk. Or it may be the case that obesity in adulthood is a marker of some other risk factor for these conditions. However, this study was limited by the relatively low prevalence of arthritis and gallbladder disease, and asthma may be subject to misdiagnosis, with respiratory problems attributable to other conditions being diagnosed as asthma. [371] Furthermore, the transient nature of asthma symptoms makes it difficult to establish the relative timings of childhood overweight, initial diagnosis of asthma, and subsequent relapse. Cases of asthma that were first diagnosed in childhood were included in this analysis; it was not possible to identify individuals with asthma isolated to childhood (and no relapse in adulthood), as health questionnaires in adulthood asked only about whether there was any history of asthma, and symptoms in the past 12 months. Inclusion of these cohort members in the analyses may have masked any relationship between childhood overweight and asthma relapse in adulthood. Analysis of larger datasets with more cases is required to establish the effects of overweight and obesity in early life on these outcomes.

A common factor that is implicated in a number of obesity co-morbidities is inflammation; pro-inflammatory molecules are known to be expressed by adipose tissue,[372] and exposure to overweight in childhood may have longer-term effects on disease risk. For example, inflammation has been associated with insulin resistance, atherosclerosis, and non-alcoholic

fatty liver disease. [372] In the case of asthma, increased adipose tissue may lead to a systemic inflammatory state, which results in chronic inflammation of the airways, and even permanent changes in lung function.[245] Persistent inflammation can also lead to joint problems including rheumatoid arthritis.[373]

The main limitations of this analysis include the use of self-reported outcomes, which may have been subject to measurement error and biases. Previous studies have indicated that misreporting is especially likely for less severe diseases or those with more transient symptoms, such as hypertension and asthma.[352] Undiagnosed conditions may be more common among healthy weight individuals who are likely to have less contact with health services, which could lead to an overestimation of the effects of overweight. On the other hand, overweight individuals are more likely to be lost to follow-up, which may produce more conservative effect sizes. Another limitation of this analysis is the use of BMI measurements at single ages to represent exposure to overweight over a period of development. Increasing evidence indicates that patterns of growth over the life course (notably small size at birth and catch-up growth in later life) are related to body composition and body size, and to increased cardiovascular risk in later life.[239] Childhood overweight, measured using BMI at a single stage of development, could not capture the dynamic processes of growth and changes in body composition[374-375] that take place over the life-course, which may have important implications for some health outcomes. [239 376] Furthermore, the developmental stages of childhood, adolescence and adulthood encompassed different lengths of time over the life-course, therefore exposure in each life period (assuming that overweight spanned the whole life period) did not correspond to an equal 'dose' of overweight or obesity. Further examination of the relationships between age at onset and duration of overweight, and patterns of growth in early life may further elucidate the mechanisms underlying these associations. These analyses have considered multiple outcomes and several groups of exposures, therefore analyses are subject to multiple testing problems [377]; given the large number of associations tested, the chance of type 1 errors (false positives) is increased, and single associations should be interpreted with caution, especially where effects are inconsistent, e.g. an association is observed with overweight but an association in the same direction is not observed with obesity. In the case of type 2 diabetes, a dose-response effect, small p-values and consistent findings across different model specifications and sensitivity analyses indicate that this association was not a spurious result.

The pooling of data from three cohorts had the advantage of increasing power over a single study, and these three British National Birth Cohort datasets have not been analysed together in this way previously. A clear benefit of using these data is that the comparability of target populations and similarities in data collection allow the harmonisation of datasets with minimal loss of information. However, there were some differences in BMI trajectories (as described in 5.3) and variation in the ages at ascertainment of disease outcomes; pooled analyses may have

masked individual cohort effects that were not detected in the test for interaction by cohort. A more general limitation of cohort studies with long-term follow-up concerns the generalisability of findings to contemporary populations of children. Notably for these analyses, children today are experiencing more extreme obesity and at earlier ages than was observed in the British national birth cohorts. The effects of obesity of this nature on long-term health may be distinct from those observed in historical cohorts; for example, the number of cases of type 2 diabetes among young people is rising, highlighting the more contracted nature of disease progression and health implications of severe obesity in childhood. However, in the absence of more robust study designs, such as randomised controlled trials of obesity interventions with long-term follow-up, data from observational studies are important for providing insight into these relationships.

Analyses based on a life-course perspective indicate that overweight in childhood and adolescence may contribute to excess risk for cardiovascular outcomes, notably type 2 diabetes, in obese adults. For other outcomes, more contemporaneous exposure to obesity appears to account for the excess risk associated with overweight. The associations between childhood overweight, adult obesity and later health outcomes have important implications for determining the nature and timing of obesity interventions.

7. CHILDHOOD OBESITY AND LONG-TERM HEALTH BURDEN

7.1 Introduction

The systematic review in Chapter 3 and analyses of the British Birth Cohort data in Chapter 6 showed that overweight and obesity in childhood and adolescence are associated with several disease outcomes in adulthood, notably cardiovascular risk. There is widespread concern about the impending disease burden associated with current levels of childhood obesity,[14-15] which is expected to present a considerable strain on health and public services and the economy over the coming decades. Consequently, reducing childhood obesity prevalence was highlighted as a major public health priority for the UK government in the 2008 *Healthy Weight, Health Lives*, [13] and 2011 *Healthy Lives, Healthy People* [378]strategies. However, while estimates of future trends in childhood obesity prevalence [379] and current burden of childhood obesity co-morbidities [159] have been published, the expected long-term burden of the childhood obesity epidemic and its associated costs have not been quantified. Furthermore, the impact of different strategies for intervention on long-term outcomes has not been assessed in the UK population.[380]

The National Heart Forum Obesity model was developed by the modelling group at the National Heart Forum (NHF), London as part of the Office for Scientific Foresight Programme, [19] which culminated in the 2007 Foresight Obesity report. The model has two components: a model of BMI trends and a micro-simulation (individual-based) stochastic model that has been used to project the future disease burden and NHS costs of current obesity trends, and to explore the impact of interventions; the estimates generated using this model have been used by the Department of Health as the basis for predictions of future obesity burden in the UK. [45] This model was developed to simulate what happens in the UK population, but has not been used for estimating childhood obesity burden specifically.

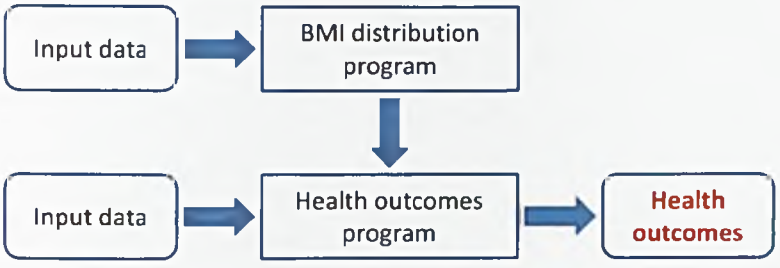
This chapter begins with a summary of the model and assumptions, based on descriptions detailed in other publications [19 163] and correspondence with the authors. The results of simulations that estimate the future disease burden and costs associated with obesity in the current cohort of UK children and adolescents are presented, and the effects of different approaches to intervention on this cohort are explored. This is followed by an examination of the model assumptions and fit of the model to historical data, with discussion of the implications of these exploratory analyses.

7.2 Overview of the National Heart Forum Obesity Model

The NHF Obesity Model comprises two distinct components (Figure 7-1). The first part is the BMI distribution model, which uses a regression model to produce cross-sectional BMI

distribution data. The second part is the health outcomes model, which implements a micro-simulation model for the longitudinal analysis of populations and quantifies the effects of BMI distribution on selected health outcomes.

Figure 7-1: Schematic overview of NHF obesity model



7.2.1 BMI distribution model

The BMI distribution model uses a series of cross-sectional datasets to estimate the distribution of user-specified BMI groups (e.g. using raw BMI cut-offs or IOTF cut-offs to define overweight and obesity) in the population over time. These distributions can be specified by age, sex, ethnicity, social class group and geographical region (data-permitting). Trends in the proportion of people belonging to any particular BMI group are extrapolated using a non-linear regression model, which allows for the total prevalence of all BMI groups in the population to add up to 100%, and any approach to 0 or 100% by any BMI group is asymptotic and cannot exceed these limits (**Equation 1**). Distributions can be extrapolated to 2050 and beyond. The posterior distribution of the parameters is used to define the confidence limits around the regression line, and can be specified by the user. The BMI distribution data that are produced using this model form the input to run the second component of the model.

$$p_{B_i}(t) = \frac{1+\tanh(a_i + b_i t)}{\sum_{k=1}^{k=N}(1+\tanh(a_k + b_k t))}$$

$a_i = a_i(\text{Age}, \text{Sex}, \ldots)$ $b_i = b_i(\text{Age}, \text{Sex}, \ldots)$

$p_{B_i}(t)$ = probability of belonging to bmi group B_i at time t

Equation 1[19]

For projections in the 2007 Foresight report, and in this thesis, data from the Health Surveys for England (HSE) were used. The HSE data are a series of annual cross-sectional surveys carried out by the Joint Survey Unit of the National Centre of Social Research and the Department of Epidemiology and Public Health at University College London. [381] The surveys are designed to monitor trends in health. The survey focuses on different health issues each year, but core variables including height and weight are measured each year. Children have been included in

the surveys since 1995, and data are available up to 2008. All private households in the general population are eligible for inclusion, and a multi-stage stratified random sample is used to select up to two children aged 2-15 years from each household. The number of children included in the surveys has ranged from around 4,000 in most years, to 7,000 in boost years (1997, 2002, 2005-2007). To account for the sampling method in the HSE, weighting factors are used. Additional data points may alter the projected BMI trends, as seen in a recent update of the childhood obesity projections presented in the Foresight report, [382] which showed that the upward trend in BMI may be levelling off.

7.2.2 Micro-simulation (health outcomes) model

The micro-simulation program can be described as five modules defining the demography, BMI distribution, disease, interventions and costs of the model population. The model simulates the changing BMI distribution and acquisition of overweight-related diseases in a population of individuals. Some individual characteristics are set from the start, such as sex, age and ethnicity, while other characteristics, notably the transition probabilities for movement between disease states, depend on events that occur during the lifetime of the simulated individuals, such as whether the individual becomes overweight and whether they have any other disease. The occurrence of events is stochastically determined, using Monte Carlo sampling from defined probability distributions. The simulation is based on rounds, with each round encompassing one year. The user can specify the number of runs, the dates at which the simulation begins and ends, any intervention scenarios, the diseases to include, and the years for which the output is required. Uncertainty is not modelled explicitly, but is quantified in error analyses which tabulate variability arising from the micro-simulation.

Demography

The demography input parameters determine the initial population composition and background mortality and fertility in the population. In the model, the most recent age- and sex-specific vital statistics from the Office of National Statistics are used, and the model does not allow these rates to vary over time (except for estimated changes due to changes in the BMI distribution). The initial population is defined by specifying the age-sex structure at the start of the simulated period (e.g. in year 2007). The age-specific fertility rates are used to calculate the number of births among women in each age group. The births are randomly allocated to women in each round. Age- and sex-specific mortality rates are used to calculate the background number of deaths in each round (before accounting for deaths due changes in BMI distribution). The model does not account for migration. Demographic outputs include disease-specific and total mortality in specified years, and life expectancy in the simulated population. Period estimates of life expectancy are calculated over 5-year intervals, based on death rates over the simulated period.

BMI distribution

User-specified age- and sex-specific BMI distributions for each year of the simulated period (which can be generated from the BMI distribution model) are used to determine probabilities of transfer between BMI groups (e.g. from overweight to obese) in each round. The model specifies that individuals stay on the same BMI centile from the start of the simulated period to the end (or until death if that occurs first). The outputs include BMI distributions and prevalence of overweight and obesity by age and sex.

Disease

Disease parameters allow simulated individuals to contract user-specified diseases with a probability calculated from the background age- and sex-specific incidence of the disease in the population, and the age-, sex- and BMI-specific relative risk of the disease, in each round. Users can also specify whether disease probabilities are conditional on other disease states, such as CHD risk conditional on type 2 diabetes. Individuals who contract a disease can die from the disease with a probability determined by the age- and sex-specific disease-specific mortality rate. The model does not allow for individuals to be cured of a disease, they either continue to have the disease until the end of the simulation period or die (due to the disease or for some other reason). Disease outputs include disease incidence and prevalence by age and sex, and cause-specific mortality.

Interventions

This module changes parameters in the BMI distribution to model the impact of interventions on disease, mortality, and costs. The effect of an intervention is expressed in terms of BMI change or by imposing a cap on BMI. These intervention effects can be specified by age, sex and BMI, and target years (e.g. BMI is reduced by 1 unit in obese boys aged 6-12 in the years 2015-2018). The output in terms of disease prevalence, incidence, mortality, life expectancy or NHS costs under different scenarios can be compared to estimate the impact of different intervention approaches.

Costs

Annual costs to the NHS of obesity-related diseases (e.g. from government reports [383]) are multiplied by the number of cases to estimate the direct health costs. The costs attributable to changing BMI distribution can be estimated by comparison with costs at baseline or under different scenarios of BMI change. The model does not vary costs, inflation or the value of money over time. The model can also be used to estimate the wider economic costs of overweight and obesity by multiplying the estimated NHS costs by the current ratio of wider societal costs to NHS costs of overweight and obesity (e.g. in 2001 this ratio was estimated to be 1:6). In the model this ratio is held constant over the simulated period.

7.3 Estimating the future disease burden associated with childhood obesity

7.3.1 Methods

I obtained a copy of the NHF obesity model programme from the NHF modelling group, and ran all the projections on a standard desktop PC. Using the two-part modelling process described above, a virtual population of UK children and adolescents was projected from the year 2007 to 2050. This year was selected as the end point to enable comparison of estimates with previous projections of obesity burden in the UK population. I specified the population distribution for a population aged 2-19 years in 2007 (and therefore aged 45-62 years at the end of the simulation period) as a PF (.pf) file, based on the age-sex structure from mid-year population estimates from the Office for National Statistics. [384] The 2007 population was selected because the BMI, disease and cost data were valid for this year. The data that were used to specify the population size and age-sex structure can be seen in Appendix 4. Fertility rates were not applied, therefore the population did not increase in size over time. Using the BMI distribution model, HSE data from 1995 to 2008 were used to project BMI distributions by age (in 5 year groups) and sex to 2050. Weight categories were defined as previously, using IOTF cut-offs in childhood and WHO definitions in adulthood. In the simulation, BMI values were assigned probabilistically to individuals in the virtual population according to age, sex and year, based on the projected BMI distributions.

The disease and cost data that were used in the 2007 Foresight Obesity report were used in these simulations. Disease data were obtained from reviews of epidemiological publications, to determine age- and BMI-specific incidence, case-fatality rates, and relative risks of disease for type 2 diabetes, CHD, stroke, arthritis and obesity-related cancer. The sources of data inputs are summarised in Table 7-1. In each round of the simulation, each individual had an age-, sex- and BMI-specific probability of contracting a certain disease, if they were free of that disease in the previous year. Individuals who contracted a disease could die of the disease, depending on the survival and case-fatality data. Annual costs of each disease due to the changing distribution of BMI were estimated from governmental data or other published estimates; the direct cost per case was calculated as the total medical costs (including hospital care, healthcare professionals and drugs) divided by the number of patients. Diseases and the associated costs were assigned probabilistically to individuals as a function of their BMI history using a Monte Carlo simulation method [385] (transitions between states were randomly drawn from the specified probability distribution to determine events).

For each scenario, I simulated one million individuals ageing to 2050, and analysed the output. Estimates of annual disease prevalence, incidence and costs were extracted from the output TAB files into Microsoft Excel for analysis. The estimates based on simulations of one million individuals were scaled up to the size of the 2007 child and adolescent population (13.25

million), to generate estimates of population burden. The diseases attributable to changes in BMI distribution and associated costs were calculated as the difference between estimates for each scenario and the reference scenario, which assumed that BMI distributions were fixed at the 2007 level, therefore producing an estimate of additional burden due to rising prevalence of overweight and obesity over the years of the projection. All results were applicable to the projected cohort of children and adolescents in 2007, and did not include cases in the wider population (other age groups).

Table 7-1: Sources of data inputs used in simulation

	Source
Population characteristics	
BMI distribution	British National Birth Cohorts
Population size	British National Birth Cohorts
Incidence of disease	
Hypertension	British Heart Foundation statistics [386]
Coronary heart disease	European cardiovascular disease statistics [387]
Type 2 diabetes	British Heart Foundation statistics [386]
Stroke	British Heart Foundation statistics [386]
Cancer	Cancer Research UK statistics [388]
Arthritis	Office for National Statistics [389]
Relative risks associated with obesity	
Hypertension	UK Foresight Tackling Obesities programme [390]
Coronary heart disease	International Association for the Study of Obesity [391]
Type 2 diabetes	International Association for the Study of Obesity [391]
Stroke	International Association for the Study of Obesity [391]
Cancer	International Association for the Study of Obesity [391]
Arthritis	
Disease-specific mortality and survival	
Hypertension	<non-terminal>
Coronary heart disease	European cardiovascular disease statistics [387]
Type 2 diabetes	British Heart Foundation statistics [386]
Stroke	British Heart Foundation statistics [386]
Cancer	Cancer Research UK statistics [388]
Arthritis	<non-terminal>
Costs	
Hypertension	British Heart Foundation statistics [386]
Coronary heart disease	British Heart Foundation statistics [386]
Type 2 diabetes	NHS Information Centre [392]
Stroke	British Heart Foundation statistics [386]
Cancer	UK Foresight Tackling Obesities programme [390]
Arthritis	National Rheumatoid Arthritis Society report [393]

Interventions: exploratory analyses

The effects of different intervention scenarios on disease burden and associated costs were explored using the simulation model. Long-term weight loss in adults has been shown to be associated with lower risk of type 2 diabetes, hypertension and cardiovascular disease.[394] However, systematic reviews have shown that most interventions for the prevention of childhood obesity do not have a large effect on BMI, [165] while evidence for long-term effects of specific interventions for the treatment of childhood obesity is lacking. [395] This was also a key finding in a systematic review of pharmacotherapy for childhood obesity that was conducted as initial background work for this chapter (Appendix 5). Information on the sustainability of intervention effectiveness and associated future health outcomes is important for determining the long-term impact of childhood obesity interventions. However, current studies do not have follow-up of sufficient duration to address these data needs.[396] Therefore scenarios were specified to reflect hypothetical long-term effects of large-scale interventions for childhood obesity prevention and treatment, based on the available evidence for current obesity interventions.

Intervention scenarios were defined in terms of their effect on childhood overweight, and were broadly categorised as population (general) or individual (high risk) approaches, as described by Geoffrey Rose in his seminal paper.[397] The former term applies to interventions that are directed at the whole population, which aim to shift the entire distribution of a risk factor in a population towards a more favourable position. An example of such an intervention is the national Change4Life social marketing campaign in England, which is a government initiative that aims to help families make sustainable changes to their diet and physical activity through mass media, including television, print and online resources. The campaign presents obesity and healthy lifestyle as issues that are relevant to the whole population, rather than to any select group considered to be high risk. An evaluation of the Change4Life campaign showed that there was little impact of the print and online information on parenting behaviours or child health behaviours.[398] The effect of this campaign on childhood BMI or overweight has not been assessed, but its effects on weight-related behaviours suggest that any beneficial effect is likely to be minimal. However, with a population approach, while the benefit to any given individual in the population may be small, if large numbers of people experience the benefit, the effect at the population level is potentially large, a scenario known as the Prevention Paradox.[397] The impact of population approaches to obesity prevention on long-term burden, taking the Change4Life campaign as an example, was assessed using the simulation model.

The individual or high-risk approach refers to those interventions which target members of the population that are most susceptible to obesity or its co-morbidities. If effective, such interventions would truncate the distribution of BMI at the high risk end, while the rest of the

distribution may remain unaffected. In the case of childhood obesity, individual-based interventions would include tailored interventions for overweight and obese children, such as the MEND (Mind, Exercise, Nutrition, Do It!) 7-13 programme.[399] This intervention is aimed at children that are aged 7-13 years, and have BMIs above or equal to the 91st centile of the UK 1990 reference chart. Other MEND programmes aimed at younger children, teenagers, and adults are also available, but the 7-13 is the original and most evaluated programme. The goal of MEND 7-13 is to help families in implementing healthy lifestyle changes through education and physical activity sessions, which is delivered in 20 sessions over a 10-week period. Families are usually referred to the programme by their GP or other health professionals. MEND represents one of the most established and widely available child weight management programmes that is currently available in England and Wales, and has had more than 60,000 participants since 2004. A randomised controlled trial of obese children (BMI $\geq$98th centile of UK 1990 reference) enrolled in the programme showed that among children that received the intervention, BMI z-scores were reduced by 0.23 at 12 months, which was equivalent to a BMI reduction of 0.1 kg/m^2 (or approximately 0.5% reduction in BMI among overweight and very overweight children). The impact of this kind of targeted intervention on long-term health burden and costs was assessed.

The intervention scenarios that were simulated are outlined in Table 7-2. Scenario 1 simulated the effect of a population approach to obesity intervention in which BMI in the child and adolescent population was reduced by 0.2% at the start of the projection period. The individuals' BMI centiles, on which they remained thereafter, were adjusted accordingly. This scenario was intended to represent a campaign such as Change4Life, in which all members of the population are targeted and encouraged to make healthy changes to lifestyle. A report on the Change4Life campaign after one year indicated that 99% of families had had an opportunity to see the campaign.[400] There are no data available to indicate an effect of the Change4Life campaign on BMI, but the effects are likely to be very small [398]; a 0.2% reduction in BMI in all members of the cohort may be an overestimate of the potential effects of this type of intervention, and can therefore be considered as a best-case scenario. Scenario 2 simulated the effect of a targeted intervention modelled on the MEND 7-13 programme. It assumed that all children eligible for the programme (aged 7-13 years with BMI>91st centile of the UK 1990 reference population) in the 2007 population received the intervention and experienced a 0.1 kg/m^2 (approximately 0.5%) reduction in BMI, which is the effect size that was reported for obese children in an evaluation of the programme, described above.

The effects of interventions with comparable effects to those described in scenarios 1 and 2, but implemented in adulthood, were examined in scenarios 3 and 4. The intention was to compare whether the timing of interventions (in childhood and adolescence versus in adulthood) had a notable impact on their long-term benefits for health burden. Scenario 3 modelled the effect of

a 0.2% reduction in BMI in early adulthood among all cohort members aged ≥20 years in 2017. The intervention effects were specified to take place in 2017, when cohort members would be aged 12-29 years, therefore those cohort members aged 20-29 in 2017 would be affected. Scenario 4 simulated a 1 kg/m^2 reduction in BMI among overweight adults (BMI >25 kg/m^2) aged 23-29 years in 2017; a one unit reduction in BMI was selected to approximate a 0.23 SD reduction in BMI (based on HSE data), as achieved in childhood in scenario 2, and was equivalent to a 2-4% reduction in BMI. The age group 23-29 years was selected to include the same range of ages in the population as would be affected by the intervention in childhood (ages 7-13).

Weight regain is an important consideration in long-term evaluations of obesity interventions. Studies in adults have indicated that most people regain the weight that is lost during an intervention; a fifth of overweight individuals are able to maintain a weight loss of at least 10% of their initial body weight for at least one year.[401] Based on this, two conditions were modelled for each intervention described in scenarios 1 to 4; one condition was without weight regain (the change in BMI remained in effect for the duration of the projection period), while the other specified 80% regain of the BMI loss after 1 year.

The impact of each intervention scenario on the number of cases of each disease and the associated costs at the end of the projection period in 2050 was assessed by comparing against a scenario with no intervention, i.e. BMI growth continued unrestricted as projected using HSE data. Intervention effects are presented as the number of cases prevented (in 2050 and cumulative over projection period) and the associated gain in costs (costs given in current rates) resulting from the change in BMI. The gains in costs are compared with the estimated intervention costs to provide estimates of the net costs or savings associated with different scenarios.

Table 7-2: Intervention scenarios modelled in simulation

Scenario	Age	Years
1. 0.2% reduction in BMI in childhood/adolescence	2-19 y	2007
2. 0.1 kg/m^2 reduction in BMI in children with BMI>91st centile of UK 1990 reference population	7-13 y	2007
3. 0.2% reduction in BMI in adulthood	≥20 y	2017
4. 1 kg/m^2 reduction in BMI in adults with BMI >25kg/m^2	23-29 y	2017

7.3.2 Results

Health burden and direct costs

Based on recent trends in BMI distribution (1995-2008), it was projected that the prevalence of obesity in the cohort would be 54-82% in 2050 (at ages 45-62), compared to a prevalence of 30-37% at the same ages in 2007 (the reference scenario). The prevalence of overweight was projected to be 14-20%, while 4-26% of the cohort were projected to be normal weight (BMI <25 kg/m^2) by 2050, compared to 19-36% in 2007.

Figure 7-2 shows the prevalence of type 2 diabetes, coronary heart disease, hypertension and cancer in the simulated cohort over the projection period. This graph shows that diabetes and hypertension contribute the most to disease burden in terms of prevalence over the projection period. Hypertension shows the earliest onset, with prevalence increasing steadily over the projection period, while type 2 diabetes prevalence is relatively low over the first two decades and shows a dramatic rise from the 2030s, to increase more than six-fold and be nearly as prevalent as hypertension by 2050. CHD and cancer present a much lower disease burden, with very few cases pre-2030. However, prevalence of these conditions begins to increase over the last two decades of the projection period, to reach nearly 2,000 cases per 100,000 population by 2050.

The simulation showed that the recent trends in BMI distribution would project an additional 36,000 cases of cancer, 118,000 cases of CHD and stroke, 16,000 cases of arthritis, 768,000 cases of type 2 diabetes, and 447,000 cases of hypertension in the year 2050, compared to the reference scenario which assumed that BMI distributions were constant at the 2007 level. Figure 7-3 shows the projected prevalence of type 2 diabetes and hypertension under recent trends in BMI distribution compared with the projected prevalence under the reference scenario.

Examination of the direct health care costs showed that recent trends in BMI distribution projected substantial cost implications, with higher costs associated with increasing age. Compared to the reference scenario, recent BMI trends projected annual costs of treating obesity-related diseases in the cohort that were £1.1 billion higher in 2050, with total costs of overweight and obesity in the cohort amounting to £12 billion. These figures did not include the costs of treating obesity-related diseases in the wider population, and were not cumulative over the projection period. The costs of hypertension in the cohort presented the largest economic burden, accounting for 42% of the total expenditure on healthcare for the selected diseases, while diabetes accounted for 40%, cardiovascular diseases (CHD and stroke) for 13%, cancer for 4%, and arthritis for 2%. In 2050, obesity (BMI>30 kg/m^2) accounted for 91% of the excess costs, while overweight contributed to 9% of the economic burden.

Figure 7-2: Projected prevalence of type 2 diabetes, coronary heart disease, hypertension and cancer in the simulated cohort 2007-2050

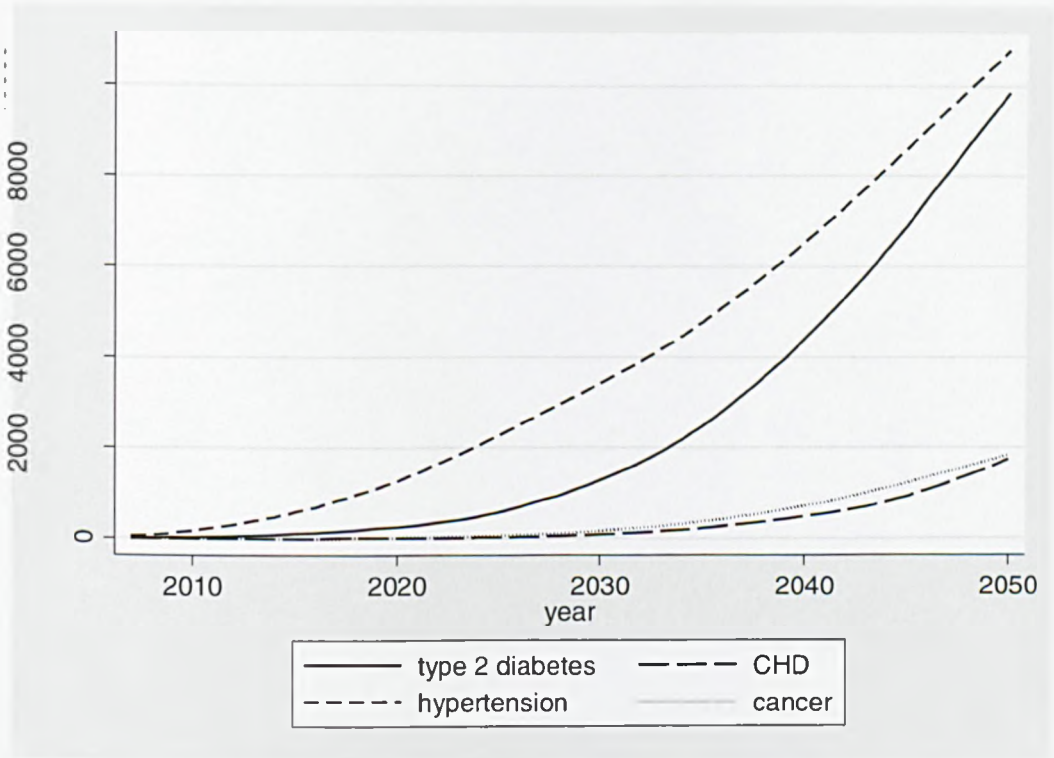
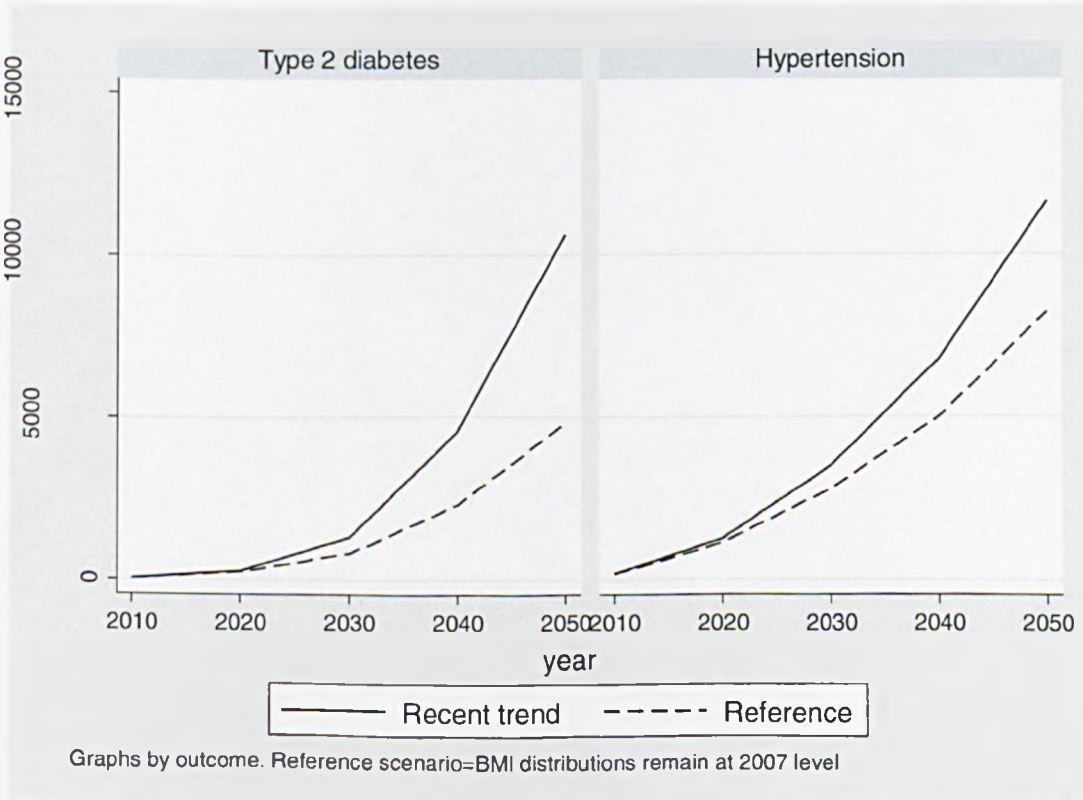


Figure 7-3: Projected prevalence of type 2 diabetes and hypertension under recent trend in BMI distribution versus reference scenario, 2007-2050



Effects of obesity interventions

The projected effects of the different intervention scenarios described in the methods are presented in Table 7-3 and Table 7-4. Compared to a scenario in which recent trends in BMI distribution continued unrestricted, a 0.2% reduction in BMI among all children and adolescents in 2007 (scenario 1) with no weight regain was associated with a reduction of 169,000 cases of type 2 diabetes, 88,000 cases of hypertension, 23,000 cases of cardiovascular disease, and a gain in direct healthcare costs of £48 million in 2050. Between 2007 and 2050, the cumulative gain in direct healthcare costs associated with the intervention was £492 million for the cohort. A comparable intervention which affected all adults in the cohort in 2017 (scenario 3) was associated with a reduction of 123,000 cases of type 2 diabetes, 64,000 cases of hypertension, 16,000 cases of cardiovascular disease, and savings in direct healthcare costs of £47 million. Over the whole projection period, cost savings associated with these prevented cases of disease were estimated at £490 million.

An intervention which reduced BMI by 0.1 kg/m^2 in overweight children aged 7-13 years in 2007 (scenario 2) projected a reduction of 253,000 cases of type 2 diabetes, 147,000 cases of hypertension, 32,000 cases of CHD and stroke, 4,000 cases of arthritis, and a gain in annual costs of £51 million. Over the whole projection period, the total gain in direct healthcare costs was estimated at £519 million. A similar intervention which reduced BMI by 1 kg/m^2 in overweight adults aged 23-29 years (scenario 4) was projected to result in a reduction of 104,000 cases of type 2 diabetes, 37,000 cases of hypertension, and 20,000 cases of cardiovascular disease in the year 2050. The annual gain in direct healthcare costs associated with these effects was £45.8 million in 2050, while the cumulative gain was estimated at £470 million.

The cumulative gains in cost over the projection period ranged from £470 million to £519 million for the four intervention scenarios without weight regain. The cost of the MEND 7-13 programme was estimated at £415.77 per child in 2010.[380] When applied to all children who would be eligible for the programme in 2007 (all children aged 7-13 years with BMI >91st centile of UK 1990 reference population, n=1.3 million), the total cost of the programme was estimated at £551 million. The cost gains associated with this intervention were estimated to be £519 million, therefore the net cost of the programme in this scenario was estimated at £32 million over the projection period to 2050. When the same costs were applied to the projected population of overweight adults in 2017 (n=4.6 million people), the estimated net cost of the intervention increased to £ 1.5 billion. In contrast, the original Department of Health budget for the Change4Life campaign was set at £75 million over three years, therefore the cumulative gain in healthcare costs associated with this intervention (scenario 1, £492 million) was

associated with a net saving of more than £400 million by the year 2050, and similar savings were associated with a population-wide intervention effect in adulthood.

When the effects of weight regain were included in the simulations, the estimated numbers of prevented cases of disease and associated gains in healthcare costs were substantially reduced (Table 7-4). For example, when 80% weight regain was incorporated into scenario 2, which modelled the effect of an intervention for overweight children aged 7-13 years, the number of cases of type 2 diabetes that were prevented decreased from 253,000 to 48,000, hypertension cases from 147,000 to 21,000, and cardiovascular diseases from 32,000 to 7,000. The cumulative gain in costs associated with this scenario was reduced from £519 million to £155 million. Similarly, the cumulative gains in costs associated with scenarios 1, 3 and 4 were reduced from £470-492 million to £143-151 million. The net costs (or savings) associated with each intervention were increased (or reduced) accordingly. Scenarios 1 and 3 (population approaches) remained associated with net savings, while scenarios 2 and 4 (interventions targeted at overweight and obese members of the cohort) were associated with substantial net costs (between £396 million and £1.8 billion).

Table 7-3: Projected effects of intervention scenarios on disease prevalence and related health costs in 2050, compared to scenario reflecting recent trends in BMI distribution

Cases per year x1000 (SE)	Intervention scenario			
	1	2	3	4
Arthritis	−3 (3)	−4 (3)	−3 (3)	− 1 (3)
Hypertension	−88 (13)	−147 (12)	−64 (13)	−37 (13)
Type 2 diabetes	−169 (12)	−253 (12)	−123 (12)	−104 (12)
CHD and stroke	−23 (6)	−32 (6)	−16 (6)	−20 (6)
Cancer	−5 (5)	−4 (5)	−3 (5)	−1 (5)
Gain in costs in 2050 (£million)	£ 47.9	£ 50.6	£ 47.1	£ 45.8
Cumulative gain in costs 2007-2050 (£million)	£ 491.6	£ 518.8	£ 489.9	£ 469.6

Scenario 1=0.2% reduction in BMI in children and adolescents aged 2-19 years in 2007; Scenario 2=0.1 unit reduction in BMI in overweight and obese children aged 7-13 years in 2007; Scenario 3=0.2% reduction in BMI in adults aged 20 years and older in 2017; Scenario 4=1 unit reduction in BMI in overweight and obese adults aged 23-29 years in 2017. Scenarios do not specify weight regain. Gain in costs calculated as healthcare costs for scenario with no intervention minus the healthcare costs associated with intervention. All figures are cases x1000 (SE), unless stated.

Table 7-4: Effects of intervention scenarios on healthcare costs in 2050, with and without weight regain, compared to a scenario that reflects recent trends in BMI distribution

Scenario	Age of target group (y)	Intervention effect (BMI change)	Weight regain after 12 months	Gain in costs in 2050 ¶ (£million)	Cumulative gain in costs 2007-2050 (£million)	Cost of intervention (£million)	Net cost ¥ (£million)
1	2-19	-0.03 kg/m^2*	0	£ 47.9	£ 491.6	£ 75 †	− £ 417
1	2-19	-0.03 kg/m^2*	80%	£ 20.5	£ 143.1	£ 75 †	− £ 68
2	7-13	-0.1 kg/m^2	0	£ 50.6	£ 518.8	£ 551 ‡	£ 32
2	7-13	-0.1 kg/m^2	80%	£ 22.1	£ 155.1	£ 551 ‡	£ 396
3	≥20	-0.06 kg/m^2**	0	£ 47.1	£ 489.9	£ 75 †	− £ 415
3	≥20	-0.06 kg/m^2**	80%	£ 20.4	£ 142.6	£ 75 †	− £ 68
4	23-29	-1.0 kg/m^2	0	£ 45.8	£ 469.6	£ 1,921 §	£ 1,451
4	23-29	-1.0 kg/m^2	80%	£ 21.4	£ 151.2	£ 1,921 §	£ 1,770

*Approximate change in BMI associated with 0.2% reduction in BMI in childhood and adolescence, based on mean BMI from Health Survey for England data; ** Approximate change in BMI associated with 0.2% reduction in BMI at age 20-30 years, based on projected BMI distribution in 2017; † Based on original Department of Health budget for the Change4Life campaign; ‡ Based on estimated cost per child of MEND 7-13 of £415.77,[380] and number of overweight and obese children aged 7-13 years in 2007; § Based on projected number of overweight and obese adults aged 23-29 years in 2017 (n=4.6 million people) and assumed cost of £415.77 per person (same cost as in childhood); ¶ Gain in costs calculated as difference between obesity-related healthcare costs with no intervention and obesity-related healthcare costs associated with the intervention scenario; ¥ Net cost calculated as cumulative gain in costs (undiscounted) minus cost of intervention, negative number indicates net saving.

7.4 Model assumptions and comparison with observed data

As an exploration of the suitability of the NHF model for estimating childhood obesity burden and intervention effects, key model assumptions underlying the projections were examined. Simulations were run with input parameter values that were selected to approximate the BMI distributions and trajectories observed in the British National Birth cohorts, and the model output was compared with the observed cohort data.

Implementation of changes to the model which required additional programming, such as coding the simulation model to write individual-level data to an output file, was carried out by Martin Brown from the NHF modelling team. I prepared the baseline data specifying the cohort structure, performed the simulations, and managed and analysed the output data.

7.4.1 Methods

The face validity of model assumptions was examined by comparing model output with observed data from the British National Birth Cohorts. BMI centile trajectories of individuals in the three birth cohorts were plotted, and movement between weight categories was examined by cross tabulating weight categories at different ages (childhood, adolescence and adulthood). A weighted kappa statistic for agreement between weight categories at different ages was calculated, such that staying in the same weight category between time points counted for perfect agreement, and movement across one category, e.g. normal weight to overweight, or obese to overweight, counted for 50% agreement.

Scenarios corresponding to the population structure and BMI trajectories in each of the three birth cohorts were fitted, and the disease probabilities associated with different patterns of overweight over the life course were analysed. Population size and sex-age structure were taken from each of the three birth cohorts (as described in Chapter 5.3) to define the initial population. Observed BMI histories were assigned to the simulated individuals; the model required annual BMI data, therefore BMI values between any two measurements were interpolated assuming linear change. The model assumptions were constrained by specifying that age-, sex- and BMI-specific disease probabilities should be the same in all three cohorts, and probabilities were assigned as a function of the individual BMI histories. Disease simulations were modelled to start at the age of first BMI measurement and end at the last observed measurement. For NSHD, this period was between 1948 and 1999, for NCDS between 1965 and 2000, and for BCS70 between 1980 and 2004.

The Health Outcomes micro-simulation model Version 9.6.1 was used. For the purposes of these analyses, the model was programmed to produce individual-level output as a text file, displaying the annual BMI and assigned probability of disease for each simulated individual. Individual-level data allowed analysis of different BMI histories and their relationships with

disease probabilities. Overweight and obesity were defined using IOTF criteria in childhood and adolescence and the WHO criteria in adults, and eight overweight patterns were defined as described earlier in the thesis (see Chapter 4.7.2), using the same ages to define life stages. The main comparison of interest was of mean probability of disease at the end of the simulation period against the observed proportion of disease at the same age (last-follow-up) for each pattern of overweight in childhood, adolescence and adulthood in the three cohorts. Output text files were converted and analysed in Stata 12.

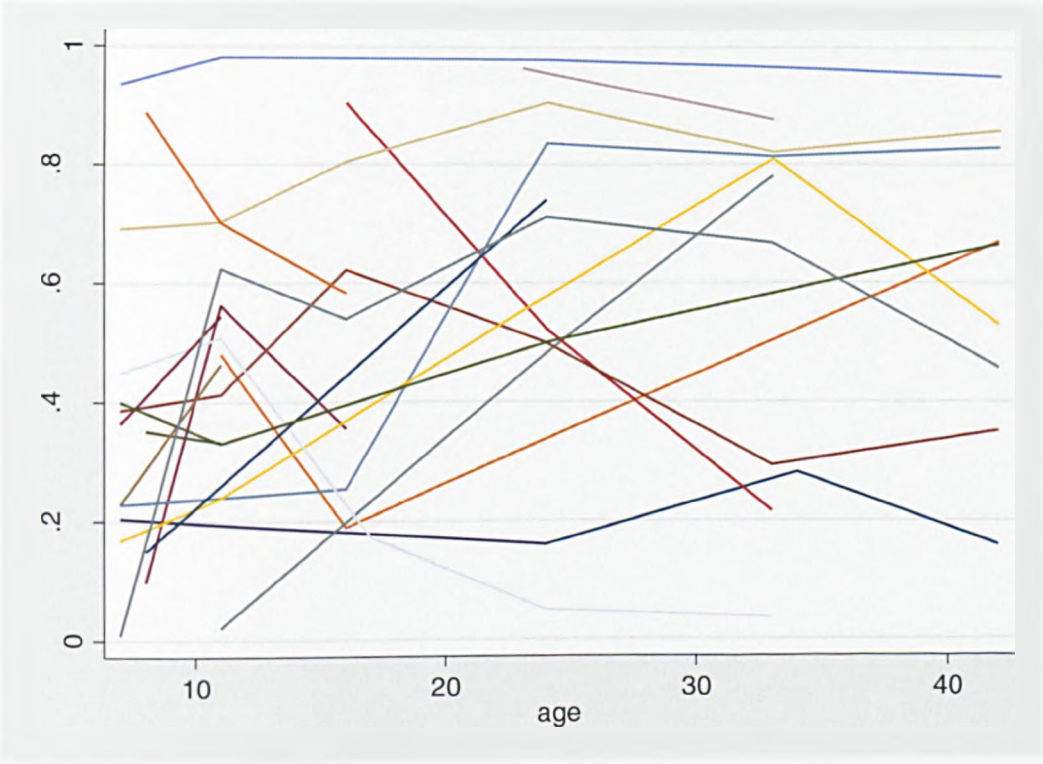
Direct comparisons of disease probabilities in observed data with estimated probabilities were limited by the different ways in which outcomes were defined. In the observed cohort data, self-reported outcomes were used to estimate probabilities of ever having had a condition, while the input data used in the model were based on objectively measured outcomes. For these reasons, comparisons between model outputs and observed data were based on graphical plots and largely qualitative descriptions, focusing on general patterns and trends rather than using quantitative techniques such as goodness-of-fit tests, which have been recommended for validation of model components. [402]

7.4.2 Results

BMI trajectories

The simulation model specified that individuals stay on the same BMI centile over the duration of the simulated period. Examination of cohort data showed that centile crossing in the British National Birth Cohorts was substantial, particularly pre-adulthood (example from NCDS cohort presented in Figure 7-4). Furthermore, analyses showed that a substantial proportion of individuals moved from overweight to normal weight, and between overweight and obese categories between childhood and adulthood. For example, in the NCDS cohort, 24% of individuals that were overweight and 12% that were obese at age 7 years were normal weight at age 42 years, while 29% of cohort members that were obese at age 7 were in the overweight category at age 42. The weighted kappa statistic for agreement between weight categories, was 0.01, indicating poor agreement. In contrast, when a simulated cohort was generated to have the same BMI distributions at ages 7, 16 and 42 as the NCDS cohort (with linear interpolation between time points), but did not allow for movement between centiles, there was no downwards movement between weight categories due to the rising prevalence of overweight and obesity with age; all individuals that were overweight at age 7 were overweight or obese at age 42, while all individuals that were obese at age 7 were obese at age 42. The weighted kappa statistic for agreement between child and adult weight categories was estimated at 0.454 for this simulated cohort, much higher than observed in the actual cohort data. Similar patterns were observed when agreement between adolescent and adult weight categories was examined, and when analyses were repeated for the 1946 and 1970 cohorts.

Figure 7-4: BMI centile crossing in twenty randomly selected cohort members in NCDS



Overweight patterns

For the next stage of model validation, the observed BMI trajectories in the three British birth cohorts were incorporated into the simulation model to reproduce the movement of individuals across BMI centiles and weight categories. The distribution of patterns of overweight through childhood, adolescence and adulthood in simulated individuals was similar to the distribution in the observed data (Table 7-5). The proportions of individuals with overweight in childhood were slightly overestimated and the proportions with overweight in adolescence were underestimated in the simulated population, which can be explained by the linear interpolation between BMI measurements that was used to estimate missing data.

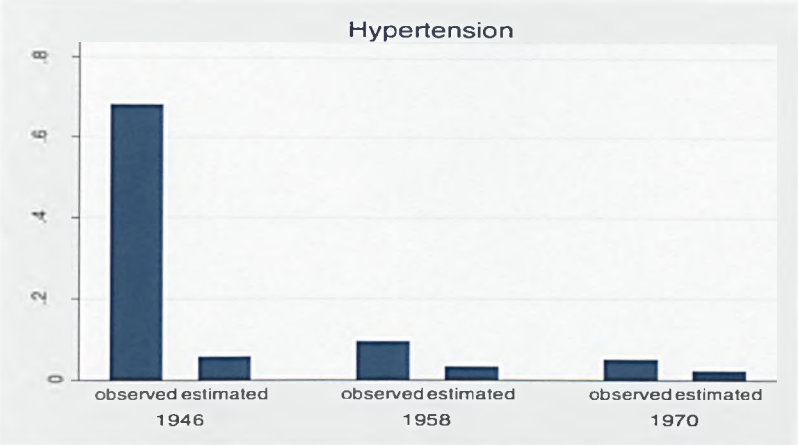
Table 7-5: Distribution of overweight patterns in British National Birth Cohorts and in simulation

Overweight pattern	%	
	Cohort	Simulated population
Never overweight	75.0	71.8
Childhood only	3.3	6.2
Adolescence only	3.5	1.9
Adulthood only	10.0	11.3
Childhood + adolescence	1.4	1.5
Childhood + adulthood	1.1	1.9
Adolescence + adulthood	3.4	2.3
Persistent overweight	2.3	3.0

Disease probabilities

Annual probabilities of disease for the simulated individuals were examined. Overall, the estimated disease probabilities at the end of each projection period had the expected distributions, with hypertension being the most prevalent condition, and stroke and cancers being relatively rare. Simulated disease probabilities also showed the expected age-dependent trends, with the lowest probabilities of disease in the youngest cohort (1970) and the highest probabilities in the oldest cohort (1946). However, the simulated disease probabilities in years 1999, 2000 and 2004 did not generally provide a good fit to the data in corresponding years in NSHD, NCDS and BCS70, respectively. The model simulated lower probabilities of all outcomes, and estimates were notably lower for hypertension, gallbladder disease and arthritis. However, there was evidence of a cohort effect, with improved fit to the data for more recent cohorts. For example, the probability of hypertension was 42% lower in the simulated 1946 cohort than in the observed data, compared to 6% lower in the 1958 cohort, and 3% lower in the 1970 cohort (Figure 7-5). The same trend was observed when ratios of observed to estimated disease probabilities were compared, to account for the lower prevalence of disease in younger cohorts. The respective figures for coronary heart disease were 4%, 0.5% and 0.4%, and 1.5%, 0.4% and 0.3% for type 2 diabetes.

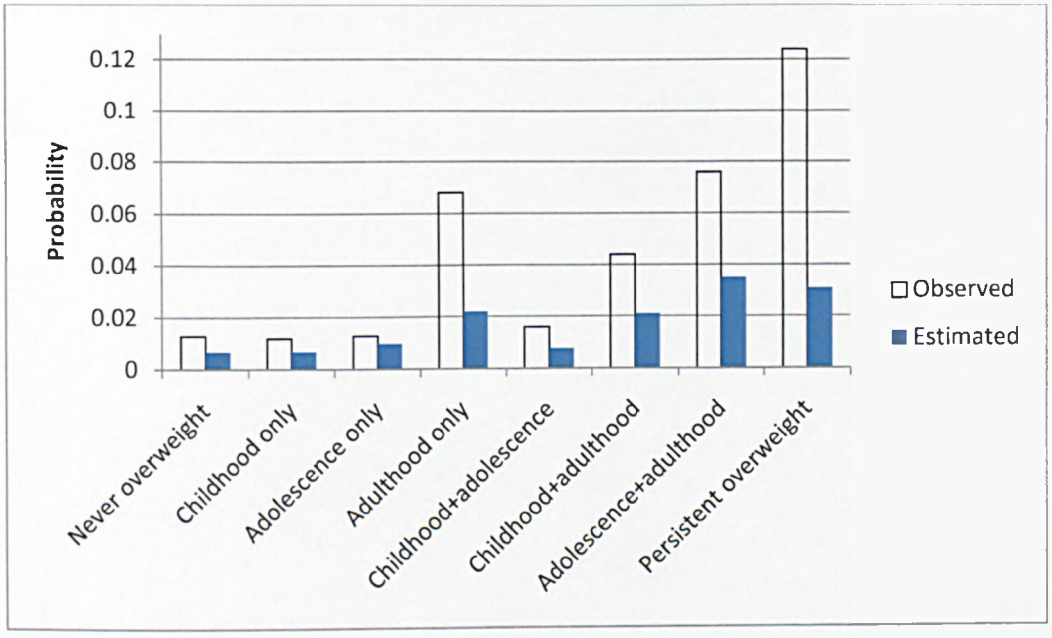
Figure 7-5: Observed and simulated probabilities of hypertension at the end of the simulation period in 1946, 1958 and 1970 cohorts



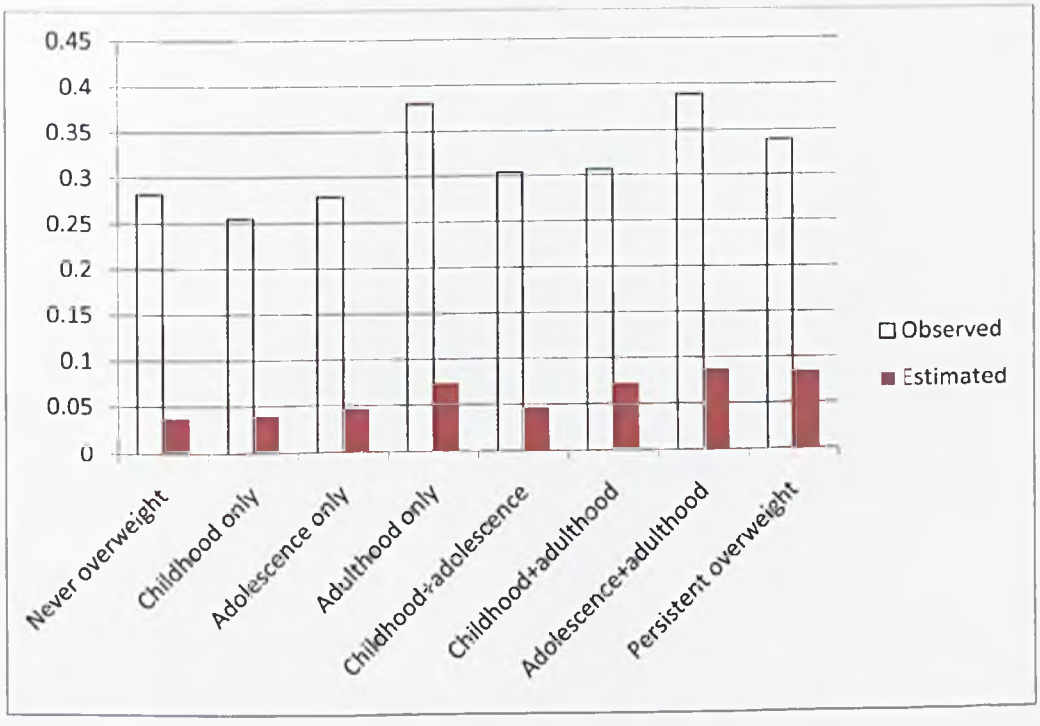
Associations between overweight patterns and disease

The associations between overweight patterns and disease probabilities from the simulation showed a similar pattern for all outcomes; the lowest probabilities were associated with never overweight or overweight in childhood and/or adolescence, with similar probabilities observed for both patterns of overweight. Higher probabilities were associated with exposure to obesity in adulthood. A cumulative effect was observed for hypertension and type 2 diabetes outcomes; higher probabilities for these outcomes were associated with overweight in adolescence plus adulthood and persistent overweight patterns, compared to obesity in adulthood only, although the effect of persistent overweight on type 2 diabetes was not as apparent as in the observed data (Figure 7-6). The effect of persistent overweight was not observed for CHD, although the increased risk associated with obesity in adulthood was evident, and probabilities associated with all overweight patterns were small.

Figure 7-6: Comparison of observed and simulated probabilities of a) type 2 diabetes and b) coronary heart disease, associated with different patterns of overweight in 1946, 1958 and 1970 birth cohorts



a)



b)

7.4.3 Summary of comparison with observed data

The analyses in this section showed that individuals do not stay on the same BMI centile over time as assumed in the simulation model, and that overweight and obese children may become normal weight adults. Analyses of more recent cohorts, with higher prevalence of overweight and obesity in youth, have shown that there is still some degree of centile-crossing and movement between weight categories. For example, data from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort of more than 6,000 children born in 1991-1992 showed that 21% of children who were overweight at age 7 became normal weight by age 11.[403] This is relevant to understanding the future burden associated with childhood obesity because, as indicated by the analyses in Chapter 6, overweight history may be an important risk factor for some outcomes in adulthood, notably type 2 diabetes. However, these analyses also showed that exposure to overweight in childhood and/or adolescence only was associated with comparable disease risks as never being overweight, therefore it may not be necessary to model this downwards movement in weight categories.

The estimated disease probabilities from simulations provided a poor fit to historical data. The poor fit to data may be explained in part by data validity issues. The disease data used in this thesis were valid for the years 2004-2010 (see Table 7-1), therefore use of these data for projections outside of these years may have limited validity. The cohort trends indicated that the model parameters produced estimates of disease risk that were more accurate for more recent cohorts, and were in line with what is known about recent trends in the incidence of cardiovascular diseases and their risk factors. For example, analyses of global data have shown that between 1980 and 2008, systolic blood pressure fell by more than 2 mm Hg per decade among men and women in Western Europe, despite increasing BMI in the population, [404] accounting for a reduction in age-standardised hypertension and cardiovascular disease burden.[405] As expected given these trends, results in this chapter showed that current disease input data simulate a much lower burden of hypertension and cardiovascular disease than is observed in historical cohorts. The trend towards more accurate estimates in younger cohorts indicates that the model may be suitable for predicting disease risk in more contemporary cohorts. A model which is able to predict future trends in the population is not necessarily informative about what happens to individuals in past populations, as these populations are likely to be different in terms of their characteristics and disease risk. The problems of data validity arising from differences between historical and contemporary populations are a central issue for long-term modelling exercises, and an important consideration when interpreting estimates from such projects. However, the main benefit of this kind of comparison between projection estimates and existing data is that it provides some empirical basis on which to evaluate the model output, and identify where the main limitations may arise. True predictive validation of the model would require waiting until the end of the projected time period and

comparing the predictions of the model with observed data; although short term projections could reasonably be validated in this way, the usefulness of the model for predicting long-term future scenarios, which are the main outcomes of interest with regards to childhood obesity, would be diminished with this approach due to the lag-time involved. By examining model assumptions and parameters against historical data, we are able to assess whether the model produces reasonable or expected results over long time periods, and gives some indication of the usefulness of estimates derived from this approach.

7.5 Summary and implications

Projections of future disease burden for a contemporary cohort of children and adolescents in the UK have considered the potential implications of the current childhood obesity epidemic for disease and healthcare costs by 2050. A continued increase in obesity prevalence was projected to result in an extra 36,000 cases of cancer, 118,000 cases of CHD and stroke, 16,000 cases of arthritis, 768,000 cases of type 2 diabetes, and 447,000 cases of hypertension in the year 2050. These increases in obesity-related diseases were associated with excess healthcare costs in the region of £1.1 billion a year, with hypertension and type 2 diabetes accounting for the majority of these costs. This is in relation to an estimated cost of £5.5 billion associated with increased overweight and obesity in the whole population in 2050,[45] indicating that overweight in the current cohort of children and adolescents could account for around one fifth of the obesity-related burden in 2050. These projections also demonstrated the changing nature of the burden over the projection period, with the earlier onset conditions, type 2 diabetes and hypertension, being important causes of obesity-related ill health throughout adulthood, and cardiovascular diseases and cancer becoming increasingly important in late-adulthood. These estimates are based on recent trends in BMI distribution nationally, but close monitoring of trends in obesity prevalence will be important over the next few years, to gauge whether obesity in the population is likely to level off faster than would be indicated by recent trends.

The potential health burden and healthcare cost savings associated with different intervention scenarios were explored. These projections indicated that a 0.2% reduction in BMI in the whole child and adolescent population in 2007, equivalent to around 0.1kg weight loss for an average adolescent (based on BMI distribution from HSE data), could result in reductions in cases of type 2 diabetes, hypertension and cardiovascular disease, and around a 5% reduction in associated healthcare costs. The largest reductions in disease prevalence and costs were associated with an intervention targeted at overweight children, in a scenario modelled on the MEND programme, in which all of the target population benefited from the intervention. Confidence intervals could not be generated for these cost estimates, therefore it is possible that the gains in costs were not different; previous studies that have used the NHF model have

indicated that there is a great degree of uncertainty associated with these estimates.[163] However, bearing this uncertainty in mind, the projections are useful for indicating general trends and patterns. These examples illustrate the potentially large cost savings associated with small, population-wide reductions in BMI, which could be implemented at lower cost than more intensive, targeted interventions, and at much lower net costs. However, it is important to note that the effectiveness of the Change4Life campaign in terms of BMI reduction has not been demonstrated in any studies, and this projection is based on a hypothetical scenario. Furthermore, it is unlikely that any intervention would benefit all members of its target group, as there would be individuals that could not be reached, others that would opt not to engage with the intervention, and some that would not respond to or benefit from the intervention. These factors combined would reduce the effectiveness of the interventions, and lead to lower gains in health burden and associated costs. In addition to this, among those that did participate in a given programme, there may be differential effects on BMI, with some groups of individuals benefiting more than others. For example, differences by degree of overweight, ethnicity, sex, SEP or age, or the skills of the individuals involved in delivering the intervention. Individuals who have a smaller response to an intervention may require more intensive approaches or multiple interventions, which are likely to be associated with a larger cost.

Most data on effectiveness of obesity interventions in children and adolescents come from studies with short-term follow-up, therefore the estimates of sustained intervention effects in this chapter are likely to represent optimistic scenarios. The modelling of the two weight regain conditions and comparison of the associated savings for each intervention highlight the importance of sustainable intervention effects for long-term benefits. Intervention scenarios which accounted for weight regain were associated with much smaller gains in health burden and costs. Scenarios which incorporated the effect of weight regain following a successful intervention are likely to reflect a more realistic situation, as studies of long-term weight loss maintenance have shown that most individuals regain some or all of the weight loss within a year. The cumulative gains in costs over the projection period ranged from £143 million to £155 million for the four intervention scenarios with weight regain, with larger net costs (or lower net savings) associated with each scenario. As with intervention effectiveness, the extent of weight regain may also vary according to an individual's characteristics or environment. For example, in the case of child weight management, it has been demonstrated that children with obese parents begin to regain weight sooner than those with non-obese parents after similar weight loss in the first 6 months, and those with non-obese parents were more likely to maintain their weight loss after several years.[406] This long-term perspective leads to consideration of the potential intergenerational effects of interventions; parental behaviours and the home environment are known to be important determinants of childhood overweight status,[407] therefore changes in lifestyle behaviours and social norms as a result of effective interventions

could lead to additional benefits in subsequent generations, with few additional costs. Sustainability of effects and the potential intergenerational implications are important considerations when evaluating interventions. Future studies of interventions should aim to report on long-term outcomes, and also provide detailed information on differential responses to interventions where these occur. This would enable the modelling of group-specific effects, and determine where different interventions would have the greatest impact.

One limitation of the modelling used in this chapter is that health burden and intervention effectiveness were considered only in terms of BMI change. It may be possible for an intervention to lead to positive changes in behaviour or other risk factors which impact on disease risk, without a measureable effect on BMI. On the other hand, an intervention may lead to reductions in BMI, but these may have to be balanced against adverse effects that lead to increased morbidity. Anti-obesity drugs provide examples of such effects; in January 2010, marketing authorisations for sibutramine, a drug shown to be effective in reducing overweight, were suspended across Europe following concerns about increased cardiovascular disease events in adults at high risk of heart disease.[408] One way in which the NHF model may be developed in the future is to model the effects of different risk factors acting simultaneously on disease risk. For example, a model for estimating cardiovascular disease burden may include the various components of the metabolic syndrome, and the effects of changing any single risk factor versus changing multiple risk factors may be explored. However, the data requirements for this approach would be substantial, involving detailed information about the relationships between these risk factors and their associations with cardiovascular disease risk over the life-course, which may not be available.

These projections have focused on direct healthcare costs and have not included productivity losses, which are likely to make up a large proportion of the cost burden associated with childhood obesity.[409] As described in Chapter 2, in addition to the concurrent productivity losses such as inability to work due to illness, there may be long-term productivity costs associated with overweight in childhood, such as lower income and poorer employment prospects. Furthermore, there may be other diseases or limiting conditions with less well established associations with obesity that will be shown to present an additional burden in the future, such as common mental disorders.[410] Consequently, the estimates of disease and cost burden in this chapter may be considered to be conservative. Although exploration of different intervention scenarios has indicated reductions in disease burden and gains in healthcare costs associated with intervention effects, it is difficult to state whether there are likely to be overall cost savings at the population level, as individuals who do not become overweight may be associated with other costs over their lifetime. For example, projection over a longer period of time may show varying health burden and medical costs at later ages, as late-onset diseases become more prevalent and mortality has a larger impact on the population.[160 411-412] Rates of

survival associated with obesity-related diseases may also change as a result of medical advances; improvements in survival would extend the number of years of life lived with a condition and contribute further to healthcare costs, particularly in the situation where improved survival is the result of a costly intervention. Predictions of future BMI distributions can also vary substantially according to the data points used. This issue was illustrated in a report by the NHF modelling team, which examined the effect of additional HSE data on estimated obesity trends for children aged 2-11 years. [382] This report compared projected obesity prevalence in 2020 based on data from 1995 to 2004, to projections based on data from 1995 to 2007 (three additional data points), and showed that predicted prevalence decreased from 16% to 12%. This finding reflects the recent levelling off in childhood obesity prevalence in the UK. [60]

Previous studies of long-term childhood obesity burden have linked childhood overweight to adult overweight, and then linked adult overweight to health outcomes; they have not included potential effects of overweight pre-adulthood on the outcome. For example, one study by Wang et al incorporated the association between overweight at age 16-17 years to overweight at age 40 (fixed proportions of individuals in each weight category in adolescence became obese adults), and linked this to the health consequences and medical costs associated with adult overweight after the age of 40, in the US population.[413] Using this model, a 1% reduction in prevalence of overweight and obesity in adolescence was associated with 52,821 fewer obese adults, savings in lifetime medical costs of $0.5 billion, and a 0.006 per capita increase in QALYs. Compared to this approach, a key advantage of using a micro-simulation model is that it is able to incorporate the effect of overweight history on disease risk, which has been shown to be an important consideration for some diseases (Chapter 6). The use of annual disease probabilities in the micro-simulation model allowed a cumulative effect of exposure to overweight and obesity on increased disease risk to be modelled, as demonstrated in section 7.4.2.

The potential impact of interventions has been explored by modelling effectiveness in terms of changes to BMI distribution. The findings in this chapter indicate that interventions targeted at overweight children to reduce BMI could result in reductions in disease prevalence and healthcare costs over the projection period, but may be more expensive than less intensive, population-wide interventions. Comparison of the NHF model assumptions against data from the three national British birth cohorts showed that the issue of data validity is likely to be an important consideration in interpretation of results. The model showed increasingly improved fit to disease data in younger cohorts, suggesting that the disease data used in the model are likely to be more appropriate for contemporary cohorts, and projections of future disease burden. However, it is difficult to predict how associations between obesity and disease may further change in the future, as advances in science, medicine and technology, as well as social changes, could impact on disease incidence and survival.

Despite these limitations, quantification of the disease burden and costs associated with childhood obesity creates a starting point from which to discuss service planning and resource allocation, and provides an important impetus for action. These data projections indicate that increasing prevalence of obesity in the current child and adolescent population could have a substantial impact on health burden and its associated costs over the coming decades. The projections also highlight the potential long-term health and economic benefits of successful interventions to reduce BMI in childhood versus interventions in adulthood, providing an initial basis for decisions about future research directions and policy priorities.

8. DISCUSSION

This chapter begins with a discussion of the strengths and limitations of the study, and goes on to provide a brief summary of the main findings of the thesis. This is followed by a consideration of these results in the context of the relevant literature presented in Chapters 2 and 3. Finally, the implications of the findings for approaches to obesity prevention and treatment and directions for future research are considered.

8.1 Strengths and limitations

This study has a number of strengths and limitations, which will have an impact on the way in which the results are interpreted. Some of the specific issues have been addressed in detail in the summary of each results chapter, but more general considerations and their implications for the thesis are described here.

Type 1and Type 2 errors

In the main analyses of the birth cohort data, multiple statistical tests were carried out due to the large number of outcomes and different exposures of interest. Carrying out a large number of tests in this manner will introduce the possibility of Type 1 (alpha) errors, where the null hypothesis is mistakenly rejected. In an attempt to minimise Type 1 errors and avoid data dredging, only those variables and models that were specified *a priori* based on the literature, were examined. Disease outcomes which had been shown to be associated with overweight in adulthood in previous studies, but had not necessarily been assessed in relation to childhood overweight were included to explore the potential life-course effects of exposure. Furthermore, interpretation of the findings was not based on single estimates of association, but on the whole body of results. For example, single positive associations which were anomalous in the context of other results for a given outcome, were treated as possible chance findings.

Type 2 (beta) error, failure to reject a null hypothesis when it is false, was an important consideration in this study due to the small numbers of individuals that were obese in early life and low prevalence of some outcomes, such as coronary heart disease and cancers. The pooling of data from three cohorts with similar data collection points and comparable target populations, was a way to increase study power. Overweight and obese categories in childhood and adolescence were combined to form a single exposure category, in an attempt to further maximise study power. Some outcomes that were initially selected for analysis, on the basis of the existing literature, were later excluded due to small numbers. However, the power calculations, based on initial analyses of the cohort data, indicated that the study is likely to have been inadequately powered for the less prevalent outcomes, even before accounting for the

additional covariates that were included in the final models. Consequently, some associations may not have been detectable in these analyses.

Selection bias

Selection bias is an important consideration in cohort studies. At baseline, the participation rates for the three cohorts ranged from 95.9% to 98.8%. The high participation rates indicate that the baseline samples are likely to be generally representative of the target populations, and this has been supported by comparison of the cohort characteristics with census data.[252-254] The main analyses were restricted to those cohort members with BMI data in childhood and adolescence, and data on disease outcomes in adulthood. Due to the combined effects of attrition and incomplete data, the possibility for selection bias is high. The highest rates of attrition in all three cohorts occurred in early adulthood, when cohort members became more mobile and name changes became most frequent. However, large efforts have been made to maintain contact with cohort members and to trace lost cohort members, and response rates of more than 60% have been achieved in recent follow-ups. Differential losses to follow-up between those who were overweight in childhood and those who were not overweight could introduce bias; it is known that cohort members from lower socioeconomic positions and those from ethnic minority backgrounds were more likely to have been lost to follow-up than others, and these groups are also more likely to be overweight or obese and to be at increased risk of the chronic conditions analysed in this study. If cohort members that were obese in childhood were also more likely to suffer ill health in later life and to leave the study, their exit from the cohort would underestimate the effect of childhood overweight on disease risk. The effects of missing data for some variables were examined by comparing results from complete case analyses with those incorporating last observation carried forward data, which showed that the direction and patterns of associations were similar under the two scenarios.

Measurement bias

Accurate measurement of exposures and outcomes is necessary to ensure that bias is minimised and findings are valid. Measurement bias is not likely to have been an issue for measures of weight and height for BMI in childhood and adolescence, and in adulthood in the NSHD 1946 cohort. However, the use of self-reported weight and height in adulthood in the 1958 and 1970 cohorts is likely to have introduced bias, as previous studies have shown systematic underestimation of BMI when self-reported data are used. To address this potential bias, BMI from self-reported weight and height was adjusted, based on the findings of a validation study.[329] This adjustment indicated that the underestimation of BMI due to self-report of weight and height did not bias the results, and effect sizes were very similar before and after adjustment (Chapter 6, Table 6-9).

The analyses presented in this thesis have focused on childhood overweight and its combinations with adult BMI status as categorical exposures. This categorisation may have resulted in loss of efficiency and power compared to treating BMI as a continuous exposure. [414] There is also the potential for misclassification. However, there are advantages to this treatment of the data. First, presenting risks relative to a reference group such as those who have never been overweight is easier to interpret and to communicate to the wider population; using these conventional categories, individuals and health professionals can identify the implications of weight status and history of overweight for health risk. The use of international cut-offs for overweight and obesity also allows the analyses to be replicated and compared across populations. Second, as the association between BMI and health outcomes is non-linear,[8] treating BMI as a continuous exposure could mask what is happening at the upper end of the distribution, at which public health efforts and resources are targeted; focussing on the upper end of the distribution allows us to identify what is happening among those with this more extreme phenotype.

The use of BMI as a marker of adiposity in children also has its limitations. BMI does not account for differences in body composition, which may influence the association between adult obesity and disease outcomes. For example, studies have indicated that differential gain in muscle mass and fat in childhood may be an important contributor to later cardiovascular outcomes.[374] Therefore BMI may not adequately capture the exposure (adiposity). However, as described previously, BMI is highly correlated with adiposity and is a reliable measure in large population-based studies.[41-42]

Another source of measurement bias may arise from the use of self-reported disease data as the outcome measures. As described in the methods, the validity of self-reported data varies for different conditions. This may be due to errors in recall, misdiagnosis, or undiagnosed conditions. In general, self-report of chronic disorders and acute-onset diseases tend to show good agreement with medical records. Bias is likely to be an issue where there is differential misreporting or misdiagnosis between groups, such as under-reporting of conditions among obese compared to non-obese individuals. [351415] Efforts were made to avoid missing cases and maximise information on health outcomes by including information on medical supervision for conditions and recent hospital admissions, as well as long-standing illnesses. If under-reporting of conditions is more common among overweight or obese participants than healthy weight individuals, the effect may be underestimation of the association between overweight and the disease.

Regression dilution bias

The use of just one BMI measurement as an indicator of adiposity over a period of the life-course may introduce regression dilution bias. Regression dilution occurs due to random

fluctuations in a variable, which may be due to measurement error or real deviations from usual levels of the exposure, e.g. temporary weight gain. This is likely to be especially relevant for those individuals who move in and out of the overweight categories over the three life-stages. Individuals who exhibit changes in weight status are likely to have less extreme overweight than those individuals whose overweight status is more entrenched, and are classified as being persistently overweight (as demonstrated by the higher mean BMI among those cohort members with overweight at great number of life stages). The effect of regression dilution bias is usually underestimation of the association between usual exposure levels and disease. [416]

Survival bias

Survival bias arises when an exposure which is associated with an outcome also affects the chances of an individual being included in a study, for example by shortening survival. Survival bias was not considered to be a major issue in these cohorts, as all members were recruited at birth (or in the case of some immigrants, in childhood), and data were analysed for ages at which mortality from the outcomes of interest was relatively rare. Mortality before the oldest ages considered in this study (53 years) is uncommon. For example, in England and Wales, the aggregate mortality rate for 2001-2006 was 91 per 100,000 among people aged 1-54 years (from ONS data). However, there remains the possibility that cohort members may have left the cohort for other reasons that are associated with both overweight and disease outcomes, leading to a biased sample.

Reverse causality

The potential for reverse causality was addressed by excluding individuals that reported any of the outcomes or related conditions pre-adulthood. One exception for this was for asthma outcomes, for reasons described in the methods (Section 4.5.1). A possible mechanism for reverse causality in this relationship is that asthma may inhibit exercise and other forms of physical activity, conceivably leading to reduced levels of physical activity, a more obesogenic lifestyle, and increased overweight in individuals with the condition. However, other longitudinal studies have indicated that overweight precedes the onset of asthma in adolescence.[97] In this thesis, there was no strong evidence for an association between overweight in childhood and adolescence and asthma, therefore reverse causality was not considered to be a major issue in the interpretation.

Confounding

Confounding is an important limitation in population-based cohort studies of this nature, as cohort members that are overweight or obese are also likely to differ from those who are healthy weight in ways that are important in respect to disease. Potential confounding factors were identified from the literature, and these were controlled for in the analysis by including them as

covariates in the final models. Key confounding factors that commonly affect studies of overweight and later disease include socio-economic position, ethnicity, and smoking status. Measures of socioeconomic position were based on occupation, which was classified using the Registrar General's Classification of Occupations. This classification was selected as it has been applied to all occupation data across the three cohorts, and therefore allowed comparison across studies and data harmonization for pooling. A limitation of occupation-based measures in the context of these three datasets is that the profile of occupation types has changed over the years, with manual jobs having declined, and skilled jobs having become more prominent. However, despite the change in the distribution of occupations, the classification of jobs has not changed substantially over the time period considered here.[417] There were some differences in the patterning of overweight across the three cohorts by social class at birth (Section 5.7), but associations of overweight with social class in adulthood were similar in the three datasets. A sensitivity analysis excluding the relatively small proportion of ethnic minority cohort members indicated that there was no observable effect of combining white and non-white groups in the analysis. Further investigation of ethnicity-specific effects was limited by the small number of ethnic minority individuals in the dataset. Smoking status has a complex relationship with overweight and health, as those who smoke are less likely to be overweight than those who have never smoked or those who have smoked previously, but smoking is an important risk factor for most chronic diseases. Some of those who give up smoking may do so because of ill health but go on to gain weight as a result, therefore the associations between overweight and later disease outcomes may be confounded by this relationship. An attempt to incorporate smoking history was made by treating ex-smokers as a separate exposure category, but information on reasons for giving up smoking were not available. Residual confounding due to measurement error or unmeasured confounding factors is a problem associated with observational study designs, which may have affected this study despite efforts to assess or account for the most likely confounders.

Generalisability

The data used in the main analyses are from cohorts that were born more than four decades ago, which limits the generalisability of the findings to the current childhood obesity epidemic and its implications for the future. These older cohorts are likely to be different to current cohorts of children in several ways. For example, the 1946 cohort represents babies born just one year after the Second World War, who experienced post-war food rationing during the first years of their lives. Factors such as maternal smoking and infant feeding have also changed over time; in BCS70, 35% of mothers smoked during pregnancy (from data), compared to just 12% in 2010,[418] while breastfeeding, which has been shown to be associated with lower risk of obesity in later life,[419] declined between the 1940s and 1980s, but has increased again in recent years.[418] These early life exposures may have important implications for long-term health,[182] and secular

changes in their distribution limit the generalisability of findings from any given time period to another. There are also likely to be important differences in lifestyle behaviours that are implicated in obesity and related health outcomes. For example, physical activity levels among children have shown a secular decline over recent decades, while sedentary behaviours have increased.[420] Crucially, there are key differences in the prevalence and severity of overweight and obesity between contemporary and older populations; obesity prevalence in childhood and adolescence ranged from 0.5- 2.4% in the birth cohorts used in this thesis, compared to 7-10% today.[45] Contemporary child populations are also experiencing more extreme obesity, and at younger ages than in previous generations. Results from studies of older cohorts cannot explore the effects of these aspects of the childhood obesity epidemic or changing lifestyle behaviours on long-term health. However, the limitations of these cohorts have to be balanced against the wealth of data that they provide and the advantages of the study design.

First, these are national cohorts which cover the whole of Great Britain, providing a huge breadth of coverage. The cohorts are not ethnically representative of Britain, with fewer non-white cohort members than in the general population, but in other respects are comparable to census data.[252-254] They can therefore be considered to be reasonably representative of the target population. Second, in order to study the effects of childhood and adolescent exposures on chronic diseases, a long period of follow-up is required due to the late-onset nature of these conditions. Analysis of younger cohorts that are more comparable to contemporary populations is limited by the small numbers of cases that arise in them. While a number of studies have assessed cardiovascular risk factors,[121] fewer have assessed clinically relevant disease end-points. Third, the similarities between the three cohorts in terms of their target populations, the data collected and the frequency of follow-up mean that the datasets can be harmonised and analysed using the same models. They have all collected detailed information on socio-demographic and lifestyle characteristics at several points, which allowed assessment of the effect of important confounders. Cross-cohort comparisons and tests for an interaction effect by cohort indicated that the pooling of data was appropriate, despite the differences in BMI trajectories and ages at follow-up. Other studies that have adopted similar approaches to pooling data have been limited by differences among the cohorts in the availability of variables, such as SEP.[174] The great advantage of pooling data from these three cohorts is that study power has been increased without loss of information.

Data validity

The main limitations of the modelling aspects of this thesis relate to data validity issues, as described in Chapter 7. Disease and BMI distributions, and the associations between them, may change as a consequence of technological, medical or social changes, and data on the long-term effectiveness of obesity interventions are lacking. There are inherent limitations to this kind of

projection exercise, due to the strong assumptions on which they are based. Relatively small changes in any of these assumptions can produce vastly different results. For example, inadequate adjustment for variation in relative risks of disease by age and sex can bias estimates attributable to obesity.[421] There have been few attempts to model the long-term health consequences and healthcare costs associated with childhood obesity for these reasons. Cross-cohort comparisons of the fit of model estimates to cohort data indicated that the fit of the model improved for younger cohorts, therefore it is proposed that the model is suited for estimating health outcomes in the current population. Furthermore, unlike other models of childhood obesity burden that have been described previously, the model used in this thesis incorporated the cumulative effect of exposure to overweight over the life-course. Estimates of obesity intervention effects modelled on existing interventions provide a starting point for discussion of resource allocation and prioritisation for public health policy.

Summary

In this section, the strengths and limitations of the thesis have been described, building on discussions in previous chapters. Important limitations that need to be borne in mind when interpreting the findings are that selection bias may lead to a non-representative sample, and there may be measurement biases associated with outcome measures. It would be expected that these limitations would generally result in underestimation of the true effects. A wider limitation concerns the generalisability of findings from older cohorts to more contemporary populations. However, these limitations are balanced against the advantages of using cohort data with follow-up in childhood, adolescence and adulthood to investigate long-term outcomes from a life-course perspective.

8.2 Summary of findings

This thesis has examined the relationships between overweight and obesity in childhood and adolescence and long term health outcomes, and has explored the potential contribution of overweight in childhood to future health burden in the UK. The question of whether excess weight in early life contributes to future disease is important in light of the rising prevalence of childhood overweight. The answers to this question will help in our understanding of the implications of childhood obesity for future disease burden, and the impact that different interventions may have in mitigating these effects.

A systematic review of the literature revealed a gap in knowledge regarding the effects of obesity in childhood on adult health. In particular, the review highlighted the limitations of the methods that have been widely used to examine this topic. To address this evidence gap, pooled data from three cohorts were analysed, using methods designed to examine relationships between life-course exposures and later outcomes. The findings from these analyses showed

that overweight in childhood and adolescence was associated with increased risk of type 2 diabetes among obese adults, indicating that exposure to excess weight in childhood may contribute to long-tem risk, possibly through a cumulative exposure effect. There was weak evidence that overweight in childhood, adolescence and adulthood may also be associated with increased risk of CHD compared to obesity in adulthood alone. However, individuals that were overweight in childhood or adolescence but later became normal weight in adulthood did not have increased risk of these outcomes compared to those who had never been overweight. For the other outcomes examined in this thesis, there was little evidence for a contribution of overweight in childhood and adolescence to long-term risk.

Following on from these findings about the potential long-term effects of overweight in childhood and adolescence, it was of interest to know how overweight and obesity in the current child population may impact on health burden in the future, and to explore the potential effects of different approaches to obesity prevention in the population. Projections from a micro-simulation model showed that overweight and obesity in the current child and adolescent population could account for a fifth of all obesity-related healthcare costs in the year 2050. They also indicated that early interventions to reduce BMI in childhood may lead to reductions in health burden. The need for assessment of the long-term effectiveness and costs of interventions was highlighted.

8.3 The long-term impact of childhood overweight

The findings of this thesis indicate that overweight impacts on different health outcomes at different stages of the life-course, and that the relationship between overweight and health should be viewed with a long-term perspective in mind. This is illustrated by the cardiovascular outcomes that have consistently been shown to be associated with overweight in childhood and in adulthood. Overweight in childhood and adolescence may be an important risk factor for type 2 diabetes when combined with obesity in adulthood, while hypertension risk appears to be more affected by weight status in adulthood. Given the relationship between type 2 diabetes and cardiovascular disease, childhood overweight may also have an impact on long-term cardiovascular outcomes. For the other outcomes considered in this thesis, there were associations with overweight and obesity in adulthood, but effects of childhood overweight were not evident.

Compared to studies which have used standard adjustment for weight status in adulthood to determine the independent effect of childhood overweight on long-term health,[422] the approach adopted in this thesis has provided a different perspective on the role of childhood overweight, considering the more nuanced question of whether there is a contribution of childhood overweight to long-term outcomes. A study which used path analysis to examine the associations between BMI measurements at several points during childhood, BMI in adulthood,

and systolic blood pressure in a Danish dataset, indicated that there was no direct effect of BMI in childhood on systolic blood pressure, i.e. the relationship between childhood BMI and systolic blood pressure in adulthood was entirely mediated through adult BMI.[265] This study did not adjust for any potential confounders, and treated BMI and systolic blood pressures as continuous measures, therefore a direct comparison of results is difficult, but it lends support to the finding that weight status in adulthood contributes more strongly to hypertension risk than weight status in childhood. One previous study has assessed the relationship between overweight patterns from childhood to adulthood and cardiovascular risk outcomes.[174] This study found contrasting effects to those reported in this thesis, with an effect of persistent overweight being observed for hypertension but not for type 2 diabetes. Key differences of this study include a younger mean age at follow-up than the British cohorts studied in this thesis, and adjustment for different confounders (notably, data on SEP were not available). In addition, this study assessed overweight at two points of the life-course (childhood and adulthood), rather than the three stages used in this thesis. The contrasting findings indicate a need for further research to clarify these relationships, and investigation of different models of disease progression for these outcomes.

Overweight in childhood and adolescence in non-obese adults was not associated with increased disease risk compared to not being overweight in childhood or adolescence and non-obese in adulthood. Therefore the effects of persistent overweight from childhood through to adulthood on cardiovascular risk may be attributable to the duration of exposure to overweight rather than any long-term change attributable to childhood overweight. A similar finding has been reported in a previous study, which showed that cardiovascular risk in individuals that were overweight in childhood but normal weight in adulthood was similar to the risk in normal weight adults that had not been overweight in childhood.[174] Analysis of data from the Framingham Cohort Study indicated that the number of years lived with obesity in adulthood was associated with mortality, including cardiovascular mortality,[247] indicating that the duration of exposure to overweight may be an important factor in cardiovascular risk. The evidence indicates that overweight isolated to early life does not lead to permanent changes in disease risk. However, early onset of overweight may have different implications for disease progression than becoming overweight in adulthood. For example, glucose tolerance may be more malleable at younger ages; it has been suggested that the progression from impaired glucose tolerance to type 2 diabetes is accelerated in adolescents compared to adults. [87] This suggestion is especially pertinent in light of the increasingly young ages at which overweight and obesity are emerging in the population. Those with persistent overweight from childhood may be at increased risk of cardiovascular outcomes due to longer exposure, mediated to some extent by insulin resistance and type 2 diabetes at earlier stages. Combined with the evidence for the clustering of metabolic syndrome components in children, [37 67-74] their tracking into later life, [125] and the

emergence of type 2 diabetes cases in adolescence, [85] the findings of this study emphasise the importance of focusing on early life factors in the prevention of obesity, cardiovascular risk factors and CHD.

This thesis has considered the long-term health consequences of overweight in childhood and adolescence. The rationale for focusing on this period of the life-course was that current UK public health policy emphasises childhood obesity as a priority for intervention efforts.[13] However, weight status in childhood, adolescence and adulthood may be markers of exposures that occur in earlier life. As presented in the DOHaD framework, intergenerational effects may be important in the development of obesity and other health outcomes[236]; the effects of undernutrition *in utero* and catch-up growth in later life on long term cardiovascular outcomes including hypertension,[286 376] cardiovascular disease, [173 248 288 423-424] and type 2 diabetes [237 425-426] have been examined in a number of studies, which have consistently shown that small size at birth in combination with rapid childhood growth is associated with overweight and increased risk of these outcomes in later life. Recent studies have focussed on the effects of maternal obesity and glycaemic control during pregnancy on childhood obesity, [283 427] and have indicated that overnutrition, possibly through metabolic changes to the fetal environment, increase the risk of obesity and co-morbidities in the offspring in later life. [428-430] This is likely to be an important area for future research in light of the increasing prevalence of maternal obesity [431] and gestational diabetes[432-433]; clinical diabetes was present in just 0.54% of mothers in the BCS70 cohort (89 cases), while recent estimates put the prevalence of gestational diabetes at more than 2%, with higher prevalence among Asian and Black mothers. [434] Furthermore, the family environment is likely to play a key role in the intergenerational transmission of overweight and health problems; children's dietary and physical activity behaviours are shaped by early experiences and influenced by family members,[435] and these behaviours may track over the life-course to impact on health outcomes in later life.[436] In short, childhood obesity may be a marker of some underlying vulnerability to disease risk. This risk may be programmed by environmental exposures earlier in life, or there may be genetic influences underlying the associations between birth weight, weight status in later life, and disease risk.[437] In addition, there may be obesogenic lifestyle behaviours which become established in early life that contribute to overweight and disease risk. Obesity is likely to be an embodiment of a collection of exposures over the duration of the life-course. Studying the effects of pre-childhood or genetic exposures was beyond the scope of this thesis, but they are an important consideration in understanding the development of obesity and its co-morbidities over the life-course. They also have significant implications for approaches to intervention, especially in the context of rising prevalence of obesity among pre-school children.[56]

Efforts to describe the nature of the future health burden associated with childhood obesity are necessary for public health planning and resource allocation. Projections based on recent trends

in BMI distribution showed that overweight in the current UK child and adolescent population could present a substantial health and economic burden by the year 2050, with cases of hypertension, type 2 diabetes and cardiovascular diseases accounting for the majority of the disease and direct cost burden associated with overweight. If the rise in obesity prevalence could be stopped among this age group, direct healthcare costs in 2050 could be reduced by more than £1 billion. More research is needed to establish the best approaches to intervention. A study of several different childhood obesity interventions in Australia (the ACE-Obesity Project) showed that the largest net savings in costs were associated with interventions aimed at the general population, such as restrictions on advertising of junk food to children and school-based education programmes.[438] However, evidence for the impact of such interventions on BMI is limited.[380] Analysis of cohort data in this thesis showed that overweight isolated to childhood and adolescence did not increase disease risk compared to never being overweight. This finding highlights that effective intervention pre-adulthood could potentially bring the risk of future morbidity among overweight children in line with the level of risk in normal weight children, adding weight to the notion that a focus on early life should be the priority for reducing the impact of obesity on long-term health. The timing and target age-groups of interventions, and the long-term sustainability of their effects, are important considerations for obesity prevention strategies.

However, obesity represents just one risk factor among many which contribute to the morbidities included in this thesis. There will be health implications of changes in these other exposures, which may be independent of obesity. For example, while obesity prevalence has risen in recent decades, other known risk factors for cardiovascular disease have declined; average systolic blood pressure in Western Europe has fallen by more than 2 mm Hg per decade since 1980, [404] while the prevalence of smoking has decreased by more than half since the 1950s.[439] Consequently, the age-standardised cardiovascular disease burden has fallen, despite the rise in obesity prevalence. [404] Despite a current focus on obesity, reducing future disease burden will require a multifactorial approach, which takes into consideration the relationships between the various risk factors, and their changing distributions over time.

8.4 Implications and future research

Overweight in childhood and adolescence may increase cardiovascular risk in obese adults. As cases of more severe and earlier onset obesity emerge in the population, the occurrence of persistent overweight over the life-course is likely to increase in future generations, with implications for cardiovascular disease burden. Interventions that promote healthy weight among young children and their families, with the aim of establishing lifestyle behaviours that will ensure long-term weight maintenance, are likely to be important priorities. Childhood may

be an ideal time to implement obesity interventions because unhealthy lifestyle behaviours are less established, overweight is less entrenched, and disease progression is less advanced than at older ages. Although evidence for a contribution of childhood overweight to long-term risk is limited for non-cardiovascular outcomes, obesity in adulthood is an important risk factor for all the outcomes studied in this thesis; given that obese children are more likely to become obese adults than their healthy weight peers, the promotion of healthy weight in early life is likely to have benefits in terms of reducing adult overweight and its co-morbidities in later life, regardless of whether childhood obesity itself contributes to excess risk. Furthermore, the tracking of lifestyle behaviours over the life-course, and the potential intergenerational benefits of healthy weight and lifestyle, draw attention to the longer term implications of effective interventions in early life for reducing health burden.

These considerations emphasise that there is a strong basis and justification for the UK government's focus on children as a priority group for obesity interventions. They also underline the need for a long-term perspective when considering the implications of childhood obesity and interventions for chronic disease prevention. However, focusing on childhood obesity in isolation is unlikely to yield the greatest success; it is also important to consider how the wider environment may present challenges to effective intervention. For example, the roles of urban design, the food and advertising industries, and cultural influences in creating an obesogenic environment need to be examined, and addressed in intervention efforts.[440] Such approaches will have an impact on the whole population, with potentially wider-reaching benefits. At the same time, there remains a large and increasing number of children who are already overweight or obese, who will require more intensive interventions to manage their weight and reduce their risk of obesity co-morbidities. Future evaluations of childhood obesity interventions need to consider the benefits and costs associated with multiple interventions that are implemented simultaneously, including targeted interventions for high risk children and ecological or upstream approaches, in order to explore the optimal combinations of approaches. A priority area for future studies is to establish the sustainability of childhood obesity interventions, and to investigate ways in which intervention effects can be maintained over the life-course. It will also be important to identify individual-, family-, and community-level predictors of long-term intervention success, as weight regain is an important factor in determining the net benefits of any intervention.

A number of areas for further research have been identified. The finding in this thesis that childhood overweight contributes to type 2 diabetes, and possibly CHD risk, needs to be replicated in other studies, as the current evidence regarding these relationships is mixed. The relationships between childhood overweight and the other disease outcomes in this thesis also need to be confirmed. Further research is required to understand the roles of age at onset, duration and severity of overweight, and patterns of growth in early life in determining long-

term health. A major issue with studying long-term outcomes of childhood exposures is the need for data from older cohorts, which are different to contemporary cohorts in terms of the distribution of obesity and other exposures. Analyses of such studies are further limited by the low prevalence of overweight and obesity that are typically observed, leading to a need for large sample sizes. Increasing availability of data from large cohorts internationally, including more recent birth cohorts with biomedical data, may provide one solution.

Characterisation of the relationships between overweight and other cardiovascular risk factors, such as blood pressure, lipids, and glucose, and their contributions to cardiovascular outcomes over the life-course, will add to our understanding of cardiovascular disease progression and the mechanisms underlying its relationship with overweight. Improved understanding of the evolution of obesity and other cardiovascular risk factors over the life-course, and their contributions to long-term health, will be important for identifying which modifiable risk factors should be targeted in the prevention of cardiovascular disease. It will also provide insight into how changing distributions of these risk factors in the population are likely to impact on disease burden.

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APPENDICES

Appendix 1: Ethical approval from London School of Hygiene and Tropical Medicine Ethics Committee

LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

ETHICS COMMITTEE

APPROVAL FORM
Application number: **5636**

Name of Principal Investigator **Dr Min Hae Park**

Department **Epidemiology and Population Health**

Head of Department **Professor Laura Rodrigues**

Title: **The impact of childhood obesity on long-term health burden in the UK**

This application is approved by the Committee.

Chair of the Ethics Committee ....

Date .....1 December 2009.....

Approval is dependent on local ethical approval having been received.

Any subsequent changes to the application must be submitted to the Committee via an E2 amendment form.

Appendix 2: Research publication arising from thesis

obesity reviews doi: 10.1111/j.1467-789X.2012.01015.x

Etiology and Pathophysiology

The impact of childhood obesity on morbidity and mortality in adulthood: a systematic review

M. H. Park[1], C. Falconer[1], R. M. Viner[2] and S. Kinra[1]

[1]Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK; [2]General & Adolescent Paediatrics Unit, UCL Institute of Child Health, London, UK

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Address for correspondence: Miss MH Park, Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK.
E-mail: minhae.park@lshtm.ac.uk

Summary

The objective of this study was to evaluate the evidence on whether childhood obesity is a risk factor for adult disease, independent of adult body mass index (BMI). Ovid MEDLINE (1948–May 2011), EMBASE (1980–2011 week 18) and the Cochrane Library (1990–2011) were searched for published studies of BMI from directly measured weight and height in childhood (2–19 years) and disease outcomes in adulthood. Data were synthesized in a narrative fashion. Thirty-nine studies (*n* 181–1.1 million) were included in the review. There was evidence for associations between childhood BMI and type 2 diabetes, hypertension and coronary heart disease. Few studies examined associations independent of adult BMI; these showed that effect sizes were attenuated after adjustment for adult BMI in standard regression analyses. Although there is a consistent body of evidence for associations between childhood BMI and cardiovascular outcomes, there is a lack of evidence for effects independent of adult BMI. Studies have attempted to examine independent effects using standard adjustment for adult BMI, which is subject to over-adjustment and problems with interpretation. Studies that use more robust designs and analytical techniques are needed to establish whether childhood obesity is an independent risk factor for adult disease.

Keywords: Childhood obesity, morbidity, mortality, systematic review.

Abbreviations: BMI, body mass index; BMI-SDS, body mass index standard deviation score; CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; IOTF, International Obesity Task Force; OR, odds ratio.

obesity reviews (2012)

Introduction

Overweight and obesity in adulthood are associated with multiple comorbidities, most notably type 2 diabetes, cardiovascular disease and a number of cancers (1,2). Dramatic rises in childhood obesity prevalence over the last 30 years (3) have brought increasing attention to the potential long-term health consequences of childhood obesity. However, our understanding of the associations of childhood obesity with long-term health is incomplete. In particular, because of the tracking of adiposity from childhood into later life (4), it remains unclear whether childhood obesity has an effect on adult health that is independent of adult weight status. Previous reviews have examined the relationship between childhood obesity and morbidity in adulthood (5), but have not considered whether the effects of childhood adiposity are independent of adult overweight.

The objective of this review was to systematically evaluate the current evidence on the contribution of childhood body mass index (BMI) to adult disease risk, independent

Appendix 3: Supplementary table: Odds ratio of coronary heart disease CHD for different overweight patterns through childhood, adolescence and in adulthood – effect of adjusting for type 2 diabetes and hypertension. Analysis of pooled data from three British national birth cohorts.

Overweight Pattern	Unadjusted	Adjusted for hypertension	Adjusted for type 2 diabetes	Adjusted for hypertension and diabetes
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Never overweight	1	1	1	1
Childhood only	0.44	0.48	0.48	0.52
	(0.20, 1.89)	(0.11, 2.08)	(0.11, 2.04)	(0.12, 2.22)
Adolescence only	1.63	1.70	1.68	1.75
	(0.37, 7.19)	(0.38, 7.57)	(0.38, 7.42)	(0.39, 7.77)
Adulthood only	**3.83****	**3.53****	**2.94 ****	**2.66****
	(1.98, 7.42)	(1.79, 6.96)	(1.55, 5.59)	(1.36, 5.21)
Childhood + adolescence	3.43	3.47	3.37	3.39
	(0.60, 19.64)	(0.60, 19.99)	(0.57, 19.81)	(0.56, 20.32)
Childhood + adulthood	1.10	0.97	1.15	1.00
	(0.14, 8.48)	(0.11, 8.53)	(0.15, 8.89)	(0.11, 8.78)
Adolescence + adulthood	**3.74***	**3.16***	**3.20***	2.77
	(1.35, 10.35)	(1.14, 8.70)	(1.10, 9.33)	(0.97, 7.90)
Persistent overweight	**6.62****	**6.87****	**4.84***	**4.95****
	(1.94, 22.65)	(2.14, 22.11)	(1.41, 16.63)	(1.61, 15.27)
Hypertension	-	**3.62****	-	**3.47****
		(1.80, 7.25)		(1.72, 7.00)
Type 2 diabetes	-	-	**5.01****	**4.78****
			(2.35, 10.69)	(2.28, 10.01)

OR is for odds of disease outcome compared to never overweight category; Adjusted for sex, year of birth, exact age and height at childhood BMI measurement, birth weight, SEP at birth SEP in adulthood, and smoking status in adulthood; adjusted for weighted sampling in NSHD; * $p<0.05$; ** $p<0.01$

When the CHD model was adjusted for hypertension, there was little change in the observed effect sizes. On adjustment for type 2 diabetes, effect sizes for obesity in adulthood only and persistent overweight were attenuated (OR for obesity in adulthood decreased from 3.83 to 2.94, and OR for persistent overweight decreased from 6.62 to 4.84).

Appendix 4: UK mid-2007 population estimates: estimated resident population by single year of age and sex

United Kingdom

Thousands

Age	Persons	Males	Females
2	716.7	366.9	349.9
3	706.1	361.9	344.2
4	682.1	350.2	331.9
5	663.8	339.3	324.5
6	665.0	339.2	325.8
7	680.6	348.8	331.8
8	700.9	358.6	342.3
9	713.9	364.5	349.3
10	733.4	375.2	358.2
11	728.6	372.8	355.8
12	732.7	375.8	356.9
13	749.7	384.4	365.3
14	760.0	390.1	369.9
15	788.3	404.9	383.4
16	804.8	415.3	389.5
17	796.8	410.9	385.9
18	799.8	412.0	387.8
19	826.0	425.5	400.5

Metformin for Obesity in Children and Adolescents: A Systematic Review

Min Hae Park, msc[1]
Sanjay Kinra, md, phd[1]
Kirsten J. Ward, phd[2]
Billy White, mbbs[3]
Russell M. Viner, mbbs, phd[3]

OBJECTIVE — To summarize the efficacy of metformin in reducing BMI and cardiometabolic risk in obese children and adolescents without diabetes.

RESEARCH DESIGN AND METHODS — We performed a systematic review and meta-analysis of randomized controlled trials (RCTs). Double-blind RCTs of ≥6 months duration in obese subjects age ≤19 years without diabetes were included. Our primary outcomes of interest include changes in BMI and measures of insulin sensitivity.

RESULTS — Five trials met inclusion criteria (n = 320 individuals). Compared with placebo, metformin reduced BMI by 1.42 kg/m^2 (95% CI 0.83–2.02) and homeostasis model assessment insulin of resistance (HOMA-IR) score by 2.01 (95% CI 0.75–3.26).

CONCLUSIONS — Metformin appears to be moderately efficacious in reducing BMI and insulin resistance in hyperinsulinemic obese children and adolescents in the short term. Larger, longer-term studies in different populations are needed to establish its role in the treatment of overweight children.

Diabetes Care 32:1743–1745, 2009

Metformin has been shown to reduce weight gain, hyperinsulinemia, and hyperglycemia in adults with type 2 diabetes (1,2) and to reduce progression from impaired glucose tolerance to diabetes in those without diabetes (3). These benefits have led to an increase in the use of metformin in obese children with hyperinsulinemia. However, obesity is not a licensed indication for metformin in the U.K. or the U.S., and its use has proceeded faster than the evidence of its benefits. We undertook a systematic review of randomized controlled trials (RCTs) investigating the efficacy of metformin for reducing BMI and cardiometabolic risk in obese children without diabetes.

RESEARCH DESIGN AND METHODS

— We searched Ovid MEDLINE, EMBASE, the Cochrane Register of Controlled Trials, the metaRegister of Controlled Trials, and key journals published before December 2008 (online appendix Tables 1 and 2 available at http://care.diabetesjournals.org/cgi/content/full/dc09-0258/DC1). We included double-blind RCTs of ≥6 months duration with obese subjects age ≤19 years without diabetes and without secondary or syndromic causes of obesity. Primary outcomes of interest were BMI (weight in kilograms divided by the square of height in meters) and measures of insulin sensitivity. Secondary outcomes included fat mass, blood pressure, fasting lipids, and adverse effects.

Where three or more studies reported a common outcome, treatment effect was explored in a meta-analysis (Stata Statistical Software 10.1; StataCorp, College Station, TX), pooling data from the end of the follow-up period for trial completers. A random-effects model was selected. Sensitivity analyses were performed using fixed-effects models and by dose of metformin (1,000 vs. 2,000 mg), age of participants (12–19 vs. <12 years), co-intervention (metformin vs. metformin + co-intervention), baseline BMI (mean ≥35 vs. <35 kg/m^2), and by excluding one study reporting greater treatment effects than the other studies (4).

RESULTS

— Five studies published between 2001 and 2008 met the inclusion criteria (4–8). This included one crossover trial (5).

Three studies took place in the U.S. (6–8), and one each in Australia (5) and Turkey (4). All trials lasted 6 months with metformin doses from 1,000–2,000 mg/day. Three studies used lifestyle co-interventions in either trial arms (4,7,8). Two studies included adolescents (ages 12–19 years) (6,7), one looked at younger children (ages 6–12 years) (6), and the others spanned ages 9–18 years. In the U.S. and Australian studies, a large proportion of participants (45–90%) were from ethnic backgrounds with high prevalence of metabolic syndrome (African American, Hispanic, or Asian). All participants were hyperinsulinemic or insulin resistant. Sample size ranged from 28–120 participants at randomization; in total there were 365 participants and 320 trial completers. Mean attrition rates were 11% in metformin groups and 16% in placebo groups.

In the pooled analysis, metformin reduced BMI by a mean of 1.42 kg/m^2 (95% CI 0.83–2.02) compared with placebo (I^2 = 56.2%; n = 342) (Fig. 1). Sensitivity analyses did not reveal notable differences by age, dose, or baseline BMI. When the outlier result was excluded, metformin reduced BMI by 1.15 kg/m^2 (0.73–1.57, I^2 = 0%). Reduction in fasting insulin was greater in metformin than placebo groups in three studies, but evidence for a treatment effect was weak (−5.30 μU/ml [95% CI −11.96 to 1.36], I^2 = 78.7%; n = 257) (4–7). Pooled metformin effect on the homeostasis model assessment of insulin resistance (HOMA-IR) score was −2.01 (95% CI −3.26 to −0.75, I^2 = 49.5%; n = 234) (4,6,8) and −1.28

From the [1]Non-Communicable Disease Epidemiology Unit, London School of Hygiene and Tropical Medicine, London, U.K.; the [2]Cochrane Heart Group, Non-Communicable Disease Epidemiology Unit, London School of Hygiene and Tropical Medicine, London, U.K.; and the [3]UCL Institute of Child Health, University College London, London, U.K.
Corresponding author: Russell M. Viner, r.viner@ich.ucl.ac.uk.
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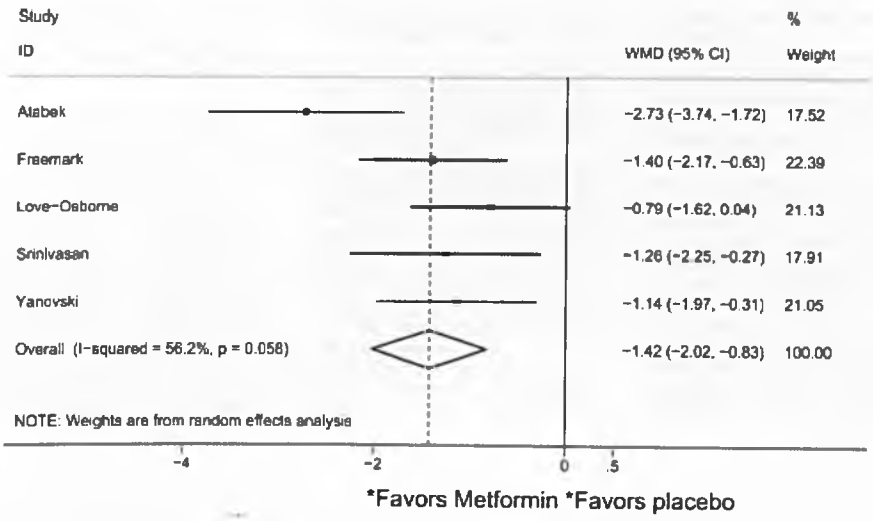

Figure 1—*Forest plot comparing change in BMI (kg/m^2) in metformin and placebo groups.*

(−2.55 to −0.21, I^2 = 0%) if the Turkish study was excluded.

Pooled mean metformin effect on total cholesterol was −0.19 mmol/l (95% CI −0.38 to −0.01, I^2 = 0%; n = 234) (4,6,7). Analyses did not provide strong evidence for a treatment effect on fasting glucose, HDL cholesterol, triglyceride levels, or blood pressure. There was insufficient data to comment on body fat outcomes. Gastrointestinal problems were the most common reported side effect (in 20–30%) and were more frequently reported in metformin than in placebo groups (risk difference 10–14%) (6,7). Only one participant reported gastrointestinal problems as the reason for leaving a study (7).

CONCLUSIONS — Our meta-analysis provides some support for a beneficial metformin effect on obesity outcomes among hyperinsulinemic children and adolescents. Treatment over 6 months may be efficacious in reducing BMI by 1.42 kg/m^2 (equivalent to 0.4 SD, based on SD for BMI in U.K. and U.S. adolescents) and HOMA-IR score by 2.01 (~0.6 SD) (9). Metformin use was also associated with a small reduction in total cholesterol level (~0.26 SD) (10), but these are unadjusted measures, and it is not possible to determine whether the effects are secondary to reductions in BMI and HOMA-IR or attributable to other factors.

To our knowledge, the effects of metformin on BMI in obese children without diabetes have been synthesized in only one published review based on three studies (11), which identified no treatment effect at 6 months (−0.17 kg/m^2 [95% CI −0.62 to −0.28]).

Metformin may not be as effective as behavioral interventions in reducing BMI: a meta-analysis of behavioral interventions in obese adolescents reported an effect of −3.04 kg/m^2 (95% CI −3.14 to −2.94) at 6 months, which was maintained at 12 months follow-up (12). When compared with drugs that are licensed for obesity, metformin has moderate effect: meta-analyses of RCTs reported an orlistat effect of −0.76 kg/m^2 (−1.07 to −0.44) and a sibutramine effect of −1.66 kg/m^2 (−1.89 to −1.43) at 6 months (12).

The results of this review must be interpreted with caution: the studies were short-term and based on small samples; participants were mainly from the U.S., and large portions were from ethnic backgrounds known to be at increased risk of metabolic disorders, limiting the generalizability of findings; and the studies presented unadjusted measures without intention-to-treat analyses, which may have overestimated treatment effects.

Metformin may be efficacious in reducing BMI and insulin resistance among obese hyperinsulinemic children and adolescents in the short term. Larger, long-term studies across different populations are needed to establish the role of metformin as therapy for obesity and cardiometabolic risk in young people.

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Anti-obesity drugs in children and adolescents: a systematic review and meta-analysis

Min Hae PARK[1], Andrei MORGAN[1], Sanjay KINRA[1 2]

[1] Non Communicable Disease Epidemiology Unit, London School of Hygiene and Tropical Medicine, London, UK

[2] Paediatric and Adolescent Division, University College London Hospitals Trust, London, UK

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Corresponding author:

Min Hae Park

Research degree student, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT

Tel: +44 (0)20 7927 2247

Email: min.park@lshtm.ac.uk

ABSTRACT

Objective: To examine the evidence on the efficacy and safety of anti-obesity drugs in obese children and adolescents.

Design: Systematic review and meta-analysis

Methods: Ovid MEDLINE, EMBASE, the Cochrane Register of Controlled Trials, and the *metaRegister of Controlled Trials* (inception-2009) were searched electronically. Double-blind, randomized placebo-controlled trials of orlistat and sibutramine, of ≥6 months duration in children and adolescents (age <19 years) with obesity, were eligible for inclusion.

Results: Six trials met inclusion criteria. Treatment with orlistat over 12 months (N=533) reduced BMI by 0.86 kg/m^2 (95% CI: 0.46 to 1.26) more than placebo, and was associated with gastrointestinal side effects. Sibutramine treatment over 6 months (N=548) reduced BMI by 2.03 kg/m^2 (95% CI: 1.31 to 2.75) more than placebo. Sibutramine use was associated with improvements in insulin resistance, but increased systolic blood pressure (+2.2 mm Hg; 95% CI: 0.4 to 3.9).

Conclusions: Orlistat and sibutramine appear to be moderately efficacious in the short term in reducing BMI among obese adolescents. However, sibutramine use is associated with systemic side effects which could contribute to cardiovascular risk; gastrointestinal side effects of orlistat may limit its long-term use. Careful consideration of the potential risks and benefits should inform decisions to continue or initiate pharmacotherapy for obesity in children and adolescents.

INTRODUCTION

The prevalence of child and adolescent obesity worldwide has more than tripled since the 1980s.[1-2] Obesity in childhood is associated with increased risk of developing type 2 diabetes, cardiovascular disease, respiratory problems, orthopaedic problems and liver disease, among other health problems.[3] These co-morbidities have been shown to track into adulthood,[4-6] and obesity may be an important preventable cause of death in adulthood.[7-9]

Anti-obesity drugs have been shown to be of benefit for weight loss [10-11] and weight maintenance in obese adults,[12] as well as slowing progression to chronic diseases such as diabetes.[13] Orlistat and sibutramine are the most widely used drug treatments that, until recently, were approved for the treatment of obesity in adults.[14] Orlistat is a lipase inhibitor, which acts in the gut to reduce the absorption of fats from the diet.[15] Sibutramine acts systemically to inhibit the reuptake of hormones serotonin and norepinephrine, which enhances satiety and reduces food intake.[15] In January 2010, marketing authorisations for sibutramine were suspended across Europe amid concerns about increased cardiovascular disease morbidity in adults.[16]

The evidence for the role of drugs in management of childhood obesity is less well established than for adults. Anti-obesity drugs are not licensed for use in children and adolescents in the USA and Europe. Despite this, prescribing prevalence of orlistat and sibutramine among patients aged 0-18 years in England increased 15-fold between 1999 and 2006, from an annual prevalence of 0.006 to 0.091 per 1000 person years;[17] orlistat accounted for 78% of all prescriptions. Prescribing of these drugs is in line with

recommendations from the National Institute of Health and Clinical Excellence (NICE) (2006) [18] and American Academy of Pediatrics (AAP) Expert Committee (2007),[19] which identify lifestyle modification as the first stage in treatment, but also recognise that pharmacological treatments (orlistat and sibutramine) may be appropriate for the management of older children and adolescents with certain co-morbidities.

Studies of anti-obesity drug treatment in children and adolescents have tended to emphasise efficacy.[20] The recent suspension of simbutramine from the European market indicate that a stronger focus on side effects may be warranted, especially in the case of children where use of these drugs is unlicensed, and the potential benefit may be modest. We undertook a systematic review and meta-analysis of randomized controlled trials to establish the role of anti-obesity drugs for the management of obesity in children and adolescents; we aimed to update estimates of efficacy, and to summarise the side effect profiles for these drugs. We focused on orlistat and sibutramine, as these are the drugs which have previously been recommended for use in this age group.

METHODS

We performed electronic searches of Ovid MEDLINE (1950-May 2009), EMBASE (1980-May 2009), the Cochrane Register of Controlled Trials (1990-2009), and the metaRegister of Controlled Trials (inception-2009). Inclusion criteria were: children and adolescents (aged $\leq$19 years), and being overweight or obese. Exclusion criteria were: known genetic syndromes predisposing to obesity; diabetes mellitus; polycystic ovary syndrome; or other known chronic disease. Double-blind, randomized placebo-controlled trials of orlistat or sibutramine of at least six months duration were selected. These criteria

were established to incorporate study quality into the analysis. Trials of drugs alone, and in combination with non-drug co-interventions were included. No limits were placed on language.

The primary outcome measure of interest was change in BMI (kg/m^2). The outcome was expressed as change in raw BMI (kg/m^2) rather than BMI standard deviation score (SDS), as BMI SDS tends to show less variability over time in obese children compared to in lean children, while raw BMI is a more stable measure of adiposity change across levels of adiposity.[21] Secondary outcomes included waist circumference, blood pressure, fasting lipid profile, and adverse effects.

Initial abstract screening was carried out by one reviewer. Second stage screening took place in a consensus meeting with two reviewers present. Data were extracted independently by two reviewers using a pre-designed form, and results compared. If extracted results differed, consensus was reached through discussion. If more than two studies reported a common outcome of interest, effect size estimates were pooled in a meta-analysis. The principal summary measures were mean differences in BMI change and other outcome measures between treatment groups. Weighted mean differences were analysed for data at 6 or at 12 months follow-up. A random-effects model was specified *a priori* to incorporate the effect of trial heterogeneity. If not reported in the paper, standard deviations (SD) of BMI change were imputed using SDs of the mean baseline and endpoint measurements, and an estimate of the correlation between baseline and endpoint values. Statistical heterogeneity was assessed using a chi-squared test and the I-squared statistic. Publication bias was not assessed due to the small number of studies included in the data

synthesis. All analyses were carried out using Stata 10.1 (StataCorp. 2007. College Station, TX: StataCorp LP).

RESULTS

840 publications were identified in the initial search, and seventeen papers were retrieved for further assessment (Figure 1). Six studies published between 2003 and 2006 met the inclusion criteria, comprising two trials of orlistat and four trials of sibutramine (Table 1). Follow-up ranged from 6 to 12 months duration. In all studies, drug intervention was used as an adjunct to lifestyle modification programs. Studies used a mixture of intention-to-treat (ITT), modified ITT, and completer analysis.

Orlistat trials

Only two orlistat trials were identified that met the inclusion criteria.[22-23] Both studies took place in North America, and participants were aged between 12 and 18 years. A dose of 120 mg three times daily (tds) was used in both trials. In view of the fact that there were only two included studies, and the small sample size of one study (n=40 individuals) [23], results were not meta-analysed and the effect estimates obtained from the larger study are principally reported.

In the study by Chanoine et al [22] orlistat (n=352 participants) reduced BMI by 0.86 kg/m^2 (95% CI 0.46 to 1.26 kg/m^2) more than placebo (n=181) at 12 months follow-up. This corresponded to a reduction in weight of 2.64 kg (95% CI 1.55 to 3.73 kg). 13.3% of those in the orlistat group had a reduction in BMI of $\geq$10% at 6 months follow-up, while only 4.5% of the placebo group had this level of response (p=0.002). Attrition (randomised participants

who did not complete the study) was similar in trial arms, at 35% in the treatment group and 36% among controls. There was no evidence of an effect of orlistat on other indicators of cardio-metabolic risk, including fasting insulin, fasting glucose, systolic blood pressure, total serum cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and body fat percent.

In the other study, there was little evidence for a real effect of orlistat on BMI at 6 months follow-up (effect size -0.50 kg/m^2, 95% CI -7.16 to 6.16 kg/m^2), based on a small number of participants (orlistat n=16; placebo n=18) [23]. Attrition rates were 20 % in the treatment group and 10 % in the placebo group.

Adverse effects of orlistat

Treatment with orlistat 120 mg tds was associated with gastrointestinal (GI) adverse events. Approximately half of the orlistat-treated participants reported fatty or oily stools, compared to 8% of placebo controls.[22] Other adverse effects that were more common in orlistat groups than in placebo controls were oily spotting, oily evacuation, abdominal pain, fecal urgency, flatus with discharge and fecal incontinence. Despite this, there was no difference in the dropout rate due to adverse effects between treatment groups (3.7% in orlistat-treated groups discontinued treatment due to adverse effects, compared to 1.5% in placebo group). Neither study found a difference in vitamin levels between orlistat- and placebo-treated groups at follow-up. Similar proportions of participants in treatment arms (<1%) dropped out due to insufficient response to treatment, and there were no notable differences in non-GI adverse events.

Sibutramine trials

In four sibutramine trials, a total of 691 participants were randomized and 525 of these completed. Attrition rates ranged from 7 to 24% in treatment groups and from 13 to 38% in placebo groups. Around a quarter of those who withdrew from trials were lost to follow-up. Sibutramine dosages ranged from 5 to 15 mg once daily (od). Two trials took place in North America [24-25], one in Mexico [26], and one in Brazil.[27] Participants were aged between 12 and 18 years.

In all four trials, sibutramine-treated groups had a greater mean reduction in BMI than controls. Meta-analysis of these data showed that sibutramine (n=377 participants) reduced BMI by 2.03 kg/m^2 (95% CI 1.31 to 2.75 kg/m^2) more than placebo (n=171), with moderately low heterogeneity in the estimates (I^2=25.9%, 95% CI 0 to 72%) (Figure 2). This estimate combined outcome data at 12 months for one study [24] with data at 6 months for the remaining three trials. When the 12 month trial was excluded in a sensitivity analysis, the effect size estimate was similar at 1.94 kg/m^2 (95% CI 1.08 to 2.81 kg/m^2), with higher heterogeneity in the estimates (I^2=47.2). Between 40% and 48% of sibutramine-treated groups lost at least 10% of baseline BMI, compared to 0 to 15% of controls.[24-27] Expressed as change in weight, sibutramine reduced weight by 6.3 kg more than placebo (95% CI 3.9 to 8.7 kg), with substantial heterogeneity in the estimates (I^2=75.3%).

All four studies reported change in waist circumference as an outcome.[24-27] Meta-analysis of these data showed that sibutramine (n=377) reduced waist circumference by 5.72 cm (95% CI 4.49 to 6.94 cm; I^2=0, 95% CI 0 to 85%) more than placebo (n=171). Two studies reported change in fasting insulin level [24, 27], and both found that reduction in fasting insulin was greater in sibutramine-treated participants than in controls. Change in insulin resistance (HOMA-IR) was analyzed in one study, which reported a greater reduction

among sibutramine-treated participants than among placebo controls (-0.69 versus -0.02, p<0.001).[24] There was evidence for a small beneficial effect of sibutramine treatment on levels of HDL-cholesterol from two studies [24, 27], with effect size +0.10 mmol/L (95% CI 0.06 to 0.14 mmol/L). These studies also reported a beneficial effect of sibutramine on triglyceride levels (effect size -0.30 mmol/L, 95% CI -0.44 to -0.16). These estimates were not adjusted for weight loss or other effects. There was no evidence for an effect of sibutramine on fasting glucose, total cholesterol, LDL-cholesterol, or body fat percentage.

Adverse effects of sibutramine

Sibutramine-treated groups did not experience more adverse events than placebo controls. However, treatment was associated with systemic side effects including increased pulse rate and blood pressure. Three studies reported a safety protocol that detailed blood pressure and pulse rate cut-offs that would be used to determine withdrawal of participants from the study or reduction of the drug dosage.[24-26] Dry mouth, constipation, dizziness, and insomnia were also more commonly reported in sibutramine than in placebo groups in one study.[24] Meta-analysis of outcome data from all four studies showed that sibutramine increased pulse rate by 5.2 beats per minute (95% CI 1.95 to 8.4; I^2=92.3%) compared to placebo, and increased systolic blood pressure by 2.2 mm Hg (95% CI 0.4 to 3.9 mm Hg; I^2=57.0%). However, these effects were not reflected in increased withdrawal: 5% of sibutramine-treated participants dropped out due to adverse events, compared to 3% of placebo controls.

DISCUSSION

This review of published trials provides evidence that orlistat and sibutramine are moderately efficacious in the short term reduction of BMI in obese adolescents. Treatment with orlistat over 12 months reduces BMI by an average of 0.86 kg/m^2 more than placebo. Sibutramine is more efficacious, with effect size of -2.03 kg/m^2, and is also associated with improvements in some indicators of cardio-metabolic risk, notably insulin resistance and dyslipidemia. Orlistat treatment is associated with gastrointestinal tract adverse events, which appear to be well tolerated in trials. Sibutramine is associated with notable systemic side effects including increased heart rate and raised blood pressure.

Comparison with other research

Two previous reviews have synthesised the evidence on anti-obesity drugs in children.[20, 28] The Cochrane review [20] meta-analysed data from the two orlistat trials identified in this review, and reported an effect size of -0.76 kg/m^2 (95% CI -1.07 to -0.44) at 6 months. McGovern et al [28] reported an effect of orlistat of -0.7 kg/m^2 (95% CI 0.3 to 1.2) at 6 months, based on three studies, including one open-label trial that did not meet our inclusion criteria.[29] In both of these reviews, the overall effect size estimate was largely driven by the results of the single large trial on which we have based our estimates.[22] This trial has the advantage of providing outcome data at 12 months rather than at 6 months only.

As in our review, the other reviews reported a greater effect of sibutramine on BMI than of orlistat. The effect size estimate in the Cochrane review was -1.66 kg/m^2 (95% CI -1.89 to -1.43), based on a meta-analysis of outcome data at 6 months from two studies.[26-27] McGovern et al reported an effect size of -2.4 kg/m^2 (95% CI -3.1 to -1.8) at 6 months (sibutramine n=354, placebo n=148) based on a pooled analysis of three studies.[24-25, 27]

Our effect size estimate of -2.03 kg/m^2 was based on four trials, and included all of the studies included in the other reviews.

Elevated blood pressure and pulse rate in sibutramine treated groups were reported in previous reviews, but these effects were not quantified as they were in our analyses. Our pooled results demonstrate that treatment with sibutramine is associated with clinically significant effects on systolic blood pressure and pulse rate, despite the presence of safety protocols relating to these indictors. The gastrointestinal side effects of orlistat appear to be well tolerated in trials, but one population based study indicated that almost half of adolescents who begin orlistat treatment cease use within one month (with average treatment duration of three months) [17], suggesting that potential for the long-term use of orlistat may be limited.

What should be the role of pharmacotherapy in management of child and adolescent obesity?

An effect size of orlistat of -0.86 kg/m^2 is equivalent to a reduction of 0.2 SD, based on the BMI distribution in the UK adolescent population (one SD is approximately 3.5 kg/m^2 [30]), while the effect size of sibutramine (-2.03 kg/m^2) is equivalent to a change of 0.6 SD. Indices of insulin sensitivity in obese children (age 6-14 years) have been shown to improve with reductions in BMI SDS of $\geq$0.5 over one year [31], while an increase in BMI in childhood of >2 kg/m^2 above the median has been shown to be associated with a 60% increase in risk of all cause mortality in adulthood [32].

A systematic review of trials of metformin, an anti-diabetes drug which has been used for the treatment of obesity in children, reported an effect size of -1.42 kg/m^2 (95% CI -2.02 to -0.83) at 6 months [33]. Used as an adjunct to lifestyle interventions, orlistat, sibutramine,

and other off-label anti-obesity drugs appear to offer moderate additional benefit in reducing overweight in obese adolescents in the short term. However, intensive behavioural interventions can also be efficacious in reducing BMI,[20] and these should continue to be used as the first line treatment where feasible.

Furthermore, the potentially beneficial effects of BMI reduction on long-term health must be weighed against the risks, especially in the case of sibutramine: its long-term use has been associated with increased cardiovascular events in adults at high risk of heart disease [34]. Our findings of raised systolic blood pressure and pulse rate associated with sibutramine use appear to be consistent with the findings in adults, as increased blood pressure and pulse rate are established risk factors for cardiovascular disease. In light of the potential long-term risks of sibutramine use and its suspension from the market in Europe, orlistat remains the only option in anti-obesity pharmacotherapy. Orlistat has its own side effects, and may not be well tolerated by children and adolescents outside of trial settings.

The trials included in this review had short-term follow up, which precludes any conclusions about the long-term effects of pharmacotherapy use in children. Trials in adults have indicated that orlistat and sibutramine can help reduce weight regain and progression to chronic diseases in the long-term [15], but this evidence is as yet lacking for young people. Further research is needed to establish the role of pharmacotherapy in the management of obesity in children and adolescents; for example, to identify which young people are likely to benefit from treatment, and to establish how pharmacotherapy can fit in alongside other interventions for long-term management of obesity.

Limitations

This systematic review was conducted using a strategy based on filters and search terms developed in Cochrane reviews. The inclusion of double-blind, randomized placebo-controlled trials ensured a minimum study quality. Reviewers were not blinded to the author or journal of publication, but neither reviewer had associations with any of the authors or journals that were reviewed. We however note that only one of the studies included in this review was non-industry sponsored.[23]

In conclusion, both orlistat and sibutramine appear to be moderately efficacious in the short-term treatment of obesity in adolescents, although less so than intensive behavioural interventions. Furthermore, sibutramine use is associated with systemic side effects which could contribute to cardiovascular risk in the long-term and outweigh benefits of BMI reduction, while orlistat has gastrointestinal side effects which may limit its long-term use. Careful consideration of the potential risks and benefits should inform decisions about initiating pharmacological treatment for obesity in children and adolescents.

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Figure 1: Flow diagram of study selection

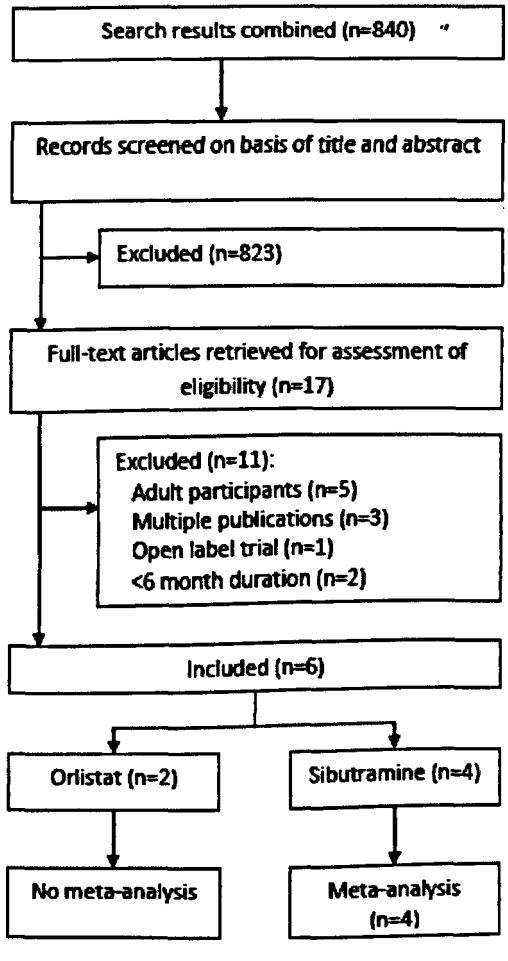

Figure 2: Forest plot comparing change in BMI (kg/m^2) in sibutramine and placebo groups

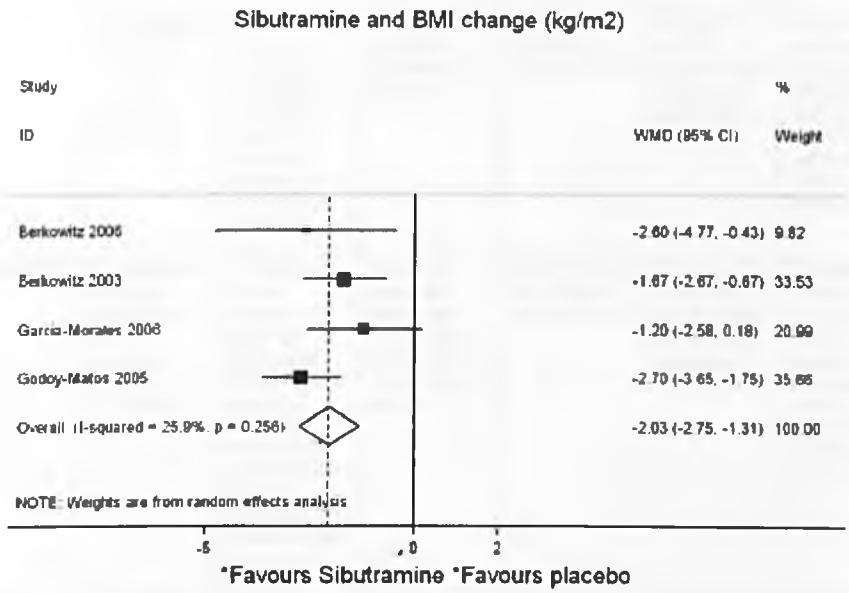

Table 1: Table of included studies

Study name	Methods	Participants and baseline characteristics	Length of intervention and follow-up	Intervention (attrition rate)	Co-intervention in both treatment arms	Notes
Maahs 2006 [23]	Randomization according to statistician generated sequence. Triple blind.	US outpatient clinic. 40 individuals randomized, 34 completed. Age 14-18 years. 68% female. BMI ≥85th centile for age and sex.	6 month treatment period and follow-up	Orlistat 120mg tds (20%) vs. Placebo (10%)	Diet and exercise therapy + daily multivitamin supplement	Subjects reimbursed $20 per visit + $10 per kg lost at 6 months. Not ITT analysis. Non-industry sponsored.
Chanoine 2005 [22]	Randomization at 2:1 ratio according to computer generated schedule. Triple blind.	32 clinics in US and Canada. 539 individuals randomized, 349 completed. Age 12-16 years. 67% female. BMI ≥2 units higher than US weighted mean for 95th centile for age and sex.	12 month treatment period and follow-up (+2 week single blind placebo lead-in)	Orlistat 120mg tds (35%) vs. Placebo (36%)	Diet + exercise + behaviour therapy + daily multivitamin supplement	Modified ITT analysis (baseline and ≥1 post-baseline assessment; LOCF). Funded by Hoffman-La Roche.
Berkowitz 2006 [24]	Randomization at 3:1 ratio, stratified by centre and baseline BMI. Double blind.	33 clinics in US. 498 individuals randomized, 361 completed. Age 12-16 years. 64% female. BMI ≥2 units higher than US weighted mean of the 95th centile for age and sex, <4 kg/m^2	12 month treatment period, follow-up at 3, 6, 9 and 12 months	Sibutramine 10 mg od, uptitrated if <10% initial BMI lost at 6 months (24%) vs. Placebo (38%)	Centre-specific behavioural program	Modified ITT analysis (≥1 dose study medication and ≥1 post-baseline BMI measurement). Sponsored by Abbott Laboratories.
Berkowitz 2003 [25]	Randomization not described. Double blind.	US university clinic. 82 individuals randomized, 62 completed. Age 13-17 years. 67% female. BMI range 32-44 kg/m^2.	6 month double-blind period (phase 1) + 6 months open-label treatment	Sibutramine 5-15mg od (7%) vs. Placebo (13%)	Family-based behavioural program	ITT analysis for BMI; completers analysis for other outcomes. Sponsor: Knoll Pharmaceutical Co and Abbott Laboratories.
Garcia-Morales 2006 [26]	Randomization according to computer generated list. Triple blind.	Outpatient endocrinology department of children's hospital in Mexico. 51 individuals	6 month treatment period and follow-up (+ run-in period of unspecified length)	Sibutramine 10mg od (19%) vs. Placebo (24%)	Diet + physical activity advice	Modified ITT analysis (excluding dropouts before 1 month of treatment; LOCF).

		randomized. 40 completed. Age 14-18 years. 57% female. BMI for age and sex >95th centile.				Sponsored by Abbott Laboratories.
Godoy-Matos 2005 [27]	Randomization not described. Triple blind.	Regular clinical setting in Rio De Janeiro, Brazil. 60 individuals randomized, 50 completed. Age 14-17 years. 80% female. BMI 30-45 kg/m^2.	6 month treatment period and follow-up (+ 4 week placebo run-in)	Sibutramine 10mg od (7%) vs. Placebo (27%)	Dietary counselling + brief physical activity instructions	Adolescents with adult bone age. ITT analysis using LOCF. Sponsored by Abbott Laboratories.

tds= three times daily; od = once daily; ITT = intention to treat; LOCF = last observation carried forward

Table 1: Studies excluded from review

Study name	Methods	Participants	Interventions	Reason for exclusion
Appolinario 2003 [35]	12 week double blind randomized trial	60 obese outpatients with binge eating disorder, Brazil. Age 18-60 years	Sibutramine 15 mg od vs. Placebo	Adult participants
Bauer 2006 [36]	16 week double-blind randomized trial	73 obese participants with and without binge eating disorder, Switzerland. Age 18-75 years	Sibutramine 15 mg od + CBT vs. Placebo + CBT	Adult participants
Broom 2002 [37]	54 week double blind randomized trial	531 patients with BMI ≥28 kg/m^2 and ≥1 obesity-associated cardiovascular risk factor. UK. Age 18-80 years	Orlistat 120 mg tds + hypocaloric diet vs. Placebo + hypocaloric diet	Adult participants
Budd 2007 [38]	6 month double blind randomized trial	US clinic. 34 African American and 45 Caucasian obese adolescents.	Sibutramine 5mg od + behavioural program vs. Placebo + behavioural program	Secondary analysis of data from trial [25]
Correa 2005 [Portuguese] [39]	Analysis of visual analogue scores in 6 month triple blind randomized trial	Brazilian clinic. Obese adolescents	Sibutramine 10mg od + lifestyle advice vs. Placebo + lifestyle advice	Repetition of data [27]
Daniels 2007 [40]	12 month double blind randomized trial	33 clinics in US.498 adolescents. Age 12-16 years.BMI 281.–46.3 kg/m^2.	Sibutramine 10 mg od + behavioural therapy vs. Placebo + behavioural therapy	Repetition of data [24]
James 2000 [12]	2 year double-blind randomized trial	605 obese patients from 8 European centres. Age 17-65 years	Sibutramine 10 mg od + individualised programme vs. Placebo + individualised programme	Adult participants
Mnls 2001 [41]	24 week double blind randomized trial	294 obese patients from 19 centres in Belgium. Age 18-70 years	Orlistat 120 mg tds + LCD vs. Placebo +LCD	Adult participants
Ozkan 2004 [29]	Randomization by alternation of successive patients. Open-label study.	Outpatient clinic in Turkey. 42 participants. Age 10-16 years. WFH >140%.	Orlistat 120 mg tds + standard care vs. Standard care	Open-label trial, no placebo
Vm Mil 2007 [42]	12 week double blind randomized trial	Research centre in the Netherlands. 24 individuals. Age 12-17 years. BMI ≥97th centile and triceps skinfold thickness ≥97th centile for age and sex.	Sibutramine 10 mg od (8%) vs. Placebo (25%)	12 week trial
Zhi 2003 [43]	21 day double blind randomized trial	32 adolescents with BMI >85th centile for age and sex.	Orlistat 120 mg tds + hypocaloric diet vs. Placebo + hypocaloric diet	21-day follow-up (<6 months)

CBT = cognitive behavioural therapy; LCD = low calories diet; WFH= weight for height

Appendix 1: Search terms used in review

Database			
Ovid MEDLINE	**EMBASE**	**Cochrane Central Register of Controlled Trials**	**metaRegister of Controlled Trials**
1. (sibutramin$ or reductil or meridian or medaria or sibutramine hydrochloride monohydrate).mp. 2. (Rimonabant or SR141716 or Acomplia or Bethin or Monaslim or Remonabent or Riobant or Slimona or Rimoslim or Zimulti).mp. 3. (Orlistat or Xenical or Alli or Tetrahydrolipstatin).mp. 4. (Anorectic or anorexigenic).mp. or appetite suppressant.tw. 5. exp Appetite Depressants/ 6. exp Metformin/ 7. exp Anti-Obesity Agents/ 8. or/1-7 9. (obes$ or obesity).mp. 10. (Overweight or loss of overweight).mp. 11. (BMI or Body mass index or Body-mass-index or Weight for height or Weight-for-height or Weight to height ratio or Weight-to-height ratio or Weight height ratio or Weight-height ratio).mp. 12. (Weight gain or Weight loss or Weight management or Weight maintenance or Weight reduction or Weight decrease or Weight control).mp. 13. (Waist circumference or Waist measurement).mp. 14. (Body fat or Body fat percent$ or Percent$ body fat or Fat mass or Adiposity or Body composition).mp. 15. (Skinfold thickness or skin fold thickness or skin-fold thickness or Calliper$).mp. 16. (Hyperinsulin?emia or Insulin resistance or metabolic risk or metabolic syndrome).mp. 17. (Dyslipid?emia or Hyperlipid?emia or Hypercholesterol?emia or Cholesterol or Total cholesterol or Low density lipoprotein cholesterol or LDL cholesterol or High density lipoprotein cholesterol or HDL cholesterol or Triglyceride$).mp. 18. (Satiety or Hunger or Appetite or Binge eating).mp. 19. ponderal index.mp. 20. (adverse effect$ or adverse reaction$ or side effect$).tw.	1. (Sibutramine or sibutramin or reductil or meridian or medaria or sibutramine hydrochloride monohydrate).mp. 2. (Rimonabant or SR141716 or Acomplia or Bethin or Monaslim or Remonabent or Riobant or Slimona or Rimoslim or Zimulti).mp. 3. (Orlistat or Xenical or Alli or Tetrahydrolipstatin).mp. 4. (Anorectic or anorexigenic).mp. or appetite suppressant.tw. 5. appetite depressant.mp. 6. (anti-obesity adj5 (agent or drug or substance)).mp. 7. antiobesity agent/ 8. or/1-7 9. (obese or obesity or overweight or adiposity or overeating).mp. 10. (BMI or Body mass index or Body-mass-index or Weight for height or Weight-for-height or Weight to height ratio or Weight-to-height ratio or Weight height ratio or Weight-height ratio).mp. 11. ponderal index.mp. 12. (Weight gain or Weight loss or Weight management or Weight maintenance or Weight reduction or Weight decrease or Weight control).mp. 13. (Waist circumference or Waist measurement).mp. 14. ((Body adj5 fat) or (Body adj5 fat adj5 percent$) or Percent$ body fat or Fat mass or Adiposity or Body composition).mp. 15. (Skinfold thickness or (skin adj5 fold adj5 thickness) or skin-fold thickness).mp. 16. (waist adj5 hip adj5 ratio).mp. 17. (Hyperinsulin?emia or insulin resistance or metabolic risk).mp. 18. (Dyslipid?emia or Hyperlipid?emia or Hypercholesterol?emia or Cholesterol or Total cholesterol or Low density lipoprotein cholesterol or LDL cholesterol or High density lipoprotein cholesterol or HDL cholesterol or Triglyceride$).mp. 19. (Satiety or Hunger or Appetite	**"sibutramine, rimonabant, orlistat", AND "child*, adolescen*, teen*" AND "obes*, overweight"** ***in*** **Title, Abstract or Keywords**	(Sibutramine OR Rimonabant OR Orlistat) AND (child% OR adolescen%) AND (obes% OR overweight)

21. exp Obesity/ 22. body weight changes/ or overweight/ 23. Adipose Tissue/ 24. exp "Body Weights and Measures"/ 25. exp Hyperinsulinism/ 26. exp Dyslipidemias/ 27. exp Appetite/ 28. or/9-27 29. exp Child/ 30. exp Adolescent/ 31. juvenile.mp. 32. exp Infant/ 33. child$.mp. 34. adolescen$.mp. 35. infan$.mp. 36. teen$.mp. 37. P?ediatric$.mp. 38. Pediatrics/ 39. or/29-38 40. Randomi#ed controlled trial.pt. 41. exp Randomized Controlled Trial/ 42. exp Random Allocation/ 43. exp Double-Blind Method/ 44. exp Single-Blind Method/ 45. Clinical trial.pt. 46. exp Clinical Trial/ 47. (clinical$ adj5 trial$).tw. 48. ((single or double or treble or triple) adj5 (blind$ or mask$)).mp. 49. Placebos/ 50. (placebo$ or random$).tw. 51. research design/ 52. Comparative study/ 53. exp evaluation studies/ 54. Follow-up studies/ 55. Prospective studies/ 56. Intention-to-treat.tw. 57. Randomi#ed controlled trial.mp. 58. (Randomi#ed adj5 controlled).mp. 59. or/40-58 60. 8 and 28 and 39 and 59	or (Binge adj5 eat$)).mp. 20. appetite/ 21. (adverse effect$ or adverse reaction$ or side effect$).mp. 22. obesity/ 23. body mass/ 24. body weight/ 25. or/9-24 26. Clinical trial/ 27. Randomized controlled trial/ 28. Randomization/ 29. Single blind procedure/ 30. Double blind procedure/ 31. Crossover procedure/ 32. Placebo/ 33. Randomi?ed controlled trial$.tw. 34. Rct.tw. 35. Random allocation.tw. 36. Randomly allocated.tw. 37. Allocated randomly.tw. 38. (allocated adj2 random).tw. 39. Single blind$.tw. 40. Double blind$.tw. 41. ((treble or triple) adj blind$).tw. 42. Placebo$.tw. 43. Prospective study/ 44. or/26-43 45. child/ 46. adolescent/ 47. pediatrics/ 48. child$.mp. 49. adolescen$.mp. 50. infan$.mp. 51. teen$.mp. 52. p?ediatric$.mp. 53. juvenile.mp. 54. or/45-53 55. 8 and 25 and 44 and 54		

mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name