Healthcare use and costs in relation to body mass index in over one million middle-aged and older women in England

Seamus Kent

Lincoln College

University of Oxford

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Abstract

Rates of overweight and obesity worldwide have increased substantially in recent decades. In England, over 60% of adults are now overweight or obese. Because excess weight is associated with higher risks of chronic conditions, including type-2 diabetes, cardiovascular disease, osteoarthritis, and certain cancers, as well as with premature death, it constitutes a major health burden. It is also associated with higher total healthcare spending, but how the associations differ in different healthcare settings is not well understood.

I undertook a systematic literature review of studies that used individual participant data to estimate annual healthcare costs in relation to body mass index (BMI; in kg/m^2). Compared to adults at healthy weight (i.e. BMI 18.5 to <25 kg/m^2), total annual healthcare costs were found to be 12% and 36% higher for overweight (BMI 25 to <30 kg/m^2) and obese (BMI ≥ 30 kg/m^2) adults, respectively. The associations were strongest for costs of medications (18% for overweight and 68% for obese adults), followed by inpatient care costs (12% and 34%), and ambulatory care costs (4% and 26%). Most of these studies used data from the United States, and were based on small-to-moderate numbers of participants, limiting their ability to reliably estimate healthcare costs in relation to grades of obesity or for different health conditions. There was no reliable evidence from individual participant data pertaining directly to the United Kingdom.

Using data on over one million middle-aged and older women in the prospective Million Women Study, linked to routine administrative data on deaths, inpatient and day-case admissions, and primary care services, I estimated annual rates and costs of hospital admissions, primary care consultations, prescription items issued, and monitoring and diagnostic tests in relation to body mass index. Every 2 kg/m^2 higher BMI beyond 20 kg/m^2 was associated with 7.4% higher annual hospital admission costs, 5.2% higher primary care consultation costs, and 9.9% higher prescription costs, but no clear association with test costs was identified. Projecting these results to the total population of women aged 55 to 79 years in England in 2013, 15% (£662 million) of hospital costs, 11% (£229 million) of primary care consultation costs, and 22% (£384 million) of prescription costs were attributable to overweight and obesity. Type-2 diabetes, and cardiovascular and musculoskeletal diseases were the major contributing conditions to the total excess weight attributable costs.

These findings will be useful to healthcare policy makers, commissioners, and providers in making investment and prioritisation decisions, and underline calls for greater investments in cost-effective interventions to reduce excess weight and prevent weight gain.

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List of Abbreviations

A&E . . . . . Accident and emergency

APC . . . . . Admitted patient care

BMI . . . . . Body mass index

BNF . . . . . British National Formulary

CCG . . . . . Clinical Commissioning Group

CHD . . . . . Chronic heart disease

CI . . . . . Confidence interval

COPD . . . . . Chronic obstructive pulmonary disease

CPRD . . . . . Clinical Practice Research Datalink

DALY . . . . . Disability-adjusted life-year

FCE . . . . . Finished consultant episode

GLM . . . . . Generalized linear model

GP . . . . . General Practitioner

HES . . . . . Hospital Episode Statistics

HRG . . . . . Healthcare Resource Group

HSCIC . . . . Health and Social Care Information Centre

HSE . . . . . Health Survey for England

ICD-9 . . . . . International Classification of Diseases, 9^{th} revision

ICD-9-CM . . International Classification of Diseases, 9^{th} revision, Clinical Modification

ICD-10 . . . . International Classification of Diseases, 10^{th} revision

ISAC . . . . . Independent Scientific Advisory Committee

IQR . . . . . Interquartile range

kg . . . . . kilogram

kg/m^2 . . . . . kilograms per metre squared

MRC . . . . . Medical Research Council

NHLBI . . . . National Heart, Lung and Blood Institute

NHS . . . . . National Health Service

NHSBSP . . . National Health Service Breast Cancer Screening Program

NIC . . . . . Net ingredient cost

NIHR . . . . . National Institute for Health Research

OPCS-4 . . . . Office for Population Censuses and Surveys classification of surgical operations and procedures, 4^{th} revision

PAF . . . . . Population attributable fraction

PCA . . . . . Prescription Cost Analysis

PSSRU . . . . Personal Social Services Research Unit

QOF . . . . . Quality and Outcomes Framework

SD . . . . . Standard deviation

UK . . . . . United Kingdom

US . . . . . United States

WHO . . . . . World Health Organisation

1
Introduction

1.1 Background

Excess weight is a leading cause of death and disability worldwide [1], and, in many developed countries, accounts for a significant share of healthcare spending [2]. The global prevalence of individuals with excess weight (defined as body mass index [BMI] $\geq$25 kg/m^2) has increased substantially in recent decades: 37% of adult men and 28% of adult women are now overweight or obese [3]. The prevalence tends to be even higher in Western populations: in the United Kingdom (UK), 68% of adult men and 58% of adult women are overweight or obese.

Excess weight is associated with premature mortality [4], and a large and diverse range of chronic health conditions and adverse health events including: metabolic conditions like type-2 diabetes mellitus, ischaemic heart disease, ischaemic stroke, chronic kidney disease, and non-alcoholic fatty liver disease; musculoskeletal conditions like osteoarthritis and lower back pain; several cancers, including cancers of the oesophagus, colon, rectum, liver, gallbladder and biliary tract, pancreas, breast (post-menopausal), uterus, ovaries, kidney, thyroid, and blood; and other conditions, such as depression, sleep apnoea, asthma, and gallbladder disease [1, 5–12]. Perhaps largely as a consequence of these conditions, excess weight is also strongly associated with poorer health-related quality of life [13].

As a result of its high prevalence and its substantial and wide ranging effects on health, high BMI is a leading contributor to life-years lost and disability-adjusted life years (DALYs): it was estimated to account for 4.0 million of all deaths ($\approx$7%) and 120 million of all DALYs ($\approx$5%) worldwide in 2015 [1]. It is estimated to be the sixth largest cause of DALYs in men globally after high blood pressure, tobacco smoking, household air pollution, poor diet, and alcohol consumption, and third in women after high blood pressure and household air pollution [14]. In Western societies, it is often estimated to be an even greater contributor to ill health: in the UK, excess weight is the third largest cause of DALYs in men after tobacco smoking and poor diet, and the second largest in women after tobacco smoking, with 10% of DALYs in men and 9% in women due to high BMI [15].

Because excess weight is associated with higher incidences of a number of chronic conditions, each of which increases healthcare utilisation and adversely impacts on health, excess weight has also consistently been shown to be associated with substantial direct and indirect, healthcare and non-healthcare costs [2, 16, 17]. Based on reviews of published studies, overweight and obese adults were estimated to incur 10% and 43% higher annual total healthcare costs, respectively, compared to adults at healthy weight [16], and taken together, overweight and obesity were estimated to account for around 9% of total national expenditure on healthcare.

Most studies were based on data from the United States (US), and those that used individual participant data to estimate healthcare costs in relation to excess weight were typically based on small-to-moderate numbers of participants (median sample size $\approx 11,500$). Small sample sizes limit the ability of studies to reliably estimate the use and costs of different types of healthcare services in relation to detailed categories of excess weight (e.g. grades of obesity) or for different health conditions.

More fundamentally, there was no reliable evidence based on individual participant data pertaining directly to the UK. Given differences between countries in terms of healthcare organisation, delivery, and financing, and in population characteristics, it is important to generate evidence for different jurisdictions. In the absence of individual participant data, policy analyses in the UK have been informed by studies using a population attributable fraction approach to estimation [18–22]. This involves first defining a number of conditions thought to be related to obesity, identifying the incidence and costs of each condition, and, using published data on relative risks of these conditions by levels of the exposure, allocating a portion of the incidence and costs of each condition to the exposure. However, PAF studies are subject to a number of important methodological limitations: they are often unable to fully account for the large number of health conditions associated with obesity or the clustering of these conditions within individuals; they are unable to capture the potentially complex relationship between level of BMI and costs; and the estimates of relative risk which are used to estimate population attributable fractions are not always applicable to the general populations typically

of interest in such studies. Moreover, policy makers, and healthcare planners, commissioners, and providers would benefit from a more detailed understanding of the incidence of the effects of excess weight on healthcare use and costs in different care settings and for different health conditions, in order to inform investment and prioritisation decisions. Such information can be generated from large-scale, detailed, and reliable individual participant data.

1.2 Research objectives

In this Thesis, I aim to conduct a detailed analysis of the associations between BMI and the use and costs of healthcare services in the UK. I do this using individual participant data from a large prospective cohort of over one million middle-aged and older women in England, the Million Women Study [23], linked to routine administrative data on deaths, hospital admissions, use of primary healthcare services, and prescriptions. Specifically, my main objectives are to:

- Undertake a systematic literature review of studies using individual participant data to estimate healthcare costs in relation to BMI, and summarise estimates of percentage differences in annual healthcare costs for overweight and obese adults compared to adults at healthy weight, overall and for different healthcare services, in different healthcare settings, for subgroups of individuals, and according to study characteristics.

- Estimate associations between BMI and rates and annual costs of different types of healthcare services – inpatient and day-case admissions, primary care consultations, prescription medications, and monitoring and diagnostic tests - among middle-aged and older women in England, and explore the extent to which these associations vary across subgroups of individuals defined by age, health behaviours, and socioeconomic indicators.

- Project estimates of annual healthcare costs by BMI for these different healthcare services to the 2013 population of women in England aged 55 to 79 years, and estimate total annual healthcare costs attributable to excess weight, and the distribution of excess weight attributable costs by weight category, both overall and, where possible, for different health conditions.

1.3 Structure of the Thesis

In **Chapter 2**, I present a detailed overview of obesity, focusing on the use of BMI as a measure of excess weight or adiposity, the current prevalence of overweight and obese individuals and trends in prevalence over time, both globally and in the UK, the health and economic consequences of excess weight, and the evidence on the effectiveness of interventions targeted at reducing excess weight or preventing weight gain. In order to provide necessary context for later Chapters of this Thesis, I also describe the system of publicly funded healthcare in the UK, with an emphasis on the structure of healthcare delivery and healthcare expenditure.

A systematic literature review of studies using individual participant data to estimate healthcare costs in relation to BMI is presented in **Chapter 3**. Estimates of percentage differences in annual costs for overweight and obese individuals compared to those at healthy weight are summarised across studies overall, for specific healthcare services, namely, inpatient care, ambulatory care, and medications, across individual characteristics like age and gender, and according to features of study design and analytical approaches to estimation. Finally, the evidence on healthcare costs of obesity in the UK is critically discussed.

In this Thesis I use data from the Million Women Study and linked administrative data to estimate healthcare costs in relation to BMI among middle-aged and older women in England. In **Chapter 4**, I describe the Million Women Study data in detail, concentrating on recruitment into the study, and the representativeness of participants compared to the contemporary population of eligible women. A detailed description is then given of the data sources to which Million Women Study participants recruited in England have been linked, namely National Health Service Central Registers for information on deaths and cancer registrations, Hospital Episode Statistics for cause-specific inpatient and day-case admissions, and the Clinical Practice Research Datalink, for information on the use of primary healthcare services. Finally, I summarise previous research into the effects of obesity on health risks that have been undertaken using Million Women Study data.

In **Chapter 5**, rates and costs of inpatient and day-case admissions are estimated in relation to BMI overall, according to subgroups of individuals, and for a range of health conditions. Estimates of overweight and obesity attributable costs are projected to the population of women aged 55 to 79 years in England, and the contributions of different health conditions to any overall excess weight attributable costs are estimated. Comparable analyses for primary healthcare services, namely primary care consultations, prescription items, and monitoring and diagnostic tests, are reported in **Chapter 6**.

In **Chapter 7**, I summarise the findings from the work undertaken in this Thesis, interpret them in the context of other relevant research, identify the novel contributions of the work, consider the implications for policy and healthcare planning, and describe the limitations of the work and potential areas for future research.

1.4 Role of the author in the preparation of this Thesis

I was awarded a National Institute for Health Research Doctoral Research Fellowship in October 2014 to undertake the research presented in this Thesis. This fellowship application was developed with the support of the Nuffield Department of Population Health, in particular the Health Economics Research Centre (Associate Professor Borislava Mihaylova and Professor Alastair Gray) and the Cancer Epidemiology Unit (Dr. Benjamin Cairns, and Professors Jane Green and Gillian Reeves).

I led the research presented in this Thesis, devising analysis plans, performing analyses, and preparing manuscripts and Thesis chapters. My supervisors (Associate Professor Borislava Mihaylova, Dr. Benjamin Cairns, and Professors Alastair Gray and Susan Jebb) contributed to each aspect of this process for all research presented in this Thesis. Other researchers from the Cancer Epidemiology Unit (Professors Jane Green, Gillian Reeves, and Valerie Beral) contributed to the research presented in **Chapters 5** and **6**, by providing critical discussion of the analyses and commenting on drafts of the corresponding manuscripts. Dr. Francesco Fusco, from the Health Economics Research Centre, was the second reviewer for the systematic literature review presented in **Chapter 3**. I am first author on each of the three manuscripts that have been written based on the research presented in this Thesis (two published, and one in preparation; see **Appendix A**).

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2

Background to body mass index and healthcare provision in the United Kingdom

2.1 Body mass index

Definition and categorisation of body mass index

Body mass index (BMI) is a measure of an individual's weight taking into account their height. It is calculated as weight in kilograms (kg) divided by height in metres (m) squared [kg/m^2]. It is a simple but widely used measure of excess weight or general adiposity (i.e. a state of excessive fat accumulation such that health may be adversely affected [1]). The categorisation of BMI recommended by the World Health Organisation (WHO) is widely used (**Table 2.1**). In this categorisation, adults with a BMI of 18.5 to <25 kg/m^2 are considered to be at healthy or normal weight,[1] adults with a BMI of <18.5 are considered underweight, those with a BMI of 25 to <30 overweight, and those with a BMI of $\geq$30 kg/m^2 obese. Obesity can be further categorised into grades 1 (BMI 30 to <35 kg/m^2), 2 (35 to <40 kg/m^2), and 3 ($\geq$40 kg/m^2) obesity. These measures have been recommended for use in population research in all adults, irrespective of age, gender, or ethnicity [1].

Table 2.1: The World Health Organisation's categorisation of body mass index

Classification	Body mass index (kg/m^2)
Underweight	<18.5
Healthy weight	18.5 to <25
Overweight	25 to <30
Obesity	$\geq$30
Grade 1 obesity	30 to <35
Grade 2 obesity	35 to <40
Grade 3 (or morbid) obesity[a]	$\geq$40

BMI derived from self-reported height and weight

Many epidemiological studies derive BMI from self-reports rather than measurements of height and weight, which may be subject to both random and systematic reporting

[1] The WHO uses only the term 'normal weight'. Other organisations like the Centers for Disease Control and Prevention additionally use the term 'healthy weight'. Throughout the rest of this Thesis, I use the term healthy weight, even though there is some evidence that there are differential health risks even within this BMI range [2].

errors. Random errors arise when repeat measurements or reports of an exposure produce different values; in BMI research this may arise because people do not know their exact weight and make an informed guess, which may show some tendency to vary. Random errors tend to attenuate estimates of linear associations between an exposure and disease risk (i.e. pull estimates towards the null). Systematic reporting errors in BMI arise because people tend to overestimate their height (particularly men) and underestimate their weight (particularly women), and these errors tend to be larger in heavier adults [3]. Systematic reporting errors of this nature can lead to misclassification of individuals according to obesity status, and bias estimates of linear associations between BMI and disease risks away from the null. In addition, changes in BMI over time could potentially generate biases in estimates of the association between disease risks and BMI at the time of report or measurement [4]. This is relevant since most studies estimating health risks in relation to BMI use a single value of BMI, usually taken at recruitment, and assume BMI to be stable over follow-up, which may last for many years. BMI derived from self-reported height and weight has, however, frequently been shown to be highly correlated with, and close to, BMI derived from measured values [5–11], even over a decade of follow-up [12].

Limitations of body mass index and alternative measures of adiposity

Despite the widespread use and advantages of BMI as a proxy measure of adiposity, it is subject to persistent criticisms [13, 14]. BMI does not distinguish between lean mass and fat mass, and hence may erroneously classify healthy, muscular adults as overweight or obese, and there are often substantial differences in percentage body fat among individuals with similar BMI [15]. As people age, their height tends to reduce and body composition changes, with higher amounts of fat for a given BMI in older compared to younger individuals [16]. Consequently, the use of standard BMI cut-points among adults aged 70 years or older has been questioned [15]. At the same BMI, women tend to have a higher proportion of body fat than men [13, 17], and the fat is differently distributed: in women, more adipose tissue tends to be accumulated in the hips and thighs rather than around the waist [18]. And some

epidemiological evidence suggests that the consequences of excess weight depends on its distribution, with abdominal fat more strongly associated with coronary heart disease and diabetes than fat distributed elsewhere [19–21]. There is evidence that the consequences of excess weight on health are greater for a given BMI in Asian compared to Caucasians adults [22, 23], and the use of alternative BMI cut-points for Asian populations has been proposed [23], although not recommended by the WHO [24, 25]. Similarly, for any given BMI, percentage body fat tends to be higher in black adults than in white adults [16].

Some other measures of adiposity provide information on the distribution of fat. Waist circumference and waist-to-hip ratio focus on abdominal fat, and have been shown in some [19, 21, 26], but not all [27], studies to be better at predicting the incidence of coronary heart disease, diabetes, and mortality than BMI alone. However, both measures are subject to important limitations. Neither measure can distinguish between abdominal visceral fat and abdominal subcutaneous fat [28]. Disease risk varies considerably at given levels of waist circumference and waist-to-hip ratio by gender and ethnicity, and so globally applicable cut-points are not available [1]. Finally, self-reports of these anthropometric variables exhibit greater measurement error and attenuation bias than BMI derived from self-reported height and weight [11, 12].

Methods to directly estimate total body fat and percentage body fat include densitometry, hydrometry, dual-energy X-ray absorptiometry (DXA), computer tomography, and magnetic resonance imaging. Though these methods provide more accurate measures of fat than BMI, they are expensive and time-consuming, and not practical for use in large-scale epidemiological research.

Summary

Although not without limitations as a proxy of adiposity at the individual level, BMI is useful for population research because it correlates well with direct measures of body fat within groups of people defined by age, sex, and ethnicity [16, 17, 29], and shows similar associations to these measures with health outcomes and metabolic

risk factors associated with obesity [30]. In addition, it is cheap and simple to collect, is well understood, and the widespread historical use of BMI allows comparisons between studies across place and time. BMI is recommended as the most useful measure of obesity for population research by the World Health Organisation [1].

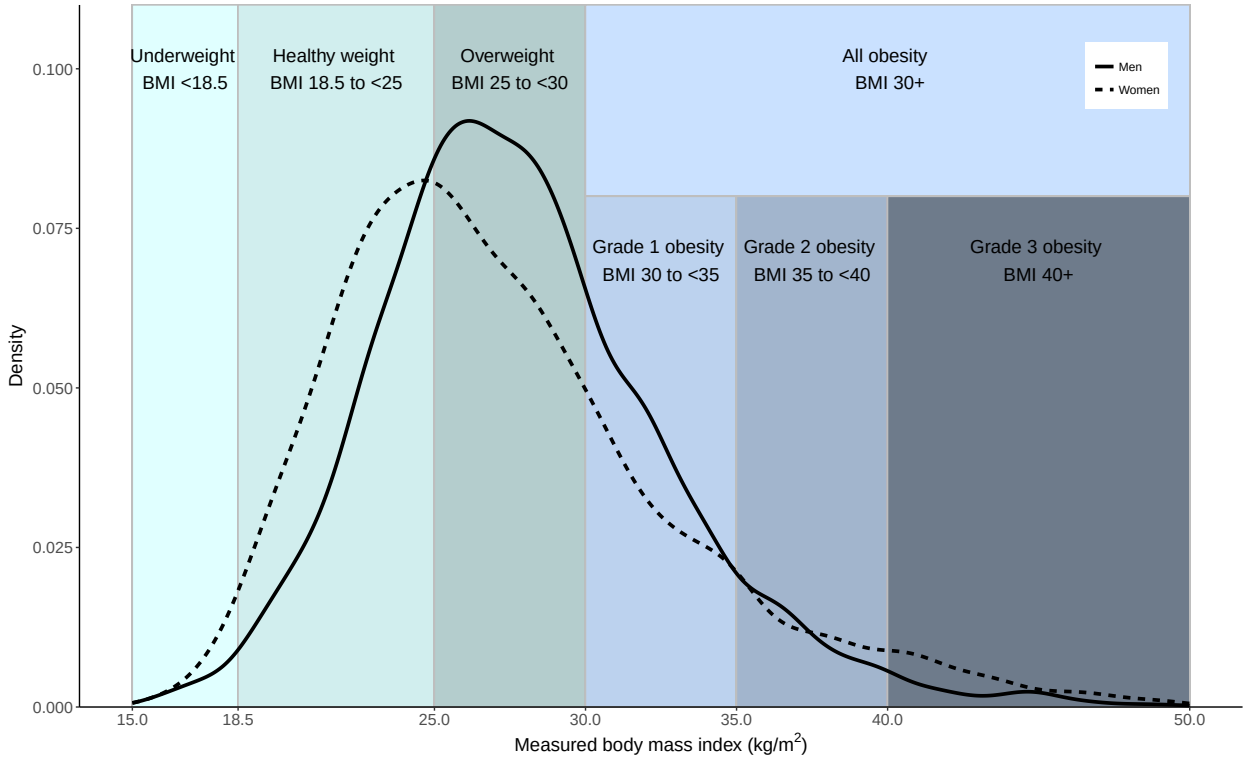
2.2 Distribution of body mass index

2.2.1 Current distribution of body mass index

Distribution of BMI by gender

Globally, mean BMI has been estimated to be 24.2 kg/m^2 in men and 24.4 kg/m^2 in women, with 37% of adult men and 38% of adult women overweight or obese [31]. The prevalence of overweight and obesity tends to be much higher in high-income countries like the UK than in low- or middle-income countries. In the UK, mean BMI is marginally higher in men than in women (27.6 kg/m^2 versus 27.1 kg/m^2), but the distribution of BMI is considerably more skewed in women (**Figure 2.1**). A smaller proportion of women than men are overweight or obese (58% versus 68%), but around 27% of both men and women are obese, meaning that a much larger proportion of those with excess weight are obese in women than in men. Morbid (or grade 3) obesity is twice as common in women as in men: 4% versus 2%.

Figure 2.1: Distribution of body mass index in England, by gender

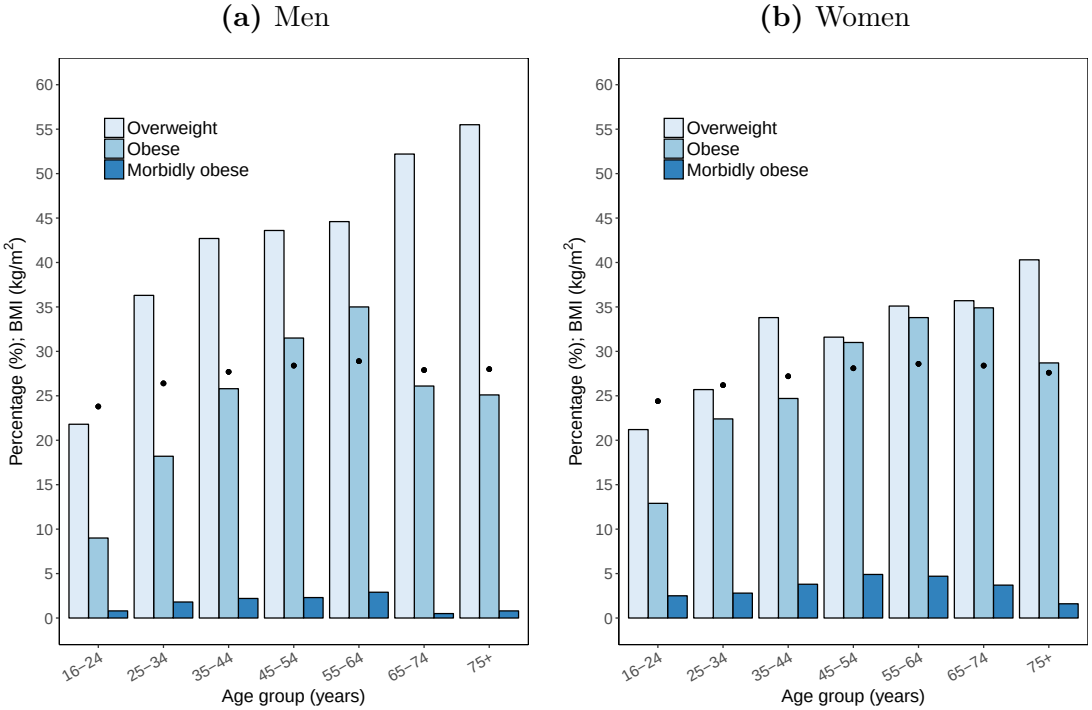


Source: Health Survey for England [32]

Distribution of BMI by age

In the UK, the proportion of the population who are overweight is continuously increasing with age in both adult men and women, while the prevalence of obesity is estimated to peak at age 55 to 64 years in men and at 65 to 74 years in women (**Figure 2.2**). Morbid obesity is most common in adults aged 55 to 64 years for both men and women. Mean BMI is increasing with age up to 55 to 64 years, after which it declines slightly. Among adults aged 55 years or older,[2] mean BMI is 28.3 kg/m^2 in both men and women, 50% of men and 43% of women are overweight, 29% and 31% are obese, and 2% of both men and women are morbidly obese.

Figure 2.2: Prevalence in England of overweight, obesity, and morbid obesity, and mean BMI, by age for (a) men and (b) women



Source: Health Survey for England [32]. The black circles represent mean BMI in kg/m^2.

[2]This age range is chosen because it accords most closely to the age range of the participants (55 to 79 years) at follow-up in Chapters 5 and 6 of this Thesis.

2.2.2 Time trends in the distribution of body mass index

Global trends

Between 1975 and 2014, the global age-standardised mean BMI was estimated to increase from 21.7 kg/m^2 to 24.2 kg/m^2 in adult men and from 22.1 kg/m^2 to 24.4 kg/m^2 in adult women [31], while the age-standardised prevalence of overweight and obesity increased from 29% to 37% in men, and from 30% to 38% in women [33]. Although absolute rates of overweight and obesity are higher in high-income countries than in low- and middle-income countries, the rates of growth have been higher in low-income countries; in fact, in many high-income countries there is some evidence that rates of overweight and obesity have increased less rapidly or even stabilised since around the year 2000 [31].

A critical discussion of the causes of the increase in population weight over the last few decades is beyond the scope of this Thesis. A large number of possible causes have been implicated encompassing supply-side factors, government policies, and changes in working conditions, but it has proven challenging to disaggregate the separate contributions of these [34–36]. A key driver is, however, likely to be the interaction between a changing food environment, in which energy dense foods have become more abundant, accompanied by more sedentary lifestyles [34, 37, 38].

UK trends

Trends in the prevalence of overweight and obesity in the UK are similar to those in many other high-income countries. Between 1975 and 2015, mean BMI was estimated to increase from 24.1 kg/m^2 to 27.6 kg/m^2 in adult men and from 23.4 kg/m^2 to 27.1 kg/m^2 in adult women [31, 32]. The prevalence of overweight and obesity increased from 45% to 68% in men and from 33% to 58% in women. Since around 2000, the combined prevalence of overweight and obesity has remained relatively stable. This, however, masks important differences by weight class: the prevalence of individuals who are overweight but not obese may have declined slightly in recent years, while the prevalence of obesity and morbid obesity has actually increased.

Healthcare investment and prioritisation decisions require forecasting future trends in the prevalence of overweight and obesity. Forecasting is, however, highly uncertain and different decisions, for instance, on whether to use only data from recent years or additional historical data, to guide estimates of future prevalence, have led to large differences in derived estimates of obesity-associated costs [26, 34].

2.3 Body mass index and health

2.3.1 Aggregate health burden of high body mass index

High BMI has been shown to be associated with premature mortality, and higher risks of a range of debilitating conditions, including type-2 diabetes, cardiovascular disease, osteoarthritis, and certain cancers. Because high BMI is also a common condition, the global health burden is substantial. Worldwide, high BMI was estimated to account for 4.0 million deaths ($\approx 7\%$) and 120 million disability-adjusted life years (DALYs)[3] [$\approx$5%] in 2015 [37], and to be the sixth largest cause of DALYs in men after high blood pressure, tobacco smoking, household air pollution, poor diet, and alcohol consumption, and the third largest in women after high blood pressure and household air pollution [39]. In the UK, where high BMI is more common, it is estimated to be the third largest cause of DALYs in men after tobacco smoking and poor diet, and the second largest in women after tobacco smoking [40]. 10% of DALYs in men and 9% in women in 2013 were due to high BMI.

Globally, the majority of deaths and DALYs associated with high BMI are estimated to be due to cardiovascular diseases (65% of deaths and 52% of DALYs annually, respectively), followed by type-2 diabetes (14% and 8%), chronic kidney disease (7% and 24%), cancers (9% and 7%), and musculoskeletal conditions (0% and 4%) [37]. The distribution of the health burden of high BMI across health conditions is likely to vary according to factors like population, setting, and age and gender. In England, the largest contributors to the DALYs due to high BMI are estimated to be cardiovascular disease (54% in men and 42% in women), diabetes and endocrine disease (25% and 31%), musculoskeletal conditions (8% and 14%), and neoplasms (13% and 13%) [40].[4]

[3] A DALY is a year of healthy life lost. It is a combination of years of life lost and poor health as a result of disability.

[4] No similar breakdown by age has been identified.

2.3.2 Mortality

Recent meta-analyses estimating all-cause mortality in relation to BMI using summary data [41] and using individual participant data [2, 42, 43] have reported higher rates of mortality with higher BMI beyond healthy weight. Using data on more than 10 million participants from 239 prospective studies globally, the Global BMI Mortality Collaboration reported the lowest rates of mortality among adults with BMI 20 to <25 kg/m^2 [2]. Every 5 kg/m^2 higher BMI beyond 25 kg/m^2 was associated with 31% higher mortality globally and 39% higher mortality in European cohorts. Mortality was positively associated with higher BMI in both men and women, and in adults of all ages. However, mortality was more strongly associated with BMI in men than in women, and in younger than in older adults: in European cohorts, every 5 kg/m^2 higher BMI beyond 25 kg/m^2 was associated with 70% higher mortality in men and 30% higher mortality in women,[5] and, for men and women combined, with 61% higher mortality in those aged 35 to 49 years at the time at which height and weight were measured or reported (median follow-up was 14 years), 43% in those aged 50 to 69 years, and 21% in those aged 70 to 89 years.

There has been some controversy surrounding the impacts of BMI on mortality risk. In an influential meta-analysis of published studies, Flegal *et. al.* [44], reported that, compared to being at healthy weight, being overweight was associated with reduced mortality and being mildly obese was associated with no additional mortality risk. This has, however, been demonstratively contradicted in meta-analyses using both published summaries and individual participant data [2, 41]. The results reported in Flegal *et. al.* [44] result from inadequate control for residual confounding by ill-health and smoking behaviour.

The association between BMI and cause-specific mortality was examined in an individual participant data meta-analysis of over 900,000 adults from 57 prospective studies [43], a subset of the studies contributing to the Global BMI Mortality Collaboration estimates [2]. Higher BMI was associated with elevated mortality

[5]The Million Women Study was the largest contributor to data on mortality in women in this study.

from diabetes (116% higher mortality risk for every 5 kg/m^2 higher BMI beyond 25 kg/m^2), ischaemic heart disease (39%), stroke (39%), other vascular disease (47%), non-neoplastic liver disease (82%), non-neoplastic kidney disease (59%), respiratory disease (20%), and cancer (12%; not including lung cancer).

2.3.3 Morbidity

Overview

High BMI has been linked to an increased incidence of a large number of health conditions [37, 45]. The Global Burden of Disease Obesity Collaboration [37] identified 20 health conditions for which associations with high BMI were likely to be causal, as assessed using the Bradford-Hill criteria [46]. The Bradford-Hill criteria consist of nine principles which can help understand whether an observed association may be causal: strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy. Higher BMI was considered to be causally associated with higher incidence of the following conditions: type-2 diabetes mellitus; cardiovascular diseases, namely, ischaemic heart disease, ischaemic stroke, and hypertension; musculoskeletal problems, namely osteoarthritis of the hip and knee, and lower back pain; chronic kidney disease; and several cancers, in particular cancers of the oesophagus, colon, rectum, liver, gallbladder and biliary tract, pancreas, breast (post-menopausal), uterus, ovaries, kidney, thyroid, and blood. Strong evidence of a lower risk with higher BMI for pre-menopausal breast cancer was also identified. High BMI has also been associated with increased risks of a range of other conditions including depression [47], sleep apnoea [48], asthma [49], gallbladder disease [50], and non-alcoholic fatty liver disease [51]. Probably as a result of these multifarious and wide-ranging effects, higher BMI is consistently associated with poorer health-related quality of life [52].

Diabetes

One of the strongest associations between higher BMI and higher incidence of disease is for type-2 diabetes [45, 53]. Compared to adults at healthy weight, overweight

and obese adults are 4 and 12 times more likely to develop type-2 diabetes in women, and three and seven times more likely in men [45]. Every 5 kg/m^2 higher BMI above 22 kg/m^2 was associated with 130% higher incidence of type-2 diabetes in men and 170% higher incidence in women [54]. There is some evidence that this association tends to be stronger in younger adults than in the elderly [55]: estimates of higher risk per 5 kg/m^2 higher BMI range from 207% among those aged 35 to 44 years to 38% among those aged 85 years or older. Overall, around three-quarters of cases of type-2 diabetes have been attributed to overweight and obesity [56].

Abdominal fat is thought to play an important role in insulin resistance and the development of metabolic syndrome: the chemicals released by fat cells in adipose tissue induce chronic inflammation that makes the body less responsive to the insulin it produces [57]. And there is strong evidence to suggest that abdominal fat is more strongly linked to diabetes than fat distributed elsewhere [58]. Weight gain, particularly in early compared to middle-to-late adulthood [59], and longer durations of exposure to obesity are associated with higher risks of developing type-2 diabetes [60].

Type-2 diabetes is a common condition, particularly in Western societies: in the UK around 6.2% of the adult population are diagnosed with type-2 diabetes [32]. The age-standardised prevalence of type-2 diabetes is about 40% greater in men than in women, and is strongly increasing with age for both men and women, with around 12% of adults aged 55 years or older having a type-2 diabetes diagnosis. Diabetes itself is associated with an increased incidence of a range of conditions including artherosclerosis, diabetic nephropathy, and diabetic retinopathy [61], reduced health-related quality of life [62], and premature death [63]. Diabetes mellitus has been estimated to be the eleventh largest single cause of DALYs in the UK, accounting for just over 1% of all DALYs [64]. Type-2 diabetes has been estimated to account for around 9% of government spending on healthcare in the UK, 90% of which is incurred in treating the complications of diabetes [65].

Cardiovascular disease

Using individual participant data on 220,000 participants from 58 prospective studies, the Emerging Risk Factors Collaboration estimated associations between BMI and cardiovascular diseases [27]. Every 5 kg/m^2 higher BMI beyond 20 kg/m^2 was associated with a 29% higher risk of coronary heart disease (CHD) and a 20% higher risk of ischaemic stroke. For both CHD and ischaemic stroke, the associations with higher BMI were similar in men and women (24% versus 30% for CHD, and 29% versus 27% for ischaemic stroke) but were weaker in older adults: for CHD, every 5 kg/m^2 higher BMI was associated with a 43% higher risk in those aged 40 to 59 years (at the time at which height and weight were reported or measured), 27% in those aged 60 to 69 years, and 14% in those aged 70 years or older; for ischaemic stroke the corresponding estimates were 39%, 27%, and 13%. Among middle-aged and older women in the UK from the Million Women Study, every 5 kg/m^2 higher BMI above 20 kg/m^2 was associated with a 23% higher risk of coronary heart disease [66] and a 21% higher risk of ischaemic stroke [67].

Both CHD and ischaemic stroke are usually caused by atherosclerotic narrowing of arteries due to the progressive accumulation of lipids and other fibrous elements in lesions within the arterial wall [68]. Other risk factors for cardiovascular disease include age, family history of cardiovascular disease, smoking, diabetes, blood pressure, and cholesterol levels. Higher body mass index is associated with higher incidence of diabetes, elevated blood pressure and hypertension, higher low density lipoprotein cholesterol, and lower high density lipoprotein cholesterol [57], and it is largely through these mechanisms that higher BMI increases the risk of cardiovascular disease [69]. The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration found that blood pressure, cholesterol, and glucose levels collectively accounted for 46% of the excess risk for CHD associated with excess weight and 76% of the excess stroke risk,[6] with blood pressure the most important mediator [69].

[6]This included both ischaemic and haemorrhagic stroke. However, some studies have reported flat or even inverse associations of haemorrhagic stroke risk with higher BMI [67].

In England, 4.6% of adults have a history of CHD and 2.4% have had a stroke. Prevalence is strongly increasing with age, with around 12% of adults aged 55 years or older having a history of CHD, and 6% a history of stroke [32]. The age-standardised prevalences of CHD and stroke are 85% and 45% higher, respectively, in men than in women. CHD was estimated to be the leading cause, and stroke the third leading cause, of years of life lost in England in 2013. CHD and stroke were the second and third leading causes of DALYs: collectively, they accounted for around 12.5% of all DALYs (8.5% CHD and 4% stroke). It was estimated that around one-fifth of total governmental healthcare expenditure in the UK is spent on treating cardiovascular diseases, of which around 22% and 30% were for CHD and stroke, respectively [70].

Chronic kidney disease

High BMI is associated with higher risks of developing chronic kidney disease and of its progression to end-stage renal disease [71]. Based on a meta-analysis of over 100 prospective studies, each 5 kg/m^2 higher BMI was found to be associated with a 10% higher risk of developing new-onset chronic kidney disease [72]. Obesity can cause CKD because it increases the risks of diabetes and hypertension, which are, in turn, independent risk factors of kidney disease. However, obesity may also exert independent effects on renal function, possibly by affecting hyperfiltration, glomerular capillary wall tension, and podocyte stress [73].

In the UK, the age-standardised prevalence of CKD stages 3 to 5 (not on renal replacement therapy) is estimated to be 11% in women and 6% in men [74]; 0.1% of people require renal replacement therapy [75]. The prevalence of CKD stages 3 to 5 is strongly increasing with age: from 6% in adults aged 45 to 64 years to 41% in adults 75 years or older. CKD was estimated to be the thirteenth largest contributor to DALYs in the UK, accounting for almost 1% of all DALYs [40, 64]. It was estimated that around 1.3% of UK governmental healthcare expenditure is on the treatment of CKD, around half of which is for renal replacement therapy [76].

Musculoskeletal conditions

Obesity is the most important modifiable risk factor for both the development and progression of osteoarthritis [77]. Two recent meta-analyses of the effects of excess weight on osteoarthritis of the knee [78] and hip [79], reported that each 5 kg/m^2 higher BMI was associated with a 35% higher risk of knee osteoarthritis and an 11% higher risk of hip osteoarthritis. The relationship between BMI and hip osteoarthritis was similar in men and women, while for knee osteoarthritis, the relationship was stronger in women than in men: 38% versus 22% higher risk of developing osteoarthritis for each 5 kg/m^2 higher BMI. A corollary of the higher risk of osteoarthritis is the greater need for knee and hip replacements, the rates of which are both substantially elevated in overweight and obese individuals. In middle-aged and older women in the UK from the Million Women Study, being obese was associated with 10.5 and 3.5 times higher risks of knee and hip replacements with a diagnoses of osteoarthritis, respectively, compared to being at healthy weight; 69% of knee replacements and 27% of hip replacements were attributed to excess weight [80]. Obesity was estimated to be associated with a 53% higher risk of lower back pain in the preceding 12 months compared to healthy weight, based on a meta-analysis of cohort studies [81]; the association was stronger for women than for men. High BMI is, however, associated with lower risks of osteoporotic fractures in women [82].

Obesity is thought to cause musculoskeletal damage as a result of both mechanical factors, including increased loading on weight-bearing joints and the spine, and effects on the biomechanics during everyday activities [83], as well as metabolic factors[7] [77, 81, 84], possibly by increasing levels of adipokines like leptin and adiponectin, which cause chronic inflammation and increase cartilage turnover, in obese patients [77]. However, the precise metabolic pathways remain unknown, as do the relative contributions of mechanical and metabolic factors. The inverse association with osteoporotic fracture may partly result from the production of oestrogens by adipose tissue, which are involved in bone metabolism [85].

[7]The risk of osteoarthritis is also increased for non-weight bearing joints like those in the hand.

Osteoarthritis is the most common musculoskeletal problem in older people: in the UK, around one-third of adults aged 45 years or older have sought treatment for osteoarthritis in primary care; around half of these cases were for knee osteoarthritis, and one-quarter for hip osteoarthritis [86]. Osteoarthritis prevalence is strongly increasing with age, and is more common in women than in men. Most people will experience some form of lower back pain in their lives, but in most cases the pain will persist for only a short period of time. Around one-third of UK adults will be affected by lower back pain in a given year [87], and prevalence is unrelated to age [88]. Collectively, musculoskeletal conditions have been estimated to be the single largest cause of disability globally [89], and to account for around one-third of all years lived with disability in the UK; lower back pain accounted for around 55% of this burden, while osteoarthritis accounted for about 8% [64]. Around 5% of governmental healthcare expenditure in the UK is estimated to be spent on treating osteoarthritis [90] and 2% on treating back pain [91].

Cancer

A number of studies have estimated associations between BMI and site-specific cancer incidence and mortality, with some variation in the types of cancer found to be associated with high BMI [92–94]. A systematic review and meta-analysis of 221 studies with 280,000 incident cancers [92] reported higher incidence rates per 5 kg/m^2 higher BMI for oesophageal adenocarcinoma (52% higher incidence rate), malignant melanoma (17%), and with thyroid (33%), colon (24%), renal (24%), and rectal cancers (9%) in men, and endometrial (59%), gallbladder (59%), oesophageal adenocarcinoma (51%), and with renal (34%), postmenopausal breast (12%), pancreatic (12%), thyroid (14%), and colon cancers (9%) in women. Each 5 kg/m^2 higher BMI was associated with an 8% lower risk of pre-menopausal breast cancer. The mechanisms by which adiposity influences cancer risk are not fully understood, but three hormonal systems which create cellular environments that favour tumour formation have been strongly implicated: the insulin and insulin-like growth factor axis, sex steroids, and adipokines [92]. In Western Europe, 3% of

all incident cancers in men and 8% of those in women were attributed to excess weight, with the difference being largely due to the sex hormone related cancers of the female reproductive system [95].

In the UK, around 670 women and 550 men in every 10,000 are diagnosed with a new cancer each year (excluding non-melanoma skin cancer) [96]. Half of all cancers in the UK are diagnosed in people aged 70 years or older, and more than half of new cases of cancer are breast, prostate, lung, or bowel cancer. Cancer is a leading cause of lost years of life and DALYs globally [97]. In England, neoplasms accounted for around 17% of all DALYs, similar to cardiovascular diseases (15%), around 85% of which was due to premature death [40, 98]. Cancer accounts for around 3% of governmental healthcare expenditure in the UK [99].

2.4 Body mass index and healthcare and non-healthcare costs

Because overweight and obesity are associated with large increases in the incidence of a range of chronic conditions, each of which is associated with poorer health and higher healthcare utilisation, excess weight has been consistently shown to be associated with substantial healthcare and non-healthcare costs [100–102]. Direct healthcare costs are those consumed when providing healthcare services to treat obesity and its sequelae. Non-healthcare costs are largely formed of foregone economic production as a result of illness.

Healthcare costs

Based on a systematic review of studies from around the world (mostly from the US), Withrow and Alter [100] reported that annual healthcare costs for obese individuals were 30% higher than for individuals at healthy weight, and that overweight and obesity accounted for 9% of national healthcare expenditure. Using only studies from the US, Tsai *et. al.* [101] reported higher annual costs for overweight and obese adults of 10% and 43%, respectively, compared to adults at healthy weight. There was also evidence from a number of studies that costs were increasing in the severity of obesity [103]. No prior systematic review has collated estimates of costs of overweight and obesity for different types of healthcare services.

Although there is clear evidence that excess weight is associated with elevated annual healthcare costs, because excess weight is also associated with premature mortality, the direction of difference in lifetime healthcare spending (which is often relevant for decision making [104]) by weight class is *a priori* ambiguous. Most studies based on either economic models of obesity [105–107] or individual participant data [108] report that obesity is associated with higher lifetime healthcare costs; however, others have reported lower costs [109].

Scarborough *et. al.* [110] estimated the annual costs of ill-health due to excess weight, poor diet, physical inactivity, smoking, and alcohol to the NHS in the UK. Overweight and obesity was estimated to account for £5.1 billion of NHS

expenditure in 2006-07. This is larger than corresponding estimates for physical inactivity (£0.9 billion), smoking (£3.3 billion), and alcohol (£3.3 billion), and exceeded only by the costs of poor diet (£5.8 billion).

Estimation was undertaken using a population attributable fraction (PAF) approach. This involves identifying conditions related with the exposure of interest, identifying the incidence and costs of each condition, and, using published data on relative risks of these conditions by levels of the exposure, allocating a portion of the incidence and costs of each condition to the exposure. Most evidence on the costs of excess weight pertaining to the UK were based on such indirect calculations [26, 34, 110–112].

PAF studies are often unable to fully account for the large number of health conditions which may be associated with obesity or the clustering of these events within individuals [100, 113], and cannot capture what is expected to be a complex relationship between level of BMI and healthcare costs [114]. In addition, the estimates of relative risks which are used to calculate attributable fractions are not always applicable to the population of interest in PAF studies. High-quality studies of individual participant data can help overcome many of these limitations, and allow for estimation of more nuanced associations between BMI and healthcare costs [100, 115]. However, there is no reliable evidence from individual participant data pertaining directly to UK.

Non-healthcare costs

Overweight and obesity are associated with large indirect costs to society because of increased presenteeism, absenteeism, disability, and premature mortality [102, 116]. The health conditions associated with excess weight including arthritis, fatigue, breathlessness, impaired concentration, and depression, mean that employees may not be able to work at their full capacity (i.e. presenteeism) or may take more sick-days (i.e. absenteeism) [116–121]. Particularly because of the musculoskeletal, circulatory, and mental disorders resulting from excess weight, that limit an individual's capacity to meet occupational demands, overweight and obese individuals are

more likely than healthy weight individuals to have short- or long-term absences from the labour market [116, 117, 122]. Finally, premature mortality due to the higher risk of death associated with higher BMI, in people of all ages, leads to fewer years of potentially productive labour market participation. Costs arise from foregone production and, in the case of disability, from disability payments by either governments or insurance companies. The total indirect costs of obesity have been estimated to be up to $66 billion in the US [116], the largest contributor to which is premature mortality. The Foresight report estimated the indirect costs of obesity to be £15.8 billion in the UK in 2007 [34, 111], of which 60% was due to sickness absence, and 40% to premature mortality. This is considerably larger than the estimated £4.2 billion in costs to the NHS [34].[8]

The costs of excess weight also fall on the overweight and obese individuals themselves due to lower probabilities of getting a job and lower wages conditional on getting a job [123]. The extent to which lower wages for obese adults are a result of discrimination, job absenteeism, or lower productivity on the job is unclear.

[8]This estimate differs from the £5.1 billion estimate reported in Scarborough *et. al.* [110] because of several important differences in methodology including in the diseases modelled. The Scarborough *et. al.* [110] estimate was also reported because it directly compared the costs attributable to obesity to those attributable to other health behaviours and characteristics using a common methodology.

2.5 Prevention and treatment of high body mass index

Overview

The high prevalence of excess weight in the population, and the increased recognition of its harmful effects on individual's health, as well as its impact on society, have prompted an increased focus on interventions designed to reduce excess weight or prevent weight gain. These range from population based interventions aiming to shift the distribution of BMI in the population to pharmacological, surgical, and behavioural lifestyle interventions targeted at individuals [35, 124, 125].

Interventions targeted at populations

Population based programs include: fiscal measures like taxes or subsidies on selected foods (e.g. sugar tax) [126–128]; health information or communication campaigns to increase awareness of the benefits of healthy eating and exercise, and promote healthy behaviours [125]; and regulatory measures such as the improvement of food packaging [128, 129] or restrictions on the advertising of unhealthy foods to children and adolescents [130]. Although such interventions generally have modest effects on individuals, because they affect a large number of people and are typically cheap to deliver, they have often been found to be highly cost-effective [124, 125]. However, most of the evidence on the effectiveness of such programs comes from retrospective observational or modelling studies, rather than randomised control trials or even before-after studies [124].

Interventions targeted at individuals

Interventions targeted at individuals include lifestyle behavioural interventions, and pharmacological and surgical treatments. Recent meta-analyses of behavioural weight loss programmes in primary care demonstrated that lifestyle interventions are, on average, associated with modest but clinically significant reductions in weight [131, 132]. Some studies have also reported that lifestyle interventions are cost-effective [133].

Based on systematic reviews of trials investigating the effectiveness of pharmacological treatments for obesity in adults, it has been shown that a range of drugs - orlistat, lorcaserin, naltrexone-bupropion, liraglutide, and phentermine/topiramate-ER - combined with lifestyle interventions increase weight loss by 1-5%, and improve cardiometabolic risk factors, compared to lifestyle interventions alone; however, no evidence of a reduction in cardiovascular morbidity or mortality has been observed [134–137]. Pharmacological treatment to reduce weight may also be cost-effective in the UK [137].

Finally, meta-analyses of bariatric surgery trials for weight loss reported greater weight loss, higher remission rates of type-2 diabetes and metabolic syndrome, and greater improvements in quality of life for surgical versus non-surgical treatment [138, 139], and surgery is likely to be cost-effective [140, 141].

Studies of interventions targeted at individuals have generally been based on small numbers of participants, with limited follow-up, and assessed intermediate, rather than hard, endpoints. Short-term follow-up is problematic because of the well-established tendency for participants in interventional studies who initially lose weight to regain weight. Franz *et. al.* [142] undertook a systematic review and meta-analysis of trials including diet, exercise, and pharmacological interventions, and found evidence of reductions in weight over the first six-months, followed by weight regain; however, participants at two years had still lost weight compared to baseline. In addition, some studies with long-term follow-up observed sustained benefits in terms of reduction in diabetes risk despite the tendency for weight to be regained [143, 144]. More reliable evidence on the effectiveness and cost-effectiveness of such interventions requires studies with longer follow-up and larger numbers of participants.

Summary

Although a diverse range of interventions have been shown to be effective in reducing weight or preventing weight gain, no single intervention is sufficient to reverse obesity at the population level. Instead, only a comprehensive, systemic program of multiple

interventions, targeted at both reducing weight among those already overweight and preventing weight gain, and involving a range of players, including national and local governments, retailers, consumer-goods companies, employers, media organisations, healthcare providers, and individuals, is likely to be effective [34–36].

2.6 Healthcare in the United Kingdom

2.6.1 Public healthcare in the UK

Public healthcare in the United Kingdom is provided by the National Health Services (NHS) of its constituent countries. The NHS was founded in 1948 and was based on three core principles: to meet the needs of all people, to provide free care at the point of delivery, and for access to be based on clinical need, not ability to pay [145]. The public health systems in Scotland and Northern Ireland were created separately from the NHS in England (which included Wales at inception) with their own legislation [146]. Responsibility for the NHS in Wales was transferred to the Secretary of State for Wales in 1999.

This Thesis uses data from England only, and so the rest of this section focuses mostly on the NHS in England. The NHS in England provides healthcare to all permanent residents in the UK. Healthcare is mostly funded through general taxation and largely provided free at the point of use; there are, however, charges associated with eye tests, dental care, prescriptions, and many aspects of personal care.

2.6.2 Healthcare provision

Primary care

The first point of contact with the healthcare system for most individuals in England is their general practice in primary care. General practices typically consist of partnerships of four to six physicians (general practitioners [GPs]), employing two to three practice nurses, and six to ten administrative staff. Practices also work closely with a wider primary healthcare team employed directly by the NHS, which generally includes health visitors, midwives, community psychiatric nurses, allied health professionals, and, less commonly, social workers [147]. There are around 7,500 GP practices in England, each providing care to an average of 6,500 people [148]. The average adult in England has around five consultations with staff from their GP practice each year, of which two-thirds to three-quarters are with a GP [149, 150]. Primary care is largely provided through face-to-face consultations in

the practice (≈ 86%), but also through telephone consultations (12%) and home visits (2%), for those who are unable to travel [149]. Primary care services also include dentistry, ophthalmology, and pharmacy.

Secondary care

GPs treat patients for conditions or illnesses that do not require specialist care. Where specialist care is required, individuals must be referred to outpatient clinics by their GP; individuals are not able to self-refer to these services. For emergency care, individuals can attend an accident and emergency (A&E) department or a minor injuries unit without appointment, from where they can be referred to specialist outpatient clinics for treatment (minor procedures) or investigation. Outpatient appointments are generally led by a consultant and do not use a hospital bed. There are around 70 million outpatient attendances annually in England, approximately 1.3 per person [151].

When a patient requires a hospital bed, they must be admitted to hospital. Individuals can be admitted to hospital as elective or emergency admissions. Elective admissions are planned procedures that have been booked either by the GP or the patient. There are around 15 million hospital admissions per year in England or 0.3 per person (i.e. around one admission every three years). Elective admissions account for around 50% of hospital activity in the UK, emergency admissions for 35%, and maternity and babies for the remaining 15%. Over 80% of elective admissions are day-cases, in which a patient is admitted to hospital, has the surgery and is then discharged on the same day, with no overnight stay [151]. Emergency admissions are defined as admissions which are unpredictable and occur at short notice because of clinical need. Patients can arrive as an emergency admission through various routes including A&E and Acute Medical Units (also known as clinical decision units, observation units, or acute assessment units).

Tertiary and community care

A&E, outpatient, and inpatient services, as well as longer-term care, rehabilitation facilities, and mental health hospitals, all constitute secondary care. Tertiary

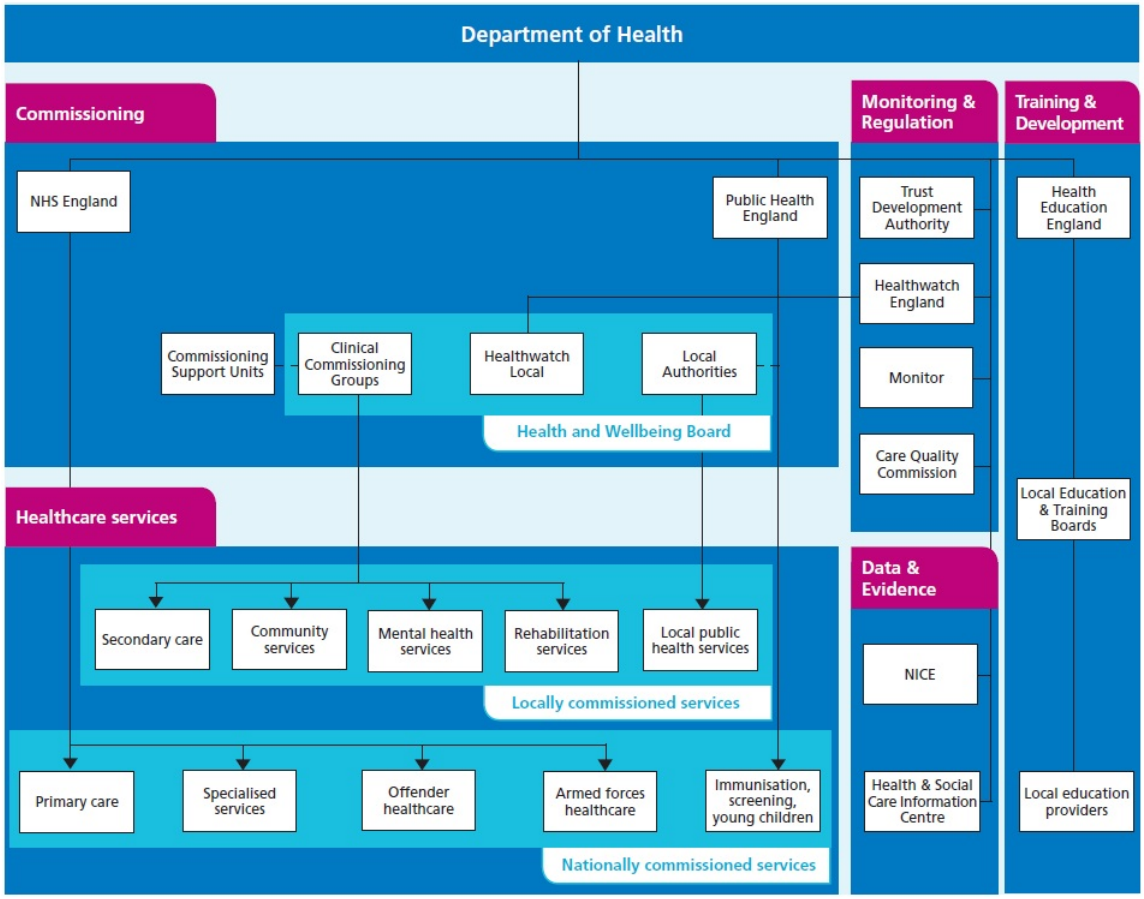
care, sometimes known as specialised care, is provided through highly specialised hospitals for illnesses that are uncommon or particularly complex, or that require highly specialised and expensive equipment. This includes neurosurgery, cardiac surgery, transplants, cancer management, and secure forensic psychiatric facilities. Community health care, which includes district nurses, health visitors, school nurses, community specialist services, hospital at home, NHS walk-in centres, and home-based rehabilitation, is provided in conjunction with social services to certain groups such as the elderly or people with learning disabilities living in the community.

2.6.3 Organisation of the NHS in England

The structure of the NHS in England is presented schematically in **Figure 2.3**. The Department of Health takes overall responsibility for public health, the NHS, and social care in England. It spent £119 billion in 2015-16 [152]. The Department of Health allocates around 90% of its budget to NHS England, an independent body established in 2013, which oversees the commissioning of health services in England. Around 30% of NHS England's budget is retained by NHS England to finance its operational costs and to directly commission services nationally, including primary care services (general practitioners, pharmacists), and specialised healthcare services, each accounting for around 10% of the NHS budget. The remainder of the budget is distributed to Clinical Commissioning Groups (CCGs) who are overseen by NHS England [153]. There are around 210 CCGs in England, each covering a population of around 250,000 individuals, and who commission services for their local populations, including secondary care (urgent and emergency care, and elective hospital care, including outpatient services and elective surgery), community care, mental health services, and rehabilitation services.

Acute trusts provide secondary care as well as more specialised services like tertiary care and, in conjunction with social services, community care. Most activity within acute trusts is commissioned by CCGs, but specialised services are centrally commissioned by NHS England. Inpatient and social care services for people with major psychiatric and psychological illnesses are largely provided by mental

Figure 2.3: Structure of the NHS in England



Source: BMJ and NHS England [153]

health trusts, which are commissioned by CCGs. Emergency care is provided by ambulance trusts, and community healthcare services are provided by community health trusts. Primary care services are delivered by a range of providers including general practices, dentists, optometrists, pharmacists, walk-in centres, and NHS 111.

2.6.4 Healthcare expenditure

Total spending on health and healthcare

The UK public sector spent £220 billion (in 2016-17 prices) on health, social care, and benefits to support people with disabilities and health conditions in 2015-16, around 11.5% of UK Gross Domestic Product (i.e. the value of all goods and services produced in a year) [152]. Of this, £141 billion (64%) was spent on health, £30 billion (14%) on social care, and £50 billion (23%) on benefits.

Government expenditure on health, which accounts for more than 80% of total healthcare expenditure [154], has increased greatly over time, and at a much faster rate than national income: 7.4% versus 2.8% on average per year since 1955-56. Spending per person has followed a similar trajectory over time, and shows some regional variation: in 2016-17 healthcare spending per person was lowest in England (£2100) and highest in Scotland (£2200).

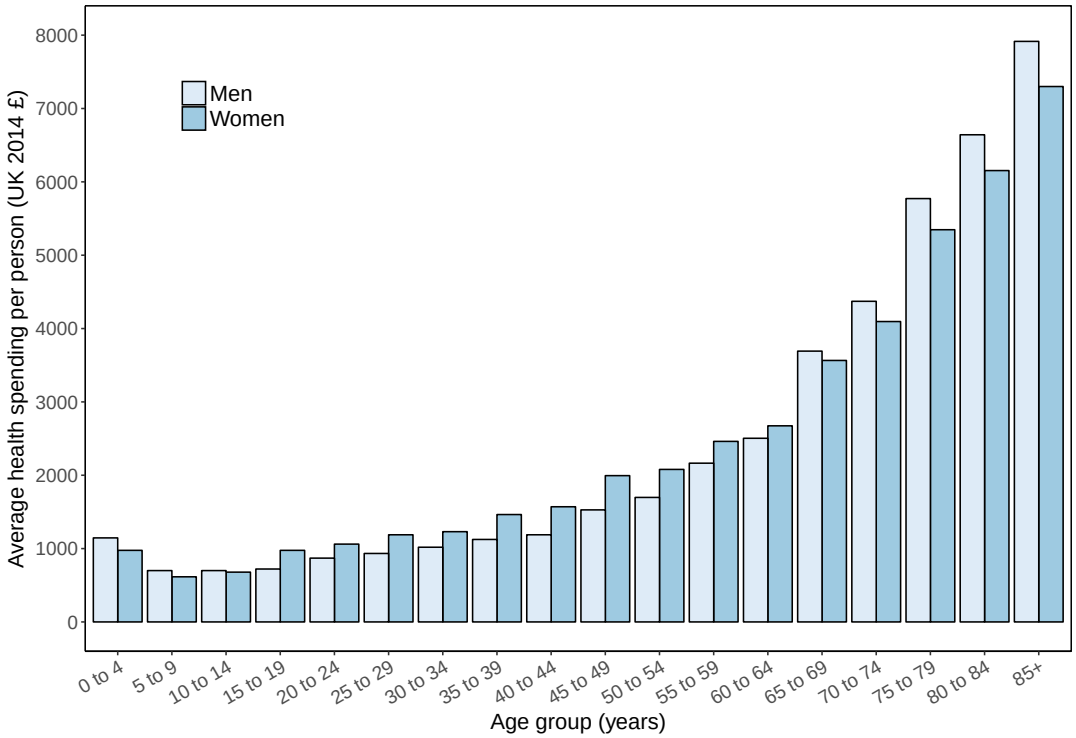
Healthcare spending by age and gender

Healthcare spending per person is strongly increasing with age for both men and women (**Figure 2.4**). Around two-thirds of NHS spending is on adults aged above 65 years or older [155]. For adults aged 60 years or older, average spending is higher for men than for women. Population ageing has been implicated as a major contributor to the increases in healthcare spending over time [156, 157], and as the age distribution of the population continues to shift rightwards in the coming decades [158], healthcare expenditure is expected to increase further [156].

Healthcare spending by activity

According to UK health accounts [159], almost 50% of all healthcare spending is on hospital care. Of this, about 70% is on admitted patient care (59% on inpatient and 11% on day-case care) and 30% on outpatient care. Only around 2% of spending is on A&E services. Non-hospital ambulatory care accounts for around one-quarter of total expenditure. Around one-third of this (or 8% of total spending) is on general practitioners, one-quarter on home healthcare, one-tenth on dental care, and the remainder on other services including community care. Medical goods, which largely consists of pharmaceuticals, and therapeutic devices and appliances dispensed in the community, account for 10% of total healthcare spending. Long-term health care accounts for about one-eighth of total spending; 60% of this is provided by residential long-term care facilities, and the remainder by ambulatory providers.

Figure 2.4: Average health spending per person in the UK 2013-14



Source: Based on data provided by the Nuffield Trust [155]

2.7 Summary

In this Chapter, I summarised the evidence on the health and economic implications of excess weight, and provided an introduction to the UK National Health System focusing on healthcare delivery, organisation, and expenditure. In the next Chapter I present a detailed critical appraisal and quantitative summary of the existing evidence on the association between BMI and healthcare costs estimated using individual-participant data.

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3

Systematic literature review of studies using individual participant data to estimate healthcare costs in relation to body mass index

Summary

Previous reviews of studies estimating healthcare costs in relation to body mass index (BMI) found consistent evidence that overweight and obesity are associated with higher total healthcare costs. However, how the associations between BMI and healthcare costs vary across different types of healthcare services has not been well described. In this chapter, I report a systematic literature review of studies using individual participant data to estimate healthcare costs in relation to BMI. EMBASE and MEDLINE were searched from January 1990 to September 2016, and 75 studies were included in the review. I describe differences in data and methods between studies, and generate and summarise estimates of percentage differences in annual healthcare costs for overweight (BMI 25 to <30 kg/m^2) and obese ($\geq$30 kg/m^2) adults compared to adults at healthy weight (18.5 to <25 kg/m^2), overall and separately for inpatient care, ambulatory care, and medications. 39 studies presented sufficient information to contribute to the quantitative summary of results. Compared to adults at healthy weight, the median percentage differences in mean total annual healthcare costs across studies were 12% for overweight and 36% for obese adults. The percentage differences in costs were highest for medications (18% for overweight and 68% for obese adults), followed by inpatient care (12% and 34%), and ambulatory care (4% and 26%). There was no reliable individual participant data pertaining directly to the UK.

3.1 Background

Previous systematic reviews of the published literature have identified consistent evidence that obesity is associated with higher total healthcare costs [1, 2]. This is a consequence of the large number of conditions for which high BMI is a risk factor, including heart disease, ischaemic stroke, type-2 diabetes, osteoarthritis, and certain cancers, all of which entail large costs of treatment. The previous reviews examined the published literature on obesity and healthcare costs up to 2009; included population attributable fraction studies, modelling studies, and individual participant data or database studies;[1] and focused on summarising the total healthcare costs in relation to obesity and comparing results across the different study types [1–3]. These reviews reported average elevated total healthcare costs of around 10% for overweight adults and 30–40% for obese adults compared to healthy weight adults based only [2, 3] or mostly [1] on studies undertaken on individuals resident in the US.

The review presented in this Chapter focuses exclusively, and in greater detail, on studies which used individual participant data to estimate associations between BMI and healthcare costs. Studies of individual participant data enable direct and more detailed investigation of associations between BMI and healthcare costs, taking account of population heterogeneity [1], and offer greater capacity to overcome epidemiological challenges such as confounding, reverse causality, and measurement error [4]. I also extend previous reviews by including relevant published literature up to 2016 and summarising data on the relationship between BMI and annual healthcare costs for different healthcare services, namely inpatient care, ambulatory care, and medications, for categories of participants by age and gender, and by study characteristics and analytical methods.

[1] This included some studies which had data at the level of, for instance, different companies but not on individuals within those companies.

3.2 Systematic literature review: methods

3.2.1 Search strategy

MEDLINE and EMBASE were searched from 1 January 1990 to 19 September 2016. The search strategies, developed from the search terms used in National Institute for Health and Care Excellence clinical guidelines in obesity [5], and in conjunction with an information specialist,[2] are presented in **Appendix Tables B.1-B.2**.

3.2.2 Inclusion criteria

Following the exclusion of duplicate records, titles, abstracts, and full texts were reviewed. Studies were excluded at each stage if they were in contravention of any of the following criteria:

- Peer-reviewed, full-text, English language research.
- Data on healthy weight people (BMI 18.5 to <25 kg/m^2) was included.
- Participants were not selected based on the presence of specific medical conditions, and the study did not exclude nonusers of healthcare services.
- For interventional studies, outcome and exposure data were both observed prior to the receipt of the intervention.
- The study sample was restricted to adults or results were estimated separately for adults.
- The direct association between body mass index (not stratified by other adiposity measures) and healthcare costs was estimated using individual participant data.
- Healthcare costs were estimated separately from other types of cost.

[2] I thank Nia Roberts from the Bodleian libraries for her advice.

Reference lists of all included studies were checked to identify any additional research not identified by the database search. I completed study screening and selection. Another reviewer independently performed the study screening and selection process based on 1,000 randomly selected articles (9%).[3] The second reviewer excluded fewer articles by title and abstract, but we identified the same set of studies as meeting all inclusion criteria after full-text review.

Where more than one study meeting all inclusion criteria used the same dataset (with at least some overlapping years of data) and methods, only the study with the highest quality rating (see below) or, if of equal quality, the study providing the largest amount of information to data extraction, was retained. Studies using the same dataset but without overlapping years of data were all retained. Studies using the same dataset with some overlapping years were retained for data extraction if the analytical methods differed materially; however, when summarising quantitative results only one of these studies was used, following the criteria defined above.

3.2.3 Quality assessment

Study quality was assessed using the National Heart, Lung, and Blood Institute's quality assessment tool for observational cohort and cross-sectional studies (**Appendix Table B.3**) [6]. This tool is focused on assessing the internal validity of a study and includes questions to help identify risk of selection bias, information bias, measurement bias, and confounding. Studies are classified as being of good, fair, or poor quality according to the reviewer's assessment of the overall risk of bias arising from these different sources. The quality assessment tool was applied to all studies which met the inclusion criteria by both reviewers, and disagreements on the overall quality assessments (regarding 11 studies [15%]) were resolved through discussion.

Resource use data was expressed either in natural units (e.g. number of outpatient appointments) with unit costs from other sources attached, or directly in costs (e.g. in claims databases or expenditure surveys). Outcome data was considered to be valid and reliable (Q11) if it was derived from administrative

[3]Francesco Fusco from the Health Economics Research Centre, University of Oxford, performed the second review.

databases or, if self-reported, validation work had been undertaken to ascertain the validity of the reported data (e.g. Medical Expenditure Panel Survey).

3.2.4 Data extraction

For each study which met the inclusion criteria, detailed information was extracted on participant characteristics, the reporting of BMI, the assessment of costs, the analytical methods, and the results. Results for each study were summarised in terms of percentage differences in mean costs for each BMI category in comparison to a healthy weight reference group where available, and otherwise in comparison to the study-specific reference group. Where possible, results were extracted for total healthcare costs, and separately for inpatient care, ambulatory care (defined to include both specialist outpatient care and primary care), and medication costs (which can include over-the-counter medications); the specific components constituting each of these categories varied between studies. Total healthcare costs were considered observed if a study included, at a minimum, inpatient, ambulatory, and prescription medication costs (some studies will include additional services like nursing care), or if the study defined the outcome as total healthcare costs without necessarily specifying the specific components. For total healthcare costs, results are also extracted for subgroups defined by age and gender, where possible. I extracted data from each study and the second reviewer independently extracted data from 14 studies (19%); no inconsistencies were identified.

3.2.5 Data analysis

Estimation of percentage differences in healthcare costs by categories of body mass index

To generate comparable summary estimates across different studies, estimates from each study were converted, where possible, to percentage differences in mean costs for adults in underweight (BMI <18.5 kg/m^2), overweight (25 to <30 kg/m^2), and obese categories (grade 1: 30 to <35 kg/m^2; grade 2: 35 to <40 kg/m^2; and grade 3: ≥ 40 kg/m^2), as well as a combined obesity category (BMI ≥ 30 kg/m^2), compared to adults at healthy weight; this categorisation is based on the recommendations

of the World Health Organisation [7]. Studies were included in the quantitative summary of results if mean annual costs (or costs over a shorter period of time, but not relating to a single medical event) were presented or could be derived for the above-defined BMI categories relative to an appropriate healthy weight group. The BMI range of the healthy weight reference group differed between studies contributing to the quantitative summary, however all were within the range 18.5 to <25 kg/m^2, except in one study which included a small number of underweight individuals. Notably, studies in Asian populations tended to use lower BMI cut-points, which were argued to be more relevant to the target population [8]. Where these were explicitly interpreted within the studies in terms of the overweight and obesity categories defined above, results were mapped to these categories.

Presentation of results

Results for underweight, overweight, and obese adults are summarised across studies by the median (and interquartile range) of percentage differences in mean costs compared to adults at healthy weight (these are henceforth referred to as median estimated effects in this Chapter). These summary statistics are presented graphically using Box plots.

Summary results are reported for total healthcare, inpatient care, ambulatory care, and medication costs. For total healthcare costs, results are also presented by gender (male, female), by study population as a proxy for age (all adults, only working age adults, only middle-aged and/or elderly; following the precedent of previous reviews [1, 2]), and according to whether the study used data from the US (as in the majority of included studies) or elsewhere. Summary results for total healthcare costs are also reported by overall study quality (good/fair, poor) and for selected data characteristics and analytical methods: mean length of study follow-up (>1 year, $\leq$ 1 year); overall study sample size ($\geq 10,000$, <10,000); whether the study was prospective (i.e. information for the calculation of BMI was taken at or prior to the start of the outcome data collection period); whether the study adjusted appropriately for confounders (defined as adjusting for basic demographic

characteristics like age and gender, measures of deprivation or socioeconomic status, and/or other health behaviours like smoking, while not adjusting for characteristics on the causal pathway between BMI and costs like diabetes or coronary heart disease); and, whether an explicit attempt was made to account for confounding by pre-existing disease (e.g. exclusion of individuals with pre-existing cancer or other conditions potentially affecting weight and costs, exclusion of early years of follow-up, or the use of statistical techniques like instrumental variable regression). These characteristics were chosen because they were the main areas of methodological variation between studies and, in some cases, had been associated with variations in results in previous studies [1, 2].

Sensitivity analyses

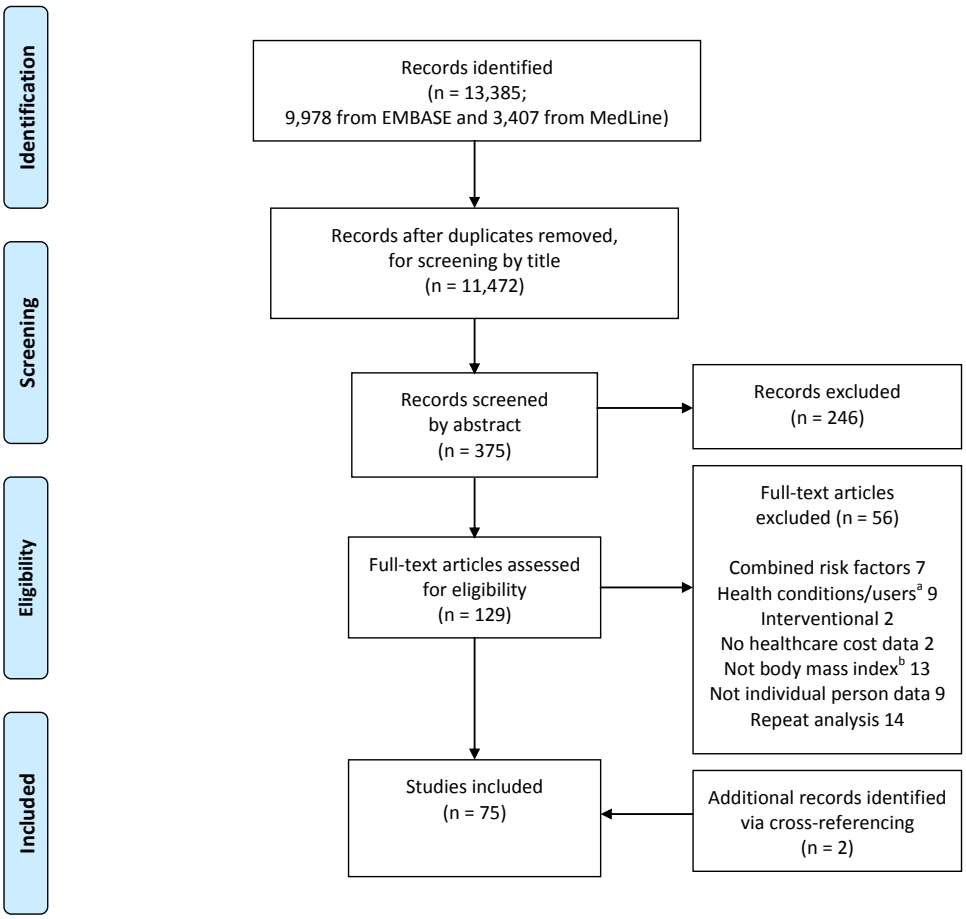
Sensitivity analyses were performed: including only studies of good or fair quality; including partial duplicate studies, i.e. studies using the same data and methods as one or more other studies, with some but not complete overlap in time periods; excluding studies in Asian populations in which non-standard BMI categorisations were used; and, excluding studies with outcome periods less than 1 year.

3.3 Systematic literature review: results

3.3.1 Search strategy

The literature search yielded 13,385 records (9,978 from EMBASE; 3,407 from MEDLINE) [**Figure 3.1**]. 129 studies were included in the full-text review after exclusion by titles and abstracts; 73 met all inclusion criteria. Two further studies were identified and included following review of the reference lists of included articles. In total 75 studies were included in the systematic review [9–83].

Figure 3.1: Search results and exclusions



[a]Individuals were selected based on the presence of certain pre-existing conditions (or because they were at particularly high risk) or because they were users of healthcare services.
[b]Includes studies which used measures of adiposity other than body mass index, stratified body mass index by other measures of adiposity (usually waist circumference), estimated costs following changes in BMI categories, or did not state how adiposity was measured.

3.3.2 Data and methods of studies included in the review

Data characteristics of included studies

Table 3.1 summarises the characteristics of included studies (complete information for each study is presented in **Appendix Table B.4**). The median sample size across all studies was 11,572 (interquartile range: 4,545 to 29,925). Most studies (n=44, 59%) were based on individuals resident in the US. Almost half of studies (n=33, 44%) sampled general, but not necessarily representative, adult populations; other studies included only adults of working age (usually 18 to 65 years; n=24, 32%), or only middle-aged or older adults (aged 40 years and above; n=18, 24%). Majorities of studies derived BMI from self-reports of either or both height and weight (n=55, 73%), obtained data on resource use or costs from mainly routine administrative data sources (n=44, 59%), and collected sufficient data to allow the calculation of total healthcare costs (n=56, 75%). Approximately half of studies (n=39, 52%) collected information on outcomes for 1 year or less, and in 31 studies (41%) BMI was derived from height and weight reported or measured prior to the outcome assessment period (the median follow-up time in these studies was 1.5 years).

Analytical methods of included studies

Most studies used regression modelling to relate healthcare costs to BMI (65; 87%) and adjusted for some key confounders without overadjustment for conditions on the causal pathway between BMI and healthcare utilisation (n=44; 59%) [**Appendix Table B.5**]. Relatively few studies (18, 24%) attempted to deal with confounding by pre-existing disease by excluding individuals with known conditions that could influence both weight and costs, or by excluding early years of follow-up to account for unobserved or undiagnosed conditions; four studies used instrumental variable regression in either the main analysis or a supplementary analysis.

BMI was almost always categorised (n=70, 93%) rather than considered as a continuous variable or results presented for each integer of BMI: 49 studies used the standard World Health Organisation BMI classification [7], while four studies, all from countries in east Asia, used other classifications, which the authors argued were

more applicable to the populations studied. 64 studies (85%) presented estimates of annual costs in relation to BMI. Among all studies, 30 did not present results by any subgroup of participants, 18 presented results by age categories, 28 by gender, and four by race and/or ethnicity. Overall, 23 studies (31%) were classified as good quality, 28 (37%) as fair, and 24 (32%) as poor (a quality score for each study is reported in **Appendix Table B.6**).

Table 3.1: Characteristics of studies included in the systematic review by study quality

		Study quality		
	All studies	Good	Fair	Poor
Number of studies				
(number contributing to quantitative summary[a])	75 [39]	23 [14]	28 [15]	24 [10]
Region				
United States	44 (59)	14 (61)	18 (64)	12 (50)
Europe	15 (20)	3 (13)	4 (14)	8 (33)
Asia	7 (9)	3 (13)	3 (11)	1 (4)
Other[b]	9 (12)	3 (13)	3 (11)	3 (12)
Study population				
All adults	33 (44)	9 (39)	12 (43)	12 (50)
Working age adults	24 (32)	8 (35)	8 (29)	8 (33)
Middle-aged or elderly	18 (24)	6 (26)	8 (29)	4 (17)
Sample size				
Median (IQR)	11572 (4545, 29925)	12520 (7544, 21669)	17118 (6743, 31205)	5990 (2204, 30132)
≥10,000 participants	39 (53)	14 (61)	16 (59)	9 (38)
<10,000 participants	35 (47)	9 (39)	11 (41)	15 (62)
Body mass index reporting				
Measured	20 (27)	6 (26)	7 (25)	7 (29)
Self-reported	50 (67)	17 (74)	21 (75)	12 (50)
Mixed[c]	5 (7)	0 (0)	0 (0)	5 (21)
Prospective study				
Yes	31 (41)	20 (87)	9 (32)	2 (8)
No	44 (59)	3 (13)	19 (68)	22 (92)
Outcome data				
Administrative records	44 (59)	11 (48)	18 (64)	15 (62)
Self-reported	16 (21)	4 (17)	5 (18)	7 (29)
Mixed	15 (20)	8 (35)	5 (18)	2 (8)
Length of outcome data collection period				
> 1 year	36 (48)	15 (65)	14 (50)	7 (29)
≤ 1 year	39 (52)	8 (35)	14 (50)	17 (71)
All types of direct healthcare costs included				
Yes	56 (75)	17 (74)	21 (75)	16 (67)
No	19 (25)	6 (26)	7 (25)	8 (33)

Values are number (%) unless otherwise stated.

[a]Studies contributing to results are presented in Appendix Table B.7. The quality score for each study is presented in Appendix Table B.6.

[b]Canada, Australia, and South Africa.

[c]Either self-reported height and measured weight, or measured height and weight for some, but not all, participants.

3.3.3 Quantitative summary of results

Characteristics of studies included in the quantitative summary

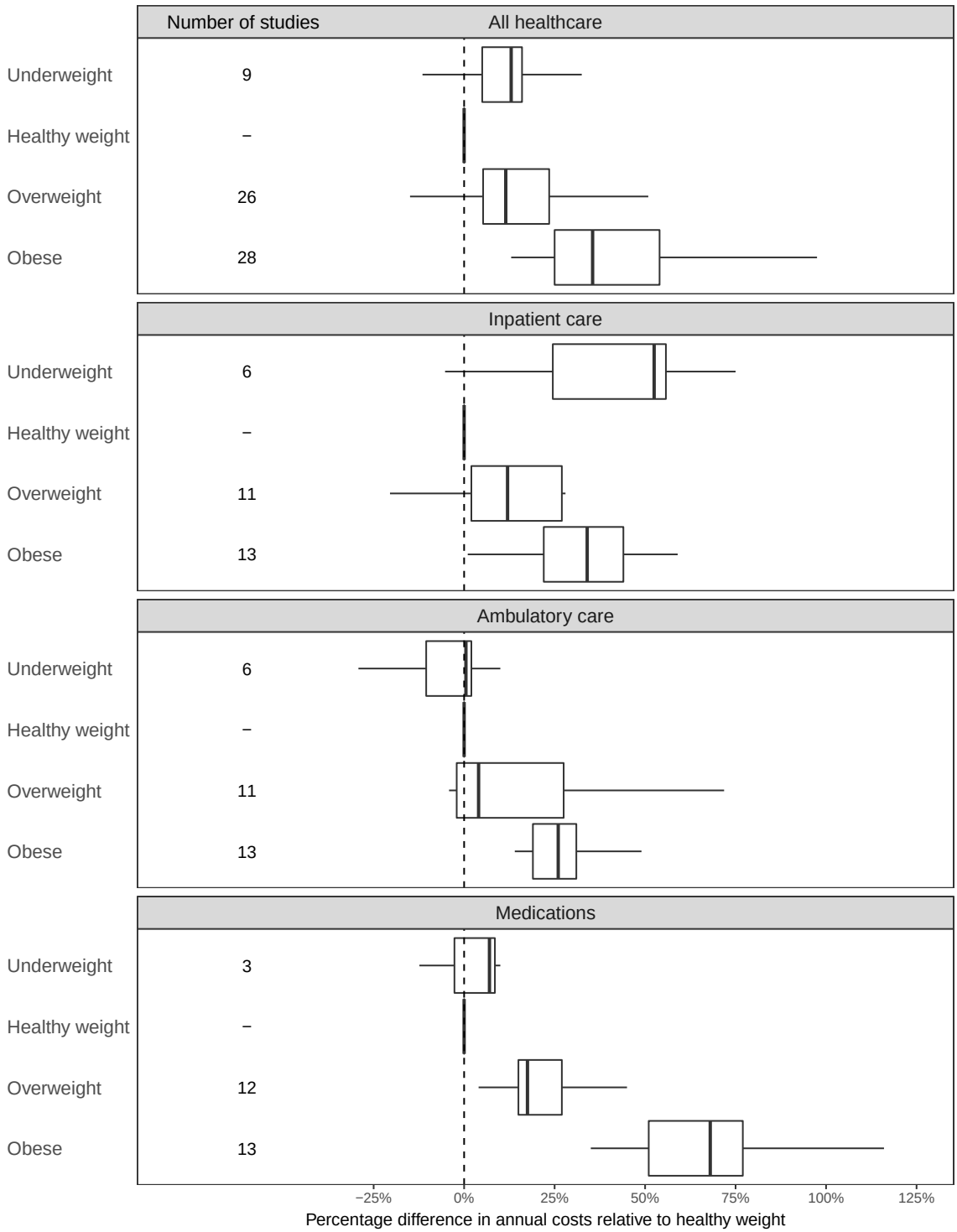
I excluded studies from the summary of quantitative results if: estimates of percentage differences in costs between BMI categories could not be derived (N=16); an appropriate healthy weight group was not used (N=11); only cumulative costs over more than one year were presented (N=5); overweight and obesity categories were combined (N=2); results were estimated as geometric rather than arithmetic means (N=1); or results were only presented by categories of cost other than those defined (i.e. inpatient and outpatient care combined, but without medications) [N=1]. A further five studies were considered partial duplicates and excluded from the main analysis, but were included in a sensitivity analysis. In total, 34 studies contributed results to the main summary of estimates. Lists of included and excluded studies, and reasons for exclusion are presented in **Appendix Table B.7**. Characteristics of included and excluded studies are summarised in **Appendix Table B.8**.

Overall results, by healthcare service

There was substantial variation between studies in estimates of mean differences in annual costs for overweight and obese adults compared to adults at healthy weight, for all types of healthcare services (**Figure 3.2** and **Table 3.2**; see **Appendix Table B.9** for detailed results from each study). Across studies, median percentage differences in total annual healthcare costs for overweight and obese adults, compared to adults at healthy weight, were 12% (interquartile range [IQR]: 5 to 24) and 36% (25 to 54), respectively. Median estimated percentage differences in annual costs for overweight and obese adults were strongest for medications (18% [15 to 27] and 68% [51 to 77], respectively), followed by inpatient care (12% [2 to 27] and 34% [22 to 44]). Ambulatory care costs were substantially higher for obese (26% [19 to 31]) but not overweight (4% [-2 to 28]) adults.

The same ordering of healthcare services by strength of association between BMI and costs was evident in most studies which presented results by more than one subcategory of healthcare costs: obesity was associated with greater percentage

Figure 3.2: Percentage differences in annual healthcare costs for underweight, overweight, and obese adults compared to adults at healthy weight, overall and for different healthcare services



The bold central bar represents the median percentage difference in annual costs. The horizontal extent of the box represents the interquartile range (i.e. 25th and 75th percentiles). Where only 3 studies are available, the lower quartile is given by the average of the lowest value and the median value, and the upper quartile by the average of the highest value and the median value. The left-hand bar is the larger of 1.5 times the interquartile range below the median or the lowest observed result. The right-hand bar is the smaller of 1.5 times the interquartile range above the median or the highest observed result.

differences in inpatient than in ambulatory care costs in 8 of the 12 studies in which this comparison could be made, and, in majorities of studies, with greater percentage differences in medication costs compared to either inpatient costs (5 of 7 studies) or ambulatory costs (7 of 7 studies).

Higher grades of obesity were associated with higher costs (**Figure 3.3**). Median estimated percentage differences in total healthcare costs for adults with grade 1 (BMI 30 to < 35 kg/m^2), 2 (35 to ≤ 40 kg/m^2), and 3 (≥ 40 kg/m^2) obesity, compared to adults at healthy weight, were 22% (IQR 20 to 25), 45% (25 to 49), and 50% (48 to 77), respectively. Among underweight women compared to women at healthy weight, inpatient care costs were substantially elevated (35% [20 to 56]), total costs somewhat elevated (13% [5 to 16]), but costs for ambulatory care (0% [-10 to 2] higher) and medications (7% [-3 to 9]) similar.

Sensitivity analyses

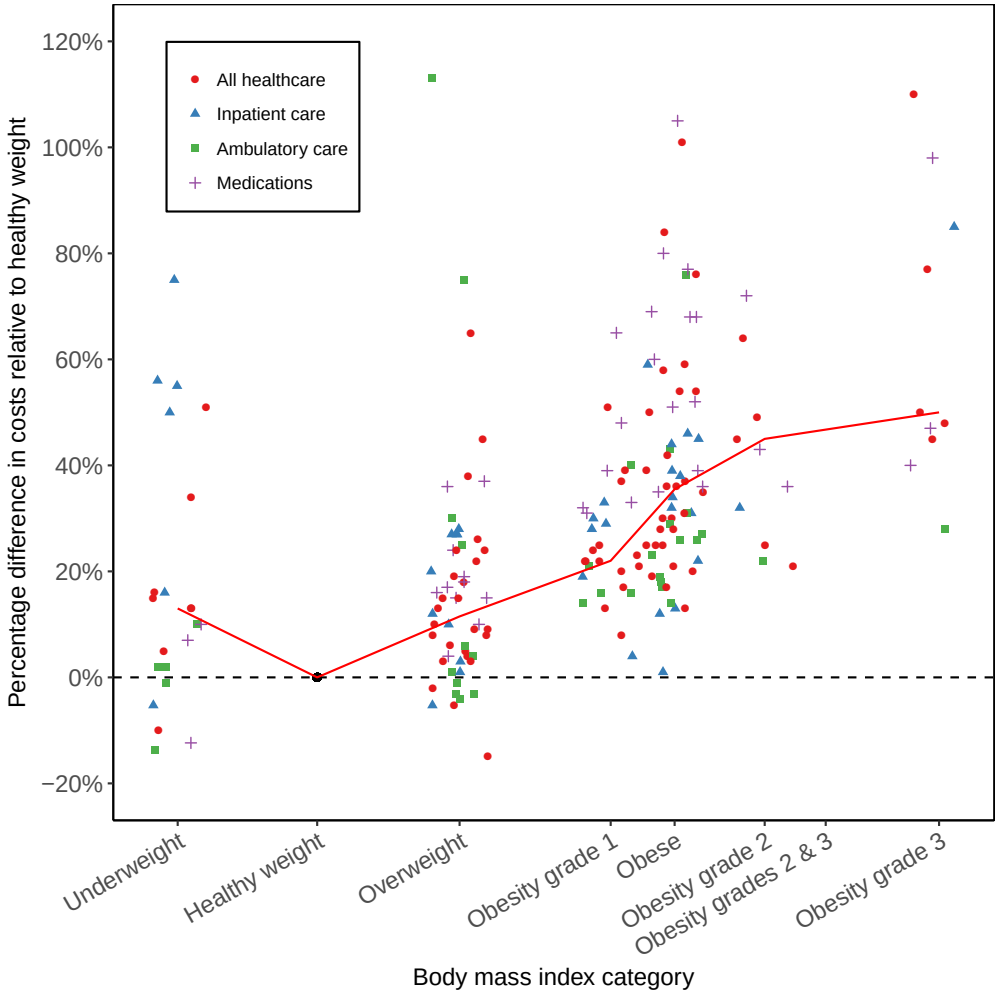
Median estimated percentage differences in costs were similar when: including only studies of good or fair quality; including the partial duplicate studies; excluding studies using BMI cut-points specific to Asian populations; or, excluding studies with an outcome period less than one year (**Appendix Table B.10**).

Results by age, gender, and country of study

For total healthcare costs, the median estimated percentage differences in costs associated with obesity across studies appeared to be slightly greater in women than in men: 50% [39 to 65] versus 40% [23 to 50]. Median differences in costs of 24% associated with being overweight were observed for both men and women (**Table 3.2**). In studies that presented results for both men and women, percentage differences in costs were higher for women than for men in 6 of 8 studies for overweight adults, and in 7 of 9 studies for obese adults (**Appendix Table B.11**).

The median estimated percentage differences in costs for obese adults were lower for older populations than for populations of only working age adults (30% [29 to 34] versus 45% [33 to 63]), but were similar for overweight adults (**Table 3.2**). Comparisons across studies presenting results for different age groups are

Figure 3.3: Percentage differences in annual costs for underweight, overweight, and obese adults, compared to adults at healthy weight, by type of healthcare service



Each symbol represents results from a single study. The red line links median estimates of relative differences in total healthcare costs for adults in each BMI category compared to adults at healthy weight.

limited by the inconsistent age categories used and the small number of studies. However, there was some indication of higher percentage differences in costs for overweight and obese adults going from young adulthood up to late middle age (up to around 60 to 65 years), after which percentage cost differences tended to be lower (**Appendix Table B.12**). The average percentage difference in costs for overweight and obese adults in studies conducted in US populations were similar to those in studies conducted in other populations (**Table 3.2**).

Table 3.2: Percentage differences in annual healthcare costs for underweight, overweight, and obese adults compared to adults at healthy weight, for different healthcare services and population categories

	Underweight		Overweight		Obese	
	Number of studies	Median cost difference (IQR)	Number of studies	Median cost difference (IQR)	Number of studies	Median cost difference (IQR)
Type of healthcare service						
All healthcare	9	13% (5, 16)	26	12% (5, 24)	28	36% (25, 54)
Inpatient care	6	53% (25, 56)	11	12% (2, 27)	13	34% (22, 44)
Ambulatory care	6	0% (-10, 2)	11	4% (-2, 28)	13	26% (19, 31)
Medications	3	7% (-3, 9)	12	18% (15, 27)	13	68% (51, 77)
Total healthcare costs, by population category						
Gender						
Males	4	7% (-3, 39)	8	24% (17, 26)	9	40% (23, 50)
Females	4	-17% (-23, -10)	9	24% (9, 40)	10	50% (39, 65)
Age distribution						
All adults	5	5% (-10, 13)	13	9% (6, 19)	14	34% (25, 48)
Working age adults	1	-	8	16% (7, 27)	8	45% (33, 63)
Middle-aged and elderly	3	34% (25, 42)	5	13% (4, 15)	6	30% (29, 34)
Study conducted in the United States						
Yes	2	-	14	12% (7, 21)	15	36% (30, 52)
No	7	13% (-2, 15)	12	12% (4, 24)	13	30% (25, 54)

IQR=Interquartile range

Results by data characteristics and analytical methods of studies

For total healthcare costs, the median estimated percentage cost differences for obese adults were marginally higher in studies considered as of good or fair quality than in studies of poor quality (36% [IQR 28 to 53] versus 28% [20 to 50]) [**Table 3.3**]. For overweight adults, the median estimated percentage differences in costs were similar for studies of good or fair quality and studies of poor quality (12% [4 to 24] versus 12% [7 to 18]).

Median estimated percentage differences in costs associated with being overweight or obese were similar across studies categorised by length of study follow-up, overall study sample size, and whether the study made an explicit attempt to deal with potential confounding by pre-existing disease. Median estimated percentage differences in costs for overweight and obese adults were higher in prospective studies than in cross-sectional or retrospective studies (21% [11 to 26] versus 9% [5 to 16] for overweight adults, and 39% [33 to 59] versus 28% [21 to 42] for obese adults), and lower in studies which made an appropriate attempt to adjust for confounding than those that did not (10% [4 to 19] versus 22% [11 to 55] for overweight adults, and 33% [27 to 37] versus 46% [25 to 77] for obese adults).

Table 3.3: Percentage difference in total annual healthcare costs for underweight, overweight, and obese adults compared to adults at healthy weight, by study characteristics

	Underweight		Overweight		Obese	
	Number of studies	Median cost difference (IQR)	Number of studies	Median cost difference (IQR)	Number of studies	Median cost difference (IQR)
Overall results	9	13% (5, 16)	26	12% (5, 24)	28	36% (25, 54)
Quality assessment rating						
Good or Fair	8	14% (1, 20)	20	12% (4, 24)	22	36% (28, 53)
Poor	1	-	6	12% (7, 18)	6	28% (20, 50)
Prospective study design						
Yes	4	3% (-13, 20)	10	21% (11, 26)	11	39% (33, 59)
No	5	13% (13, 15)	16	9% (5, 16)	17	28% (21, 42)
Length of study follow-up						
>1 year	5	13% (-10, 16)	14	12% (8, 24)	15	35% (29, 52)
≤ 1 year	4	14% (11, 24)	12	12% (5, 20)	13	36% (25, 54)
Study sample size						
$\geq 10,000$ participants	7	13% (-2, 14)	16	9% (5, 22)	17	31% (25, 50)
<10,000 participants	2	-	10	15% (11, 23)	11	36% (29, 56)
Appropriate adjustment for confounders						
Yes	7	13% (9, 25)	20	10% (4, 19)	22	33% (26, 48)
No	2	-	6	22% (11, 55)	6	46% (25, 77)
Attempt to account for confounding by pre-existing disease						
Yes	4	2% (-13, 14)	7	10% (9, 19)	8	33% (27, 37)
No	5	15% (13, 34)	19	15% (5, 23)	20	37% (25, 55)

IQR=Interquartile range

3.3.4 Contribution of health conditions to excess costs

Six studies based on data from the US [22, 29, 56, 72, 74, 84][4] and one study using data from Taiwan [57] estimated medical costs (usually inpatient and ambulatory care costs) in relation to BMI for specific medical conditions or categories of conditions. All studies classified medical events or claims using International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM) codes. In most studies, the principal ICD-9-CM codes were then allocated to major diagnostic categories.

For most diagnostic categories, medical (i.e. non-pharmacy) healthcare costs were consistently found to be higher in individuals with higher BMIs. For some categories, including neoplasms and respiratory diseases, elevated costs among overweight and obese adults were observed in some studies, while null effects were observed in others. Higher quality studies which estimated costs for a wide range of conditions, found both musculoskeletal and circulatory diseases to be the major contributors to total excess weight attributable costs, each accounting for between one-fifth and one-quarter of the total [56, 78]. Although one of the largest percentage differences in costs for overweight and obese adults tended to be for diabetes,[5] because spending on the direct treatment of diabetes in hospitals is relatively low (diabetes increases the risks of a range of conditions, including many cardiovascular diseases which are treated in hospital), the absolute contribution of diabetes to excess weight attributable costs within hospitals is also relatively low, with the highest estimates at around 10%.

Six studies estimated medication costs in relation to BMI by category of therapeutic use [33, 54, 56, 65, 70, 71]. Although the comparability between studies is somewhat limited due to the use of different therapeutic categories, these studies tended to find the strongest proportional effects of excess weight on costs for medications related to cardiovascular disease, diabetes, and pain

[4]Wang 2006 [84] was not included in the main literature review because it used exactly the same data as another paper [79], but is referred to here as it presents relevant results by medical conditions.

[5]Often incorporated into the larger major diagnostic category 10: Diseases and Disorders of the Endocrine, Nutritional, and Metabolic System.

(which was variously categorised as pain, non-steroidal anti-inflammatory drugs, drugs for osteoarthritis, and drugs for acting on the central nervous system). Cardiovascular medications tended to contribute by far the most to the total excess weight attributable medication costs, with estimates of its contribution ranging from 30% to 70%.

3.3.5 Evidence from the United Kingdom

In this Thesis, healthcare costs are estimated in relation to BMI among women in England. Only three studies were identified in the literature review which used individual participant data from the UK to estimate the relationship between BMI and healthcare costs. Two of these were based on the Counterweight Programme and one on data from the Clinical Practice Research Datalink (CPRD). The Counterweight Programme was an interventional study implemented in 65 general practices around the UK in 2002 with aim of improving weight management [28, 85]. The two studies used data prior to the intervention to estimate the relationship between BMI and healthcare costs [28, 73]. Total healthcare costs and costs of different healthcare services – hospitalisations, accident and emergency attendances, outpatient care, primary care, and prescription medications – were estimated for each integer of BMI; for total healthcare costs, the additional cost per unit higher BMI was also estimated. These studies reported higher costs at higher BMIs, overall and for most healthcare services. Every unit higher BMI was associated with £16 higher total healthcare costs.[6]

Both studies are subject to severe limitations which impinge heavily on the reliability of the results. Most importantly, individuals could only be selected into the study if they had BMI recorded at some point prior to recruitment (i.e. before 2002-03, although exact timings are unclear) in routine clinical practice. However, at the time of the study, BMI was not routinely recorded in primary care. Consequently, the decision to record BMI confounds the measurement; people in poorer health or with serious conditions are more likely to have their weight

[6] Although the relationship does not actually appear to be linear.

monitored. The impact of this selection is apparent in the data, with a large discontinuity in the association between BMI and costs at a BMI of 30 kg/m^2. In addition, estimation was based on a small sample of only 3,324 adults.

A more recent study used routine primary care records from CPRD to estimate the direct effect of BMI on healthcare costs, outwith its effects operating through comorbid conditions [64]. Around 250,000 individuals registered with primary care practices enrolled in the CPRD between 2008 and 2013 were randomly sampled from the CPRD, and annual total hospital costs were estimated as a function of BMI category (18.5 to <25, 25 to <30, 30 to <35, 35 to <40, $\geq$40 kg/m^2) controlling for age, gender, and several health conditions – type-2 diabetes, coronary heart disease, stroke, cancer, and depression. Compared to adults at healthy weight, costs were £146 and £456 higher for adults with BMIs of 30.0 to <35 kg/m^2 and $\geq$40 kg/m^2, respectively. This provides only a partial picture of the impact of excess weight on costs, because it excludes the effects operating through the conditions controlled for in estimation, and conditions with which they are correlated. In fact, the remaining difference in costs by BMI probably largely reflects unaccounted for conditions like osteoarthritis. Furthermore, the study is subject to similar limitations as Counterweight, with a lack of clarity regarding the reasons for the recording of weight and height in individuals, as well as their timing.

3.4 Discussion

3.4.1 Findings and interpretation of results

Overall summary

This systematic review summarised results from studies using individual participant data to estimate healthcare costs in relation to BMI. Despite the large variations in data and methods used, some clear patterns emerged. Overweight and obesity were consistently associated with higher healthcare costs, both overall and for major types of healthcare services. The percentage differences in annual costs associated with being overweight or obese were greatest for medications, followed by inpatient care, and then ambulatory care. These results were robust to various sensitivity and subgroup analyses. There was also some evidence of higher annual costs with increasing severity of obesity. Based on estimates of the prevalence of overweight and obesity in the UK and the US [86, 87], the estimated 12% and 36% higher total annual costs for overweight and obese adults, respectively, compared to adults at healthy weight, imply that overweight and obesity account for around 12% of adult healthcare expenditure in the UK, and 14% in the US.[7]

Results by gender

Percentage differences in healthcare costs associated with being obese, but not with being overweight, were higher among women than among men. A previous review, based on only US studies, found absolute costs of overweight and obesity to be higher for women than for men [2]. The BMI-cost association depends on a number of complex factors including the prevalence of different conditions related to excess weight, the extent to which excess weight impacts on the risks for these conditions, and the costs of these conditions, all of which may differ by gender, among other factors. A meta-analysis of the associations between obesity and a large range of conditions found obesity to have stronger associations with the incidence of diabetes, coronary artery disease, and hypertension in women than in men, and obesity is

[7] Based on estimates of the prevalence of overweight and obesity of 37% and 33%, respectively, in the US [87], and 36% and 27% in the UK [88].

also linked to various female-specific cancers [89]. Differences may also result from differences in the distribution of BMI in obese adults, with a larger proportion of obese adults being morbidly obese in women compared to men.

Results by age

It was not possible to categorise studies by mutually exclusive age categories. Instead, we followed the precedent of previous reviews in defining proxy age categories based on the distribution of age in the study population [2, 3]. We did not observe clear patterns in the association between BMI and costs according to these proxy age categories. However, individual studies which estimated the relationship between BMI and costs in separate and mutually exclusive age categories, have consistently found obesity to have a stronger impact on costs in middle-aged adults than in younger adults (<40 years) [40, 41, 57, 62, 68]. This difference may be a result of longer exposure to excess weight and the fact that many consequences of obesity including type-2 diabetes, coronary heart disease, and osteoarthritis, may take many years to manifest [90]. Those primary studies directly comparing the very elderly to the middle-aged tended to find weaker associations among the elderly [40, 44, 57, 62, 68], a result consistent with much epidemiological evidence for associations between excess weight and risk of major diseases and mortality [4, 91–94]. Healthcare costs are strongly increasing with age [95–97], and so, even if percentage differences in costs are smaller among elderly individuals, absolute differences in costs may still be greater than in younger individuals [98].

Healthcare costs for underweight adults

Being underweight was also associated with higher total healthcare costs across the reviewed studies, and this was driven predominantly by strong associations between being underweight and inpatient care costs, and in older populations. However, these associations are likely to be at least in part a result of bias due to pre-existing disease (i.e reverse causality), and residual confounding by smoking and other characteristics. Epidemiological studies have shown that excluding early years of follow-up, restricting analysis to non-smokers or to the physically active,

and excluding individuals with known cancer and other pre-existing conditions reduces the estimated risks associated with being underweight [4, 93, 99]. Similar effects have also been demonstrated in cost studies after excluding five years of outcome data or restricting analysis to those without serious illnesses [44, 57]. To a much lesser degree, residual confounding may also affect estimates of costs for overweight and obese individuals. In addition, few studies presented costs for underweight adults, and among those that did, the numbers of participants who were underweight were small.

Results by characteristics of study design and analytical methods used

Patterns of results were found to be consistent across a large range of study design and methodological features, with no evidence that percentage differences in costs for overweight or obese adults, compared to adults at healthy weight, differed systematically according to the sample size or follow-up time of studies. A previous review, based on a much smaller number of studies from only the US, found that studies based on smaller sample sizes and with shorter follow-up times reported higher relative cost differences associated with being obese [3]. Results were also similar regardless of overall study quality. However, median percentage total healthcare cost differences were larger in prospective studies (that is, studies which collected height and weight information prior to the outcome data collection period) than in cross-sectional or retrospective studies, and smaller in studies that appropriately controlled for confounding factors compared to those that did not; in studies with both of these features, results were similar to the overall results.

Contributions of health conditions to excess weight attributable costs

Relatively few studies presented results for medical or pharmacy costs for different medical conditions. Such detailed information is useful for the purposes of healthcare planning and commissioning. Excess weight was associated with substantially higher diabetes costs, but absolute differences in medical costs were small compared to those for circulatory and musculoskeletal conditions. This is because the classification of conditions was driven by the principal ICD-9-CM code, which reflects the diagnosis

for the main condition treated or investigated. Diabetes may be an underlying cause for many adverse health events, for example myocardial infarction, but this will not be reflected in cost estimates for diabetes. Circulatory conditions were typically the largest contributor to both total medical and pharmacy excess weight attributable costs. For medical costs, musculoskeletal conditions were often the second largest contributor. The small number of studies which estimated medical costs for different health conditions in relation to BMI were mostly conducted in populations of employed adults in the US. Whether the relative contributions of different conditions to overall excess weight attributable medical costs applies among different populations and in different settings is unclear.

Further limitations of the systematic literature review

This review itself is subject to a number of limitations. It was restricted to English language, peer-reviewed research, and relevant studies in other languages or in the non-peer reviewed literature may therefore have been missed. Following the precedent of previous reviews [1, 2] we searched only MEDLINE and Embase. Other databases such as EconLit or searches of the grey literature may have identified additional studies not reported here.

The NHLBI quality assessment tool for cohort and cross-sectional studies enables evaluation of all types of studies identified in this review within a single framework. It assess the risk of bias arising from various sources including sample selection, recording of exposures, and ascertainment of outcomes. There was, however, only one question pertaining to statistical adjustment for confounding, and the tool may not adequately describe features that compromise the causality of associations like reverse causality by pre-existing disease.

It was necessary to remove more than half of studies from the quantitative summary of results because of incompatible methods and poor reporting of results. Although the remaining studies differed in terms of their informational content (i.e. precision), I chose not to perform a formal meta-analysis, in which studies are given differential weights in the formation of an average. This was because of the

considerable heterogeneity between studies in terms of data, healthcare settings, and methods used, and, most importantly, the frequently poor and limited reporting of measures of uncertainty. Consequently, it is not possible to make formal inferences about differences in relative cost estimates between BMI categories.

Comparisons of relative effects across weight categories, types of healthcare services, participant characteristics, and study characteristics, may be confounded by differences between studies. However, studies which reported results for multiple categories of interest – e.g. different healthcare services or participant groups – showed similar patterns to those observed across studies.

3.4.2 Conclusions

In this Chapter, I have shown that excess weight has been consistently associated with higher healthcare costs, both overall and for a range of healthcare services, in different healthcare settings, and for different population strata. Few studies, however, were large enough to reliably estimate costs by grade of obesity or for different health conditions, and, although many studies made adjustments for potential confounders of the association between BMI and costs, few considered the potential impact of reverse causality. More fundamentally, there are no reliable studies of healthcare costs in relation to body mass index based on individual participant data pertaining directly to the UK. And because of the major differences between countries in terms of healthcare organisation, delivery, and financing, and in population characteristics, it is important to generate evidence for different jurisdictions.

3.5 Summary

In this Chapter I summarised the international evidence on the association of BMI with healthcare costs based on studies of individual patient level data, and identified limitations of existing research. In the remainder of this Thesis I aim to address many of these limitations within the context of middle-aged and older women in England using the Million Women Study. In the next Chapter, I describe the design of the Million Women Study, recruitment into the study, and the data sources to which it has been linked.

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4

The Million Women Study

4.1 Introduction

Around 1.25 million women in England and 120,000 in Scotland aged 50 to 64 years were recruited into the Million Women Study between 1996 and 2001 through routine breast cancer screening clinics [1]. The main research question to be investigated at study inception was as to the effects of hormone replacement therapy use on the risk of breast cancer [2], but the study was also envisaged as a general survey of women's health, and designed accordingly.

All participants completed a detailed questionnaire at recruitment in which they were asked to provide information on demographic, social, lifestyle, behavioural, and physical characteristics, including their height and weight, and also histories of various health conditions. All women in England were linked to NHS Central Registers for information on cancers, deaths, and emigrations, and to Hospital Episode Statistics for information on inpatient and day-case hospital admissions [3]. For around 100,000 women recruited in England, information on the use of primary care services and prescriptions issued were available via linkage to the Clinical Practice Research Datalink [4]. Women recruited in Scotland were linked to the Scottish Morbidity Database for information on deaths and healthcare utilisation [5].

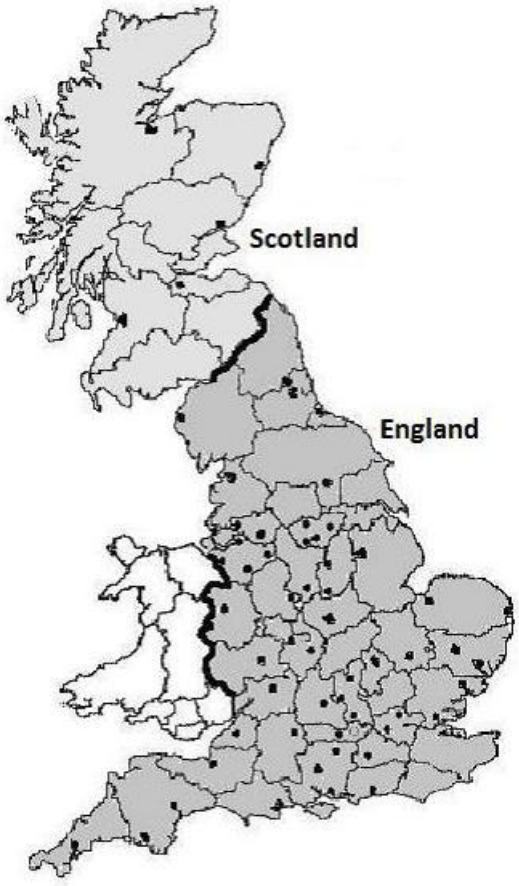
4.2 Recruitment

4.2.1 Recruitment and characteristics of participants

The Million Women Study is coordinated from the Cancer Epidemiology Unit at the University of Oxford. Recruitment was undertaken through 66 breast cancer screening centres in England (61 centres) and Scotland (5 centres) [see **Figure 4.1**], in collaboration with the National Health Service Breast Cancer Screening Program (NHSBSP). At the time of study recruitment, the NHSBSP invited women aged between 50 and 64 years, and who were registered with the NHS, to attend a breast cancer screening once every three years. Nearly three million Women were sent a study questionnaire along with their screening invitation and were asked if they would like to join the study. Questionnaires were returned by 1.36 million women: 1.25 million women in England, and 120,000 in Scotland. Around one in four women in the UK aged between 50 and 64 years at the time of recruitment participated in the Million Women Study.

A detailed analysis of the response rates and characteristics of respondents was carried out based on the first 227,000 questionnaires distributed along with an invitation to attend screening (i.e. the first printing of the Million Women Study questionnaire) [1]. 170,000 (75%) women invited to screening were actually screened, and 123,000 questionnaires were returned, representing 53% of all women contacted and 71% of women screened. However, around 7% of those who returned a questionnaire did not give signed consent, or gave insufficient personal details, for follow-up. In total, 50% of all women who were invited to participate in the Million Women Study did so. The characteristics of consenting participants were representative of women attending breast cancer screening [1, 6]. Women who did not attend breast cancer screening were more likely to come from deprived areas and were less likely to have a prescription for hormone replacement therapy, but did not differ in terms of age or recent prescriptions for various other drugs [6].

Figure 4.1: Location of National Health Service Breast Screening Centres participating in the Million Women Study



Source: Currently unpublished material from an internal report.

4.2.2 Ethical approval and funding

Ethical approval was received individually for each participating centre, and from the Oxford and Anglia Multi-Centre Research Ethics Committee. All participants gave signed consent for follow-up through their medical records. I received separate approval from the Independent Scientific Advisory Committee (ISAC) to use data on primary care from the Clinical Practice Research Datalink for the work presented in this Thesis (ISAC protocol: 16_156).

The Million Women Study is funded by Cancer Research UK (grant C570/A16491) and the Medical Research Council (grant MR/K02700X/1). I was funded by a National Institute for Health Research (NIHR) Doctoral Research Fellowship (grant DRF-2014-07-029) to undertake the research presented in this thesis. The

views expressed are my own and not necessarily of the NHS, the NIHR, or the Department of Health.

4.2.3 Recruitment questionnaire

At recruitment, women completed a detailed four-page questionnaire in which they self-reported information on socio-demographic factors (date of birth, country of birth, education), body size (height and weight), lifestyle factors (smoking status, alcohol consumption, physical activity), health history (i.e. whether they had ever had or were currently being treated for conditions including diabetes, heart disease, osteoarthritis, and depression/anxiety), family history of disease, and reproductive factors (including age at menarche, age at the birth of each child, breastfeeding behaviour, use of oral contraceptives, and use of hormone replacement therapy). The questionnaire, which was designed for electronic scanning and data entry, is presented in **Appendix C**

4.3 Follow-up

4.3.1 Overview

Follow-up questionnaires were distributed to all surviving participants on average approximately 3, 8, 12, and 15 years after recruitment. All questionnaires are available to view at: `http://www.millionwomenstudy.org/questionnaires/`. In this Thesis I use only information from the recruitment questionnaire, for two main reasons. First, there is considerable loss to follow-up in subsequent questionnaires, with the 3-year and 8-year questionnaires being completed by 67% and 52% of MWS participants, respectively.[1] Furthermore, respondents to subsequent questionnaires tend to adopt healthier behaviours than the general MWS sample, with lower rates of smoking and greater physical activity levels at recruitment. Second, using data from one point in time allows better control for reverse causality by ill-health, since the effects of ill health on characteristics like weight and on health behaviours may be affected by adverse health events.

Using their unique NHS identification number, gender, age, and postcode, Million Women Study participants in England were linked to: NHS Central Registers for information on cancer registrations, deaths, and emigrations; and, from 1 April 1997, to Hospital Episode Statistics for information on inpatient and day-case admissions [3]. For 102,000 women in England, information was also available on their use of primary care services via linkage to the Clinical Practice Research Datalink [4]. For participants recruited in Scotland, information on deaths, hospital admissions, and use of primary healthcare services were available from the Scottish Morbidity Database [5]. Measurements of height and weight were available for 541 participants via linkage to the Medical Research Council (MRC) National Survey of Health and Development [7], and in a sub-study of the Million Women Study, in which 3,999 participants had their height and weight measured in general practice, at an average of 9 years after recruitment.

[1] Data for the 12-year and 15-year surveys are still being collated, and so response rates have not been finalised.

4.3.2 National Health Service Central Registers

Participants were linked to NHS Central Registers for information on cancers, deaths, and emigrations. An incidence record of cancer is generated whenever an individual is registered with cancer, and includes new primary cancers, primary cancers in additional sites, and secondary cancers (i.e. metastasis). Cancer site is recorded using the World Health Organisation's ICD-9 or ICD-10 (International Classification of Diseases and Related Health Problems, 9^{th} and 10^{th} revisions) [8]. Information is provided on deaths and changes in registration status due to emigration or other loss to follow-up. The date of each event is given and for deaths, causes of death are recorded using ICD-10 codes. As of July 2015, when data was extracted for the analyses presented in this Thesis, the end date of follow-up was 31 December 2014 for mortality and 31 December 2013 for cancer registrations.

4.3.3 Hospital Episode Statistics

Hospital Episode Statistics (HES) is a data-warehouse managed by NHS Digital (formerly the NHS Information Centre for Health and Social Care) which contains details of all hospital admissions, outpatient appointments, and accident and emergency attendances at NHS hospitals in England [3]. It includes private patients treated in NHS hospitals ($\approx 0.5\%$ of records [9]), patients resident outside of England, and care delivered by treatment centres funded by the NHS, including those in the independent sector.

Healthcare providers routinely collect administrative and clinical information locally to support the care of the patient. The data are then submitted through the Patient Administration System to the Secondary Uses Service, who provide the central repository for the data and make it available for 'secondary' uses - i.e. uses other than direct clinical care - including healthcare planning, commissioning of services, national tariff reimbursement, development of national policy, and research. At pre-arranged dates throughout each year (since April 2008, monthly), the Secondary Uses Service takes an extract from their database and sends it to HES, where the data quality team clean and validate the extract, derive new

items, and make it available in the data warehouse. HES data is published at the financial year level (i.e. from April to March).

HES currently consists of three main datasets: admitted patient care, which includes inpatient and day-case admissions, and is available from April 1989; outpatient care, which is available from April 2003; and, accident and emergency attendances, which is available from April 2007. Adult critical care records constitute a subset of the admitted patient dataset but have been available since April 2008 as separate data (the 'Critical Care Minimum Data Set') with more detailed information on each episode.

All Million Women Study participants were linked to the Hospital Episode Statistics Admitted Patient Care (APC) file for cause-specific information on inpatient and day-case admissions from 1 April 1997 to 31 March 2011 (at the time of analysis); no linkage to outpatient, accident and emergency, or critical care datasets has been undertaken. The APC file provides information on each finished consultant episode (FCE) of care, defined as a continuous period of care administered by a particular consultant at a single hospital provider. Hence, if a patient is transferred to another consultant or to a different provider during a spell of treatment (i.e. time from admission to discharge), a new record is generated. An FCE also ends if an individual is discharged or dies. Around 8% of hospital spells consist of more than one FCE. For each FCE, information is provided on diagnoses (including a primary diagnosis and up to 20 secondary diagnoses), coded using the ICD-10, and up to 24 operations and procedures using OPCS-4 (Office of Population, Censuses and Surveys: Classification of Interventions and Procedures, 4^{th} revision) [10].

Front line clinicians generate patient notes which are converted to ICD-10 and OPCS-4 codes by trained clinical coders. Clinical coders have historically had little contact with front line clinicians, and have been required to generate clinical codes from often unstructured and non-standardised clinical notes, potentially limiting the capacity for accurate coding. There is evidence that many clinicians are not fully engaged in this process, with a lack of awareness of the use and value of the data generated [11–13]. Despite these concerns, HES data has been valuable

in addressing diverse research questions including in estimating healthcare costs of diseases [14–18]. A recent systematic review summarised the evidence of the accuracy of the recording of primary diagnoses codes and procedural codes in routinely collected hospital episode data in comparison to clinical review notes or disease registry data in the United Kingdom [19]. Diagnostic and procedural codes of three characters in length from routinely collected hospital data were found to be highly accurate, especially since the introduction of payment by results in 2004: 96.0% of ICD codes and 84.2% of OPCS codes were correctly coded.

4.3.4 Clinical Practice Research Datalink

Electronic records have long been routinely used in general practice to record patient information for the purposes of supporting day-to-day clinical care and patient registration. In more recent years, following the renewal of the GP contract and the introduction of the Quality and Outcomes Framework in 2004 [20], the data has been used to support payments made to practices. Because almost all residents in the UK are registered with a general practice, the data collected in general practice is population based, and often extends from birth, with details on a patient's diagnoses, management, and health outcomes. There are a number of primary care datasets which provide person-level information on health and healthcare use in the UK [21], including the Clinical Practice Research Datalink[2] (CPRD) [4], QResearch [22], and The Health Improvement Network [23].

CPRD is a research service jointly funded by the National Institute for Health Research and the Medicines and Healthcare Products Regulatory Agency, a part of the Department of Health. CPRD has provided anonymised primary care records for public health research since 1987; there have been over 1,700 publications using CPRD data, an up-to-date registry of which is available at: `https://www.cprd.com/Bibliography/Researchpapers.asp`. CPRD collates routinely collected, anonymised electronic health record data using the Vision GP system from general practices which have agreed to provide data on a monthly basis.

[2]Prior to 2012, it was known as the General Practice Research Datalink, which, in turn, was developed in 2003 from the Value Added Medical Products dataset

Two-thirds of practices in England, corresponding to 58% of all CPRD practices in the UK, have consented to participate in the CPRD data linkage scheme and have provided patient-level information [24]. All patients registered with the participating practices are included in the datasets unless they have individually requested to opt out. Around 102,000 MWS participants were registered in a primary care practice which is part of the CPRD data linkage scheme.

CPRD contains medical records for over 11 million patients, with around 4.4 million individuals currently contributing data to CPRD ($\approx 7\%$ of the UK population), from 674 practices across the UK. Participants in CPRD are broadly representative of the UK population in terms of age, sex, and ethnicity [24, 25]. However, age-standardised mortality rates are between 3% and 25% lower for CPRD participants than the general population, suggesting that they are in better health than the general population of the same age and gender, and practice sizes are larger than average and differently geographically dispersed [26].

CPRD contains information on patients, staff, and practices. At the practice level, information is provided on the geographical region, the last data collection date, and the date at which the practice became 'up-to-standard' (see definition given below). The staff file gives information on the role and gender of each staff member. For patients, information is collected on demographics, consultations, symptoms, tests, diagnoses, therapies, health-related behaviours, and referrals to secondary care. Consultations are defined to include all entries to a patient record, and so are not all face-to-face encounters or telephone consultations. The consultation file identifies the staff member generating the entry, the nature or type of activity, and is linked to separate files on symptoms, tests, diagnoses, therapies, health-related behaviours, and referrals by a unique consultation identifier. Clinical data are recorded using version 2 READ codes, a hierarchical classification system consisting of some 96,000 codes [27].

Prescriptions issued in primary care are automatically recorded with a product name and British National Formulary (BNF) code. The BNF, produced by the

British Medical Association and the Royal Pharmaceutical Society, is a pharmaceutical reference book in the UK which provides information on prescribing and pharmacology for medicines available on the NHS [28]. Medications can be categorised into one of fifteen chapters or therapeutic groups, describing the system of the body or the aspect of medical care to which they relate. There are an additional six pseudo-BNF chapters, defined by the NHS Business Authority, that contain mainly dressings and appliances. BNF codes are fifteen characters in length: the first two characters identify the chapter to which the product belongs, the first four, the section, and the first six, the paragraph. In the BNF (March 2016) there were 113 sections and 276 paragraphs.

CPRD undertakes internal data quality assessments at both the patient and practice level [29]. Patient records are identified as acceptable for research on the basis of their registration status, the recording of events in the patient record, and valid age and gender. The date at which each practice became 'up-to-standard' is determined on the basis of the continuity of data recording and the number of recorded deaths compared with an expected range. Despite these criteria for selecting appropriate patients and follow-up, there are large inter-practice variations in the recording of data [30]. Two reviews of validation studies using CPRD data both reported high positive predictive values for a large range of outcomes [31, 32].

4.3.5 Scottish Morbidity Records

For the 120,000 participants recruited in Scotland, information on deaths, cancers, hospital admissions, and use of primary healthcare services were available from the Scottish Morbidity Database, managed by the Information Services Division for Scotland [5, 33]. In addition to differences in data sources for healthcare use, there are also important differences between England and Scotland in terms of health governance and policy, and in healthcare utilisation [34], that render comparisons difficult.

Following national legislation that created devolved governments in Scotland, Wales, and Northern Ireland in 1999, responsibility for the NHS in Scotland was

transferred to the Scottish parliament; in England, it is the responsibility of the national parliament. In England, there is a purchaser-provider split, with Clinical Commissioning Groups commissioning services for their local communities from healthcare trusts; in Scotland, since 2004, health boards have been responsible for both the purchasing and provision of services. Hospitals in England receive around 60% of their income from the National Tariff Project, in which they are paid prospectively by activity [35]; in contrast, hospitals in Scotland are largely funded through block contracts agreed with their local health boards. This limits the comparability of hospital cost data between England and Scotland. Finally, healthcare costs per person and rates of hospital admissions are greater in Scotland than in England [34].

As a result of these differences, I use information on only women recruited in England in this Thesis.

4.4 Obesity research in the Million Women Study

The Million Women Study, either alone or in conjunction with other cohort studies, has been used to estimate associations of body mass index (BMI) with a large and diverse range of outcomes, including all-cause mortality [36], coronary heart disease [37], stroke [38], osteoarthritis and hip and knee replacements [39, 40], fractures [41–43], venous thromboembolism [44], liver cirrhosis [45], many cancers [46–52], and hospital admissions [53].

All these papers used BMI derived from height and weight reported at a single point in time.[3] The approach of using BMI derived from self-reports of height and weight at a single point in time to estimate associations with events potentially many years in the future is predicated on the assumptions that systematic and random errors in BMI derived from self-reports of height and weight, and changes in BMI over time, do not bias the association between BMI and disease risk [54]. Random errors generally attenuate estimates of linear disease-exposure associations. Systematic errors can induce bias in either direction, depending on the nature of the error; for BMI, there is evidence of underestimation (due to underestimation of weight and overestimation of height), and that the magnitude of underestimation is greater in people with higher BMI, thereby biasing estimated associations away from the null [55, 56].

Two studies have compared BMI derived from self-reports and measurements of height and weight[4] in subsets of Million Women Study participants [57, 58]. The MRC National Survey of Health and Development is a birth cohort of 2,547 women and 2,815 men, followed since their births in March 1946 [7]. Participants had their height and weight measured at a mean age of 53 years. 541 Million Women Study participants, who self-reported height and weight in the recruitment questionnaire at a mean age of 55 years, are also included in this cohort. Cairns *et. al.* [57] compared

[3] Usually from the recruitment questionnaire. However, some studies, which considered exposures recorded only in subsequent questionnaires, e.g. on lifetime body size [47], used data from these subsequent questionnaires.

[4] For simplicity, these are often referred to here as self-reported and measured BMI, even though BMI itself is not directly reported or measured.

self-reported and measured BMI in these women, and estimated regression dilution ratios, which summarise the relative attenuation of regression coefficients due to random and systematic reporting errors, or changes in characteristics over time. On average, self-reported BMI was 1.1 kg/m^2 lower than measured BMI, and the correlation between the two was high (Pearson correlation: 0.92). There was no evidence of regression dilution bias (estimate 1.04 [95% CI: 0.98 to 1.10]), suggesting that the effects of random and systematic errors, which work in opposite directions, effectively cancel each other out. Similar findings of the consistency between self-reported and measured BMIs, and in estimates of associations of disease risks with both self-reported and measured BMI, are reported in many other studies [55, 59–63].

In 2008, around 9 years after recruitment, an additional questionnaire was sent to 14,762 women who had responded to the third MWS questionnaire. These women were asked to report their current height and weight, and were invited to attend a general practice appointment for measurement; 3,999 women had their height and weight measured in general practice. Wright *et. al.* [58] found that self-reported BMI at recruitment was, on average, 1.4 kg/m^2 lower than measured BMI on average 9 years after recruitment, with a similar standard deviation, and the correlation between the two was high (Pearson correlation: 0.85). Similar results were seen across the distribution of BMI. The regression dilution bias estimate of 0.98 (95% CI: 0.96 to 1.00) suggests that reporting errors will not lead to large biases to estimates of associations between BMI and health-related outcomes over at least a decade of follow-up.

4.5 Summary

In this Chapter, I described the design of the Million Women Study, study recruitment, and follow-up through electronic health records. In the next Chapter, I use this data to estimate annual rates and costs of hospital admissions in relation to BMI, overall and for a range of health conditions, in middle-aged and older women in England.

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5

Inpatient and day-case care costs in relation to body mass index

Summary

This chapter uses data on 1.1 million participants from the Million Women Study, aged 50 to 64 years at recruitment, who were followed-up for cancers, deaths, and inpatient and day-case admissions until death or 31 March 2011. Over an average of 4.9 years of follow-up from 1 April 2006 (12.3 years from recruitment), mean annual rates and costs (in UK 2012 prices) of hospital admissions were estimated in relation to body mass index (BMI), overall and for categories of health conditions defined by the ICD-10 (International Classification of Disease, 10^{th} revision) chapter of the primary diagnosis of each admission. Associations of BMI with hospital costs were projected to the 2013 population of women aged 55 to 79 years in England. Mean annual hospital admissions and costs were lowest for women with a BMI of 20 to <22.5 kg/m^2 at 321 admissions per 1,000 woman-years (95% CI: 316 to 326) and £567 per person (556 to 577), respectively, and increased with higher BMI thereafter. Each 2 kg/m^2 higher BMI above 20 kg/m^2 was associated with a 5.0% (4.8 to 5.1) higher admission rate and 7.4% (7.1 to 7.6) higher annual hospital costs. Excess weight was associated with elevated costs for each category of treated health condition, except respiratory conditions and fractures. In England, 14.6% (£662 million) of total annual hospital costs among women aged 55 to 79 years was estimated to be due to excess weight (BMI $\geq$25 kg/m^2). 39% of total excess weight attributable costs were due to musculoskeletal admissions, mainly for knee replacement surgeries. Diseases of the circulatory and digestive systems, and neoplasms were also major contributors to these excess costs.

5.1 Background

Inpatient care is the single largest component of healthcare expenditure in many healthcare systems [1]. In the UK, it accounts for around 35-40% of total government healthcare spending [2]. Based on the systematic literature review reported in **Chapter 3**, annual inpatient costs were found to be, on average, 12% and 34% higher for overweight and obese adults, respectively, compared to adults at healthy weight. However, most studies were based on populations resident in the US, with no reliable evidence pertaining directly to the UK. Because of the differences between the UK and US in terms of population characteristics, healthcare financing and delivery, and healthcare prices [3], the results from the literature review may not be expected to translate well to the UK. Furthermore, most studies were based on small-to-moderate numbers of participants, and few were able to reliably estimate inpatient care costs by grade of obesity or for different health conditions.

In this Chapter, I estimate mean annual rates and costs of hospital admissions in relation to BMI, overall and for categories of health conditions, using routine data on hospital admissions over 12 years of follow-up for 1.1 million middle-aged and older women in England participating in the Million Women Study. The Million Women Study previously reported that overweight and obesity are associated with higher rates of first admission for 19 of the 25 most common reasons for hospital admission [4]. This chapter builds on that research by incorporating information on all admissions (regardless of cause, and including further admissions of a given cause), estimating costs associated with each admission, and fully allocating costs and admissions to one of sixteen categories of health conditions. Prior to the presentation of the analysis described above, further background information on hospital care expenditure in the UK is given, including its distribution over the life-cycle, differences by gender, and spending on different health conditions.

5.2 Hospital admissions and spending in the UK

5.2.1 Total admissions and spending on hospital care

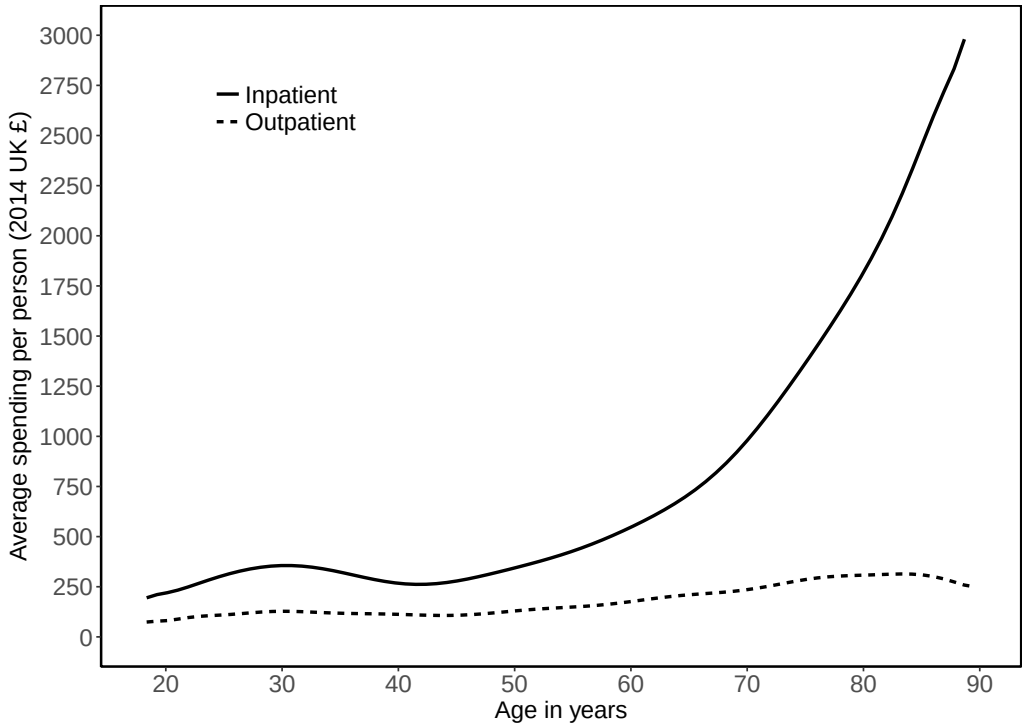
Hospital spending accounts for around half of all government expenditure on healthcare in the UK [2], of which inpatient and day-case care accounts for about 70% (or 35-40% of total expenditure). In England in 2014-15 there were around 100 emergency and 150 elective admissions per 1,000 persons [5]. Rates of emergency and elective admissions have increased markedly in recent decades in adults of most ages, and in both men and women: between 1997-98 and 2014-15, total emergency admissions increased by an average of 2.5% annually, and elective admissions by 2.9% [5]. These overall increases largely reflect increases in day-cases and short stays in hospital. Average spending on hospital care per person in 2014 was estimated to be around £910 in men and £860 in women [6]. Per person inpatient care costs are larger than outpatient care costs for individuals of all ages, but while inpatient care costs are rapidly increasing with age, outpatient care costs remain relatively stable (**Figure 5.1a**). The increase in inpatient care costs with age reflects increased use of emergency medical services and very high costs at the end-of-life [6]. Adults aged 65 years or older account for less than one-fifth of the total population in England [7] but consume around one-third of hospital resources. At younger ages, particularly in child-bearing years, hospital costs for women are greater than for men on average, but beyond around 55 years of age, per person costs are greater for men (**Figure 5.1b**).

5.2.2 Spending by health conditions

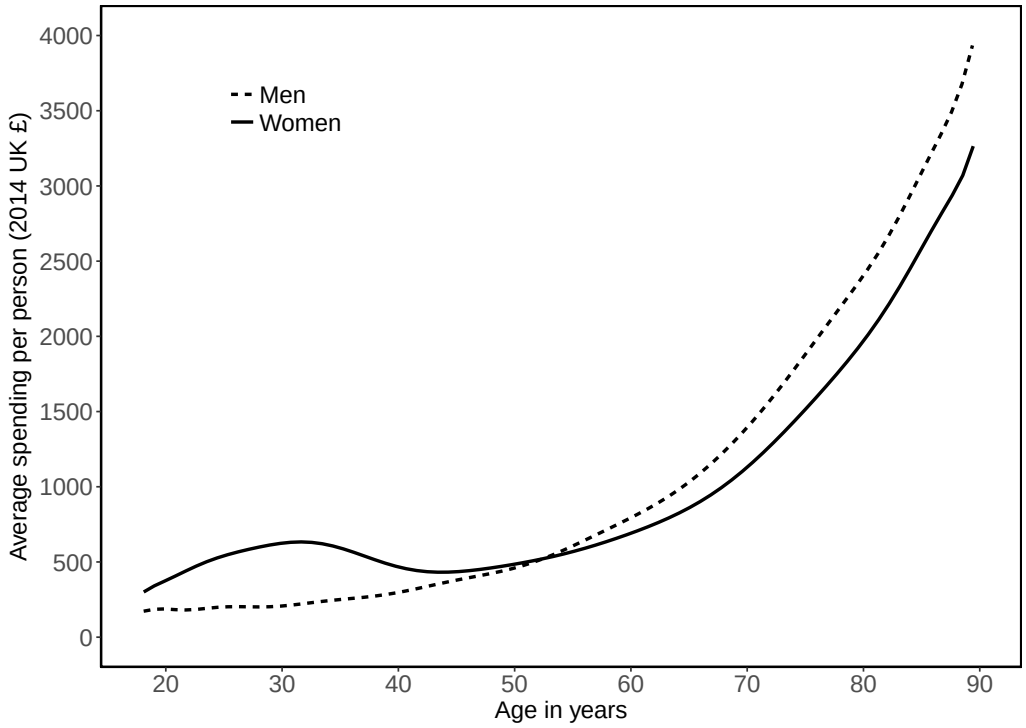
NHS England produces a toolkit known as programme budgeting which describes the allocation of expenditure by Primary Care Trusts (now Clinical Commissioning Groups) across different care settings (e.g. inpatient, outpatient, primary prescribing, community care, etc.) and diseases (or health conditions). There are 23 main categories of disease which are based on the World Health Organisation's ICD-10 (International Classification of Disease, 10^{th} revision) chapters, which, for

Figure 5.1: Average hospital spending per person by the NHS in England (2010-11 to 2014-15) by age in years

(a) Annual costs by age for inpatient and outpatient care



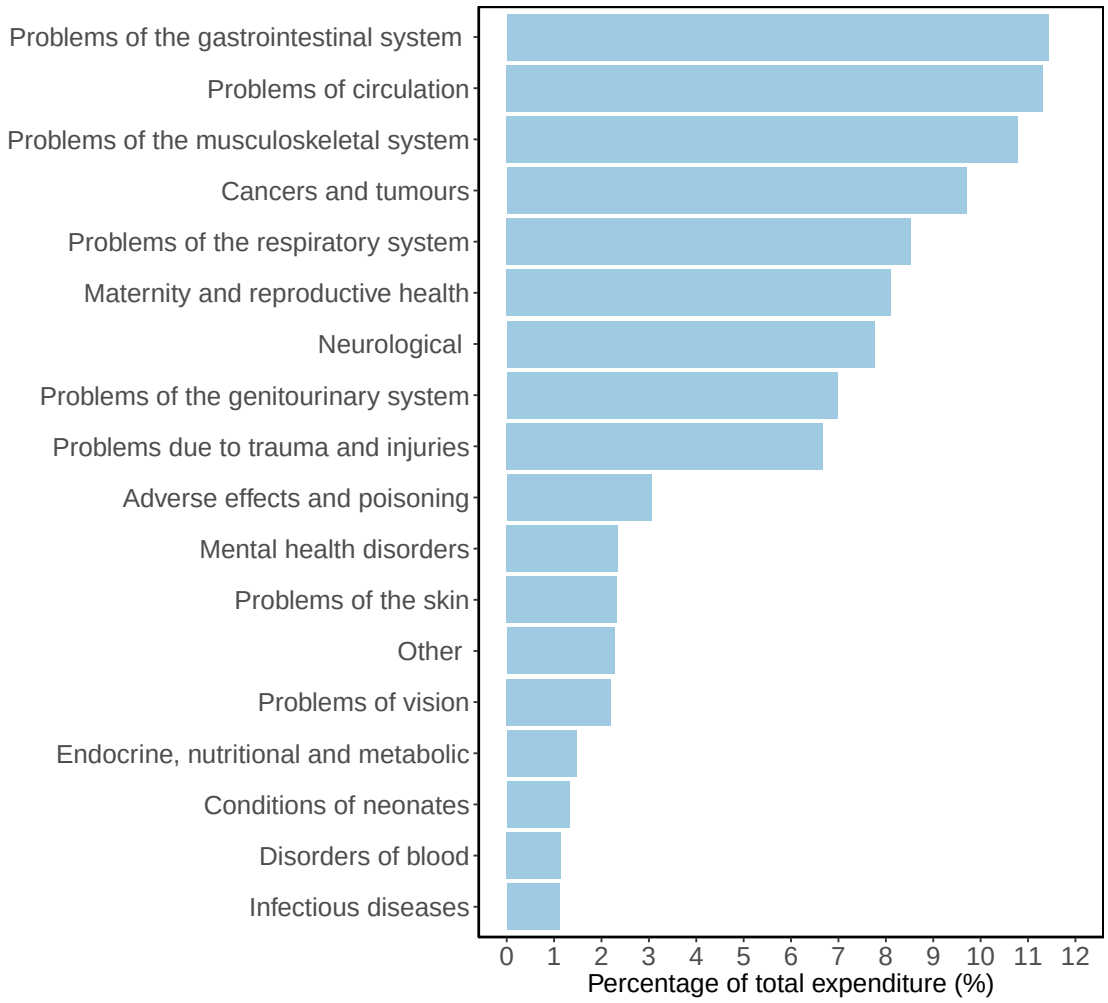
(b) Annual hospital costs by age for men and women



Source: Data extracted from an Institute for Fiscal Studies report [6]. Spending converted from US$ to £ using an exchange rate of 1$:£0.63.

admitted patient care, are derived from the primary diagnosis of the admission event [8]. The largest categories of elective and non-elective inpatient and day-case expenditure,[1] across all ages and sex, were the gastrointestinal system, circulatory system, musculoskeletal system, and cancers and tumours, each of which accounted for 10-12% of total spending (**Figure 5.2**). The distribution of spending by these categories is likely to differ by age and gender, but this cannot be ascertained from the programme budgeting toolkit.

Figure 5.2: Proportion of total inpatient and day case care cost by category of disease from programme budgetting returns 2012-13



[1] I have excluded the category 'other secondary care' which includes both unbundled goods and services like chemotherapy and critical care (which are of relevance) but is dominated by services like integrated care and specialist mental health care.

5.3 Costing hospital care

As described in detail in **Chapter 4**, all Million Women Study participants in England were linked to Hospital Episode Statistics for information on inpatient and day-case care from 1 April 1997 to 31 March 2011.[2] HES also provide information on accident and emergency cases and outpatient care, but these have not been linked to the Million Women Study, and so the remainder of this chapter focuses only on admitted patient care.

To briefly summarise, the admitted patient care data in HES contains information on each finished consultant episode (FCE; i.e. a continuous period of care under a particular consultant within a single hospital episode) including start and end dates for the FCE, admission and discharge dates, admission type (elective, non-elective, or day-case), clinical diagnoses using ICD-10 codes (a primary diagnosis and up to 20 secondary diagnoses), and up to 24 operations or procedures using OPCS-4 codes. FCEs can be combined to form admissions, i.e. time from admission to discharge; in this analysis, FCEs were considered part of the same admission if they had the same admission date, had overlapping durations, or if the admission date for one episode was the same as the discharge date for another.

Costing was undertaken using a healthcare resource group (HRG) approach. HRGs are a casemix system used to describe hospital activity in the UK and to inform the reimbursement of hospitals for the provision of certain care as part of the National Tariff Project (formerly, Payment by Results) [9]. HRGs are groupings of clinically similar treatments and events which require similar levels of resources (i.e. costs). HRGs (version 1) were first introduced into the UK in 1997, and have been used (version 3) for the reimbursement of elective treatment since 2003. In 2006, a new HRG version 4 was introduced, and the scope extended to cover additional non-elective healthcare services. In HRG 4 there are approximately 1,600 unique

[2] At the time of analysis. More recent years of Hospital Episode Statistics data are now available.

HRGs describing hospital activity; in HRG version 3.5 there were 500. HRG4+ was introduced in 2013, increasing the number of categories to around 2,100.[3]

This analysis uses the 2011-12 HRG version 4 costing grouper [10] since the HES data extends only to 2010-11 when HRG version 4 was still in use. The HRG version 4 grouper allocates each FCE to one 'core' HRG and potentially any number of 'unbundled' HRGs for high cost services in the following domains: chemotherapy, radiotherapy, diagnostic imaging, rehabilitation, critical care, specialist palliative care, and high cost drugs. Mapping to HRGs is driven in the first instance by the procedure associated with the highest resource use, and, only if the procedure is not associated with significant resource use (e.g. putting an arm in a sling or plain film X-ray) or no procedure was performed, is mapping driven by the primary diagnosis ICD-10 code. Additional diagnosis codes, and individual characteristics like age and gender, can also affect the HRG to which an episode is allocated [11].[4] It was not possible to estimate critical care costs for MWS participants because they were not linked to critical care data, which, since 2008, has been available from HES as a separate dataset ('Critical Care Minimum Dataset').

All hospitals in England are required to submit estimates every year of the costs of treating individuals within each HRG in different settings (e.g. elective, non-elective, day-case) to the Department of Health. This information is then collated by the Department of Health and published as part of the NHS Reference Costs [12].[5] Reference costs are calculated on a full absorption basis to identify the full cost of providing services. These include: direct costs, i.e. those easily attributable to a particular activity like consultants and nurses; indirect costs, i.e. those that cannot be directly attributed to an activity but can be shared among a number of activities like laundry and lighting; and, overheads, i.e. the overall

[3]The increase in the number of HRG groupings between HRG versions 4 and 4+ largely reflect further separations of certain clinical events based on clinical complication scores, derived largely from recorded comorbidities, i.e. secondary diagnoses.

[4]For the Million Women Study data, 2.1% of FCEs were not assigned a HRG in the first instance. These records were adjusted (e.g. removing or amending unrecognised codes) and the grouper reapplied.

[5]Costs of non-HRG activities like outpatient appointments and diagnostic imaging are also collected.

costs of running the organisation, like finance and human resources.[6] Despite the availability of national costing guidelines, the unit costs reported to the Department of Health vary substantially across providers, and this is likely to result in part from the application of different costing methods [13].

Unit costs, which are based on typical lengths of stay, are attached to all core and unbundled HRGs. Each core HRG has a 'trimpoint' length of stay, which is setting dependent, and is typically set at 1.5 times the interquartile range above the median for that HRG in that setting. Additional costs per day in hospital beyond this trimpoint are added to the core HRG cost. Costs of admissions are given simply as the sum of costs of all FCEs within that admission.

A sensitivity analysis was performed to assess the appropriateness of the costing method described above, i.e. applying the 2011-12 HRG grouper and 2011-12 NHS Reference Costs to all hospital admissions from 1 April 2006 to 31 March 2011. Data from 2006-07 was processed using the 2006-07 HRG grouper, and 2006-07 NHS Reference Costs were attached and inflated to UK 2012 prices using the hospital and community health services index [14].[7] The mean cost of an FCE estimated using this approach (£1,318) was similar to that derived from the base-case analysis (£1,355); differences by category of BMI were also small.

[6]These costs do not capture payments received by hospitals to finance the general running of the hospital (for example, fixed costs relating to property).

[7]A request was made to NHS Digital for access to a HRG version 3.5 grouper, in order to perform a similar sensitivity analysis on data prior to 1 April 2006, but the request was not approved.

5.4 Methods

5.4.1 Participants and follow-up

Women recruited in England with reliable linkage to NHS Central Registers and HES data were excluded from main analysis if: there was missing information on height and/or weight at recruitment; they were underweight (BMI <18.5 kg/m^2); they had a registration of cancer (other than non-melanoma skin cancer [ICD-10: C44]) before recruitment into the Million Women Study; or they were not followed up for hospital admissions beyond 31 March 2006. Women contributed person-years of outcome data from 1 April 2006 until the earliest of their date of death, emigration, or the end of follow-up for hospital admissions (31 March 2011).

Women with known cancer were excluded because cancer can cause severe weight loss and lead to high medical costs, thereby confounding the relationship between observed weight and costs [15]. All data on hospital admissions prior to 1 April 2006 was excluded, for two main reasons. First, to reduce the impact of confounding by unobserved disease status (i.e. reverse causality). Underweight women were excluded from analysis because of the substantial potential for reverse causality and residual confounding, and the small proportion of underweight women in the sample (<1%).

Individuals with undiagnosed conditions like cancer or severe respiratory problems may, as a result of their condition, have both reduced body mass index and elevated healthcare costs, thereby confounding estimates of their association. However, the higher mortality risk faced by such individuals means that they are less likely to contribute data to analysis when some follow-up data is excluded. The exclusion of early years of follow-up data after height and weight were reported or measured is a common method in prospective epidemiological studies of BMI [15]. Second, the introduction of the HRG version 4 and the separation of high-cost services (i.e. unbundling) in 2006, has increased the sensitivity of cost estimates for high-cost cases. This, and the expansion of Payment by Results to non-elective care, limits the comparability of costs derived from data prior to 1 April 2006 and after.

5.4.2 Categorisation of health conditions

Each admission was uniquely allocated to an ICD-10 chapter [16] based on the primary diagnosis of the admission episode (i.e. the main condition treated or investigated). Categorising admissions by ICD-10 codes provides a well understood and clinically meaningful categorisation, and accords well with the methods used by the Department of Health to describe NHS expenditure [8], thereby making the results useful to healthcare commissioners and policy makers.

Those ICD-10 chapters for which fewer than 10,000 admissions were observed over the follow-up period were combined into an 'other chapters' category: certain infectious and parasitic diseases (ICD-10 chapter 1); mental and behavioural disorders (ICD-10 chapter 5); diseases of the ear and mastoid process (ICD-10 chapter 8); pregnancy, childbirth and the puerperium (ICD-10 chapter 15); certain conditions originating in the perinatal period (ICD-10 chapter 16); and, congenital malformations, deformations and chromosomal abnormalities (ICD-10 chapter 17). ICD-10 chapter 19 – injury, poisoning, and certain other consequences of external causes – were split into three ICD-10 subchapters: fractures (ICD-10 codes: S02, S12, S22, S32, S42, S52, S62, S72, S82, S92, T02); medical and surgical complications (ICD-10 codes: T80-T88); and, other, which was incorporated into the existing 'other chapters' category defined above.

Musculoskeletal conditions (ICD-10 chapter 13) were further subdivided into arthropathies (ICD-10: M00-M25), dorsopathies (M40-M54), soft tissue disorders (M60-M79), and other (M30-M6 and M80-M99). Arthropathies were further categorised into knee replacements (ICD-10: M17) and hip replacements (ICD-10: M16), identified using ICD-10 and OPCS code combinations specified by the National Joint Registry [17]; other arthrosis (M15-M19 excluding knee and hip replacements with arthrosis); rheumatoid arthritis (M05-M06); and other arthropathies.

5.4.3 Statistical analysis

Statistical models

Separate estimates for annual admission rates and annual hospital costs by BMI category (18.5 to <20, 20 to <22.5, 22.5 to <25, 25 to <27.5, 27.5 to <30, 30 to <35, 35 to <40, and ≥ 40 kg/m^2) as well as for percentage differences in annual admission rates and costs per 2 kg/m^2 higher BMI (corresponding to a change in weight of around 5 kg for a woman of average height in England [164 cm]) for BMI ≥ 20 kg/m^2 (i.e. the range over which the relationship between BMI and total costs was approximately log-linear)[8] were calculated overall and for each diagnostic category using generalized linear models with a log-link function and Poisson-like variance. This model specification was selected from a wider pool of candidate models using a range of common specification tests [18] and a comparison of model fit (see **Appendix D**).

In all models, further adjustments were made for: age (<60, 60-64, 65-69, 70-74, ≥ 75 years) and financial year (2006-07, 2007-08, 2008-09, 2009-10, 2010-11) in each year of follow-up, and for region of recruitment (nine areas covered by cancer registries in England), quintiles of socioeconomic status based on the Townsend deprivation index [19], parity (nulliparous, 1, 2, ≥ 3), age at birth of first child (<25, 25-29, ≥ 30 years), smoking (never, past, current), current alcohol intake (rarely/never, <7 units per week, ≥ 7 units per week), and educational attainment (none, secondary, technical qualification, tertiary) at recruitment. In some years (<1%) participants were followed-up for less than one year (e.g. due to emigration). To address this, a variable indicating the proportion of each year with contributed data (where deaths are given a value of 1) was added to the model. Missing values for any of the adjustment variables ($\leq 5\%$ for all variables) were assigned to a separate category for that variable. These variables are all recognised confounders of the association between BMI and healthcare costs that have been used frequently in previous studies (see **Chapter 3**) or in Million Women Study research exploring the association between BMI and incident hospitalisations [4]. Ethnicity is a potentially

[8]The estimates were similar regardless of the BMI range used in estimation.

important confounder of the association between BMI and healthcare costs [20], but since 99% of participants in the Million Women Study are white, ethnicity was not included as a covariate in this analysis.

Standard errors in all models were adjusted to account for the lack of independence between admissions for a given individual across observation years. Variances for the estimate in each BMI category were derived from an estimate of the variance of the log risk specific to that category, and presented as group-specific 99% confidence intervals [21]. Such interval estimates are approximately independent, which allows comparisons between any pair of BMI categories, even if neither is the reference category.

Standardised estimates of mean annual admission rates and costs

Standardised estimates of the mean number of admissions per year and mean annual costs for each category of BMI were derived from the estimation models described above, using the method of recycled predictions (also known as predictive margins). For each observation in the dataset, annual estimates of the number of hospital admissions and costs were estimated multiple times using the estimated regression coefficients and the observed characteristics of the Million Women Study participants (except HES year which was set to 2010-11, i.e. the latest year of data) but each time changing the BMI category. As a result, eight estimates (corresponding to each of the eight categories of BMI) of annual numbers of admissions and costs were generated for each woman in each year of follow-up. These were averaged over observations to provided standardised means. Standard errors around these estimates were given by the standard deviation of mean estimates based on 1,000 bootstrap replicates, and were used to construct 99% confidence intervals.

Sensitivity analysis

It is important to assess the sensitivity of the estimated associations between BMI and total annual hospital costs to the methodological assumptions made. To explore the impact of reverse causality by pre-existing disease, the associations were estimated: (i) including women with a history of cancer at baseline; (ii) using

data on all hospital admissions since recruitment or, if later, 1 April 1998; (iii) restricting analysis to never-smokers because of concerns about residual confounding by smoking [15]; and (iv) excluding participants who self-reported heart disease or stroke at recruitment. In order to explore the impact of high costs at the end-of-life [22], we excluded the year of death and the preceding two years of observation for women who died during follow-up.

To examine the sensitivity of estimates of percentage differences in total annual costs per 2 kg/m^2 higher BMI for BMI $\geq$ 20 kg/m^2 to potential measurement error in BMI derived from self-reported height and weight, annual costs were additionally estimated after replacing self-reported BMI from the Million Women Study with the mean measured value of BMI within each category of self-reported BMI from the 2012 and 2013 Health Surveys for England (**Appendix Table D.1**), which recorded both self-reported and measured BMI [23]. Where estimates by self-reported BMI categories are presented in figures, they are plotted against these mean measured values, thereby providing a correction for both random and systematic reporting errors.

Subgroup analysis

The association between BMI and healthcare costs may not be the same in all subgroups of patients by demographic characteristics or other health behaviours. The Global BMI Mortality Collaboration [15] found weaker associations between BMI and all-cause mortality amond older compared to middle-aged adults. Socioeconomic status could affect the estimated association by, for example, influencing access to care [24]. Other health behaviours may affect also the BMI-cost association. For instance, there may be cardioprotective effects of physical activity outwith that resulting from lower weight [25]. In order to assess this, models of percentage differences in total annual costs per 2 kg/m^2 higher BMI for BMI $\geq$ 20 kg/m^2 were also estimated within subgroups of women defined by age at the start of each annual period (<65, 65 to <70, $\geq$70 years), and by smoking status (never, former, current), alcohol intake (rarely/never, <7, $\geq$7 units per week), strenuous exercise

activity (never/rarely, other), tertiles of socioeconomic status [19], and educational attainment (none, secondary or technical, tertiary) at recruitment. Heterogeneity of percentage differences in annual costs per 2 kg/m^2 higher BMI for BMI $\geq$20 kg/m^2 between categories of each subgroup was assessed using a chi-squared test.

Projection of costs to all women aged 55 to 79 years in England in 2013

Hospital costs attributable to each category of overweight and obesity and for overweight and obesity combined (i.e. excess weight; BMI $\geq$ 25 kg/m^2) were projected to all women aged 55 to 79 years in England in 2013, overall and by diagnostic category. Differences in standardised mean costs between each overweight and obesity category and healthy weight (BMI 20 to <25 kg/m^2) were estimated, and then multiplied by the number of women aged 55 to 79 years in England within the respective BMI category (**Appendix Table D.1**). These latter numbers were estimated by applying information on the distribution of self-reported BMI categories estimated from the 2012 and 2013 Health Surveys for England [23] to the Office for National Statistics mid-2013 population estimate of the total number of women aged 55 to 79 years in England: 6.6 million [7]. Standard errors around these estimates were given by the standard deviation of mean estimates based on 1,000 bootstrap replicates, and were used to construct 99% confidence intervals.

Exploratory analysis of the mediating effect of diabetes on excess weight attributable costs

The strong association between excess weight and diabetes [26], and the large impact of diabetes on healthcare costs [27], means that diabetes is likely to be a key mechanism through which excess weight leads to increased healthcare costs. However, the contribution of diabetes to hospital costs attributable to excess weight is likely to be distributed across various diagnostic categories, as defined by the primary diagnosis of the admission episode. This does not represent a limitation of the approach *per se*, but rather is a consequence of the focus here on treated health conditions rather than underlying biological or physiological pathways.

To improve our understanding of the full contribution of diabetes to total excess weight attributable costs, a mediation analysis was performed. This follows the methods used by the Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration to assess the extent to which the impact of BMI on coronary heart disease and stroke was mediated by glucose and diabetes [28].

The proportion of total annual hospital costs attributable to excess weight was estimated as described above but based on a model estimating total annual hospital costs in relation to categories of body mass index, adjusted for diabetes in addition to the previously stated confounders. Diabetes was considered present in a given annual period for each woman if diabetes (ICD-10: E10-E14 except E12) was recorded in any admission in any position (i.e. primary or secondary diagnosis) in that annual period or an earlier period, or diabetes was self-reported at recruitment. The difference in this estimate from that derived from the base-case model provides an estimate of the annual costs associated with overweight and obesity mediated by diabetes.

5.5 Results

5.5.1 Participant characteristics at recruitment and details of follow-up

There were 1,246,867 women in England recruited into the Million Women Study with linked data on cancers, deaths, and hospital admissions. I excluded 64,209 (5%) women with missing information on weight and/or height, 11,862 (1%) who were underweight (BMI <18.5 kg/m^2), 38,190 (3%) with a prior cancer registration, and 38,740 (4%) with no follow-up for hospital admissions beyond 31 March 2006 (**Appendix Figure E.1**). The remaining 1,093,866 women were followed-up for an average of 4.9 years from 1 April 2006 (12.3 years from recruitment), during which time 1.84 million admissions were observed (343 per 1,000 woman-years) [**Table 5.1**]. 46% of women had a BMI <25 kg/m^2, 36% were overweight, and 18% were obese. Average age at recruitment was 56.1 years (standard deviation 4.8) and was relatively stable across BMI categories. Overweight and obese women tended to be of lower socioeconomic status with a lower highest educational qualification, and were less likely to perform strenuous exercise, drink alcohol, or be current smokers, but were more likely to be former smokers or to report a prior health condition (one or more of: heart disease, stroke, diabetes, rheumatoid arthritis, osteoarthritis, osteoporosis, and depression/anxiety).

Table 5.1: Participant characteristics at recruitment and details of follow-up, by body mass index

	Body mass index category (kg/m^2)								
	18.5-19.9	20-22.4	22.5-24.9	25-27.4	27.5-29.9	30-34.9	35-39.9	$\geq$ 40	All women
Number of women	30,687	173,547	299,569	239,402	155,005	139,314	41,345	14,997	1,093,866
Characteristics at recruitment									
Body mass index, median (IQR)	19.4 (0.6)	21.5 (1.1)	23.8 (1.3)	26.1 (1.3)	28.6 (1.2)	31.7 (2.3)	36.8 (2.5)	42.7 (4.0)	25.4 (5.5)
Age at recruitment, mean (SD)	55.7 (4.9)	55.6 (4.8)	56.0 (4.8)	56.3 (4.9)	56.4 (4.8)	56.3 (4.8)	55.8 (4.6)	55.5 (4.6)	56.1 (4.8)
Deprivaton tertile in study population (%)									
Least deprived	35.1	37.5	36.4	33.8	31.0	27.7	24.0	20.4	33.4
Most deprived	31.7	28.5	29.6	32.6	36.1	40.0	45.3	51.0	33.3
Highest educational attainment (%)									
None	35.9	35.4	39.6	44.7	48.9	52.0	55.0	58.1	43.7
Secondary or technical	45.8	47.7	46.3	43.3	40.2	38.4	35.9	33.4	43.4
Tertiary	18.3	17.0	14.2	12.0	10.8	9.6	9.1	8.4	12.9
Smoking status (%)									
Never	50.2	52.8	52.6	51.9	51.4	51.3	51.0	49.4	52.0
Former	20.8	24.6	27.6	29.2	30.6	32.4	34.0	37.0	28.7
Current	29.0	22.6	19.8	18.9	18.1	16.4	15.0	13.5	19.4
Current alcohol drinkers (%)	75.8	80.6	81.0	78.3	74.8	69.9	63.4	57	76.9
Exercise rarely or never (%)	16.3	14.0	15.1	18.2	22.1	27.0	32.8	39.4	19.1
With prior health conditions (%)[a]	21.3	19.3	20.8	24.4	29.1	34.5	41.3	48.4	25.4
Deatils of follow-up									
Woman-years of follow-up (1,000s)	149.3	850.4	1,469.80	1,173.80	759.1	681.2	201.0	72.2	5,356.8
Total number of hospital admissions	47,623	248,683	454,560	397,553	281,820	277,603	93,192	37,751	1,838,785

Percentages exclude participants with missing data on characteristics; percentage of missing data is <3% for all characteristics except for smoking status (5%).

[a]Any of self-reported heart disease, stroke, diabetes, rheumatoid arthritis, osteoarthritis, osteoporosis or depression/anxiety.

5.5.2 Estimates of annual admission rates and costs per person

Main analysis

Rates of hospital admissions were lowest among women with a BMI of 20 to <22.5 kg/m^2 at 321 per 1,000 women-years (99% CI: 316 to 326), and rose steadily with BMI thereafter, reaching 530 admissions per 1,000 women-years (511 to 549) for women with a BMI of $\geq$ 40 kg/m^2 (**see Table 5.2**). Every 2 kg/m^2 higher BMI for BMI $\geq$ 20 kg/m^2 was associated with a 5.0% (4.7 to 5.1) higher hospital admission rate.

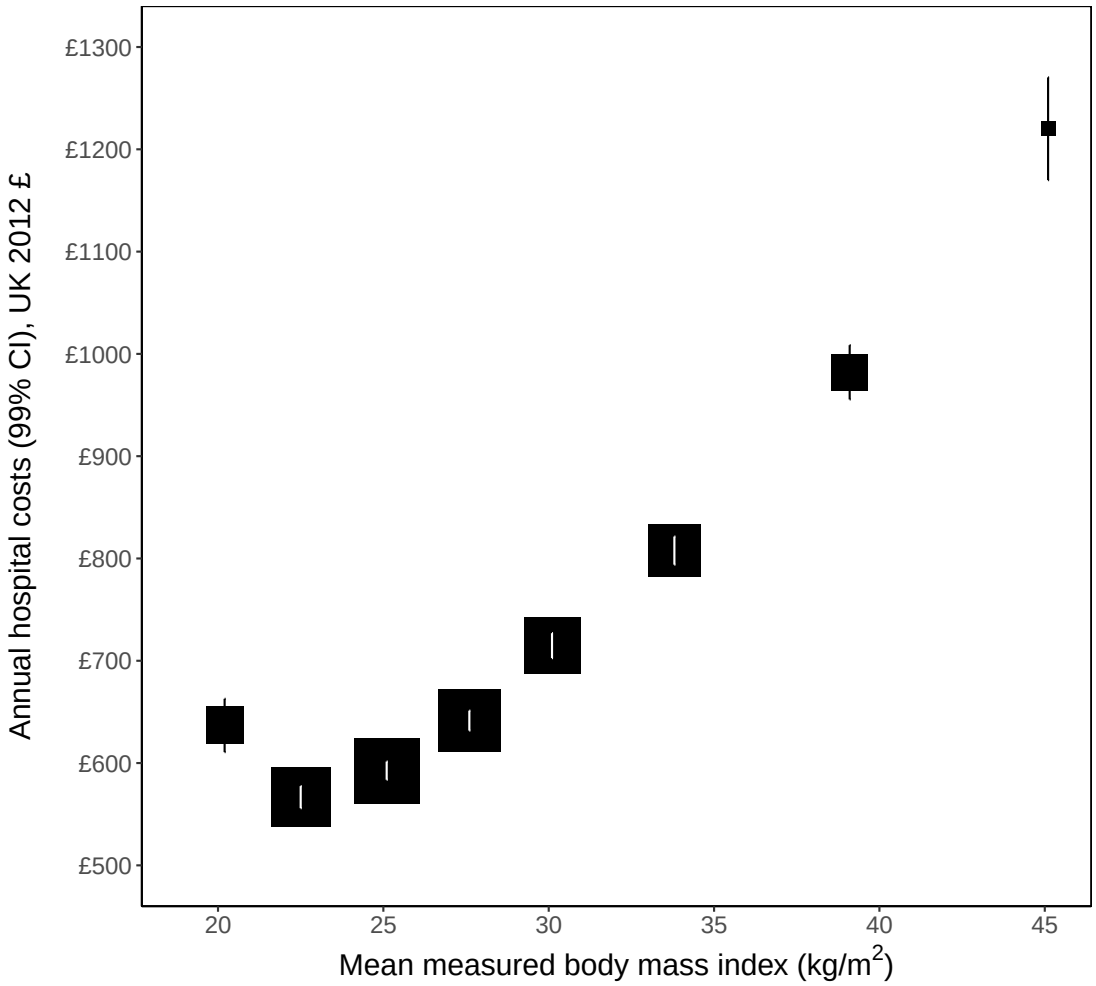
The association between BMI and annual hospital costs was stronger than for admissions: every 2 kg/m^2 higher BMI for BMI $\geq$ 20 kg/m^2 was associated with 7.4% (7.1 to 7.6) higher annual costs. Annual costs were also lowest for women with a BMI of 20 to <22.5 at £567 per person (556 to 577), and rose to £1,220 per person (1,170 to 1,270) in women with a BMI of $\geq$ 40 kg/m^2; a difference of 115.3% (106.8 to 124.2) [**Figure 5.3**; see **Appendix Table E.1** for the full regression output].

Table 5.2: Annual hospital costs and annual admission rates by category of body mass index

BMI category (kg/m^2)	Hospital admissions		Annual hospital costs	
	Difference in admission rate (%)	Admissions per 1,000 women-years	Difference in costs (%)	Annual costs (2012 UK £)
18.5 to <20	6.6 (3.2, 10.1)	342 (331, 354)	12.4 (7.9, 17.0)	637 (611, 663)
20 to <22.5 (reference)	0.0 (-1.5, 1.5)	321 (316, 326)	0.0 (-1.7, 1.7)	567 (556, 577)
22.5 to <25	4.0 (2.8, 5.2)	334 (330, 338)	4.6 (3.3, 5.9)	593 (584, 601)
25 to <27.5	10.8 (9.5, 12.1)	356 (351, 361)	13.2 (11.8, 14.7)	641 (632, 651)
27.5 to <30	19.3 (17.7, 20.9)	383 (377, 389)	26.1 (24.3, 28.0)	715 (703, 727)
30 to <35	29.6 (27.9, 31.3)	416 (410, 422)	42.5 (40.4, 44.7)	808 (794, 821)
35 to <40	47.1 (43.9, 50.4)	473 (462, 483)	73.3 (68.9, 77.8)	982 (955, 1,009)
≥ 40	65.1 (59.4, 71.1)	530 (511, 549)	115.3 (106.8, 124.2)	1,220 (1,170, 1,270)
Percentage difference in outcome per 2 kg/m^2 higher BMI for BMI ≥20 kg/m^2	5.0 (4.8, 5.1)	-	7.4 (7.1, 7.6)	-

BMI=body mass index. Values are means (99% confidence intervals), with floating confidence intervals for estimates of percentage differences in outcomes by BMI category.

Figure 5.3: Annual hospital costs per woman by category of body mass index



Standardised estimates of mean annual costs are plotted against mean measured BMI within categories of self-reported BMI from the Health Surveys for England. The area of each square is inversely proportional to the variance of the estimate. The error bars show 99% confidence intervals.

Sensitivity analysis

Estimates of percentage differences in annual hospital costs per 2 kg/m^2 higher BMI for BMI >20 kg/m^2 were very similar to, and not statistically different from, the base-case results when including women with previous cancer, using data from all years of follow-up, excluding women with BMI >50 kg/m^2 or with previous heart disease or stroke, restricting analysis to only never-smokers, excluding up to the last three years of data for women who died during follow-up, or using imputed BMI to account for measurement error in BMI derived from self-reported

height and weight (**Table 5.3**).

Estimates of percentage differences in annual hospital costs for women in each BMI category compared to those with a BMI of 20 to <22.5 kg/m^2 were not materially affected by the inclusion of women with pre-existing cancer, excluding women with BMI >50 kg/m^2 or with previous heart disease or stroke, or excluding up to the last three years of data for women who died during follow-up. Using data from all HES years generated lower percentage differences in annual costs for women with BMI $\geq$40 kg/m^2 by around 12% compared to the base-case analysis; this is likely because the introduction of HRG version 4 and the separation of certain high-cost services (i.e. unbundling) from April 2006 has enabled more accurate estimation of costs for high-cost cases, which occur disproportionately among women with BMI $\geq$40 kg/m^2. Restricting analysis to only never-smokers, led to higher percentage differences in costs for women in each category of overweight and obesity compared to those at healthy weight, consistent with some degree of residual confounding by smoking.

Subgroup analysis

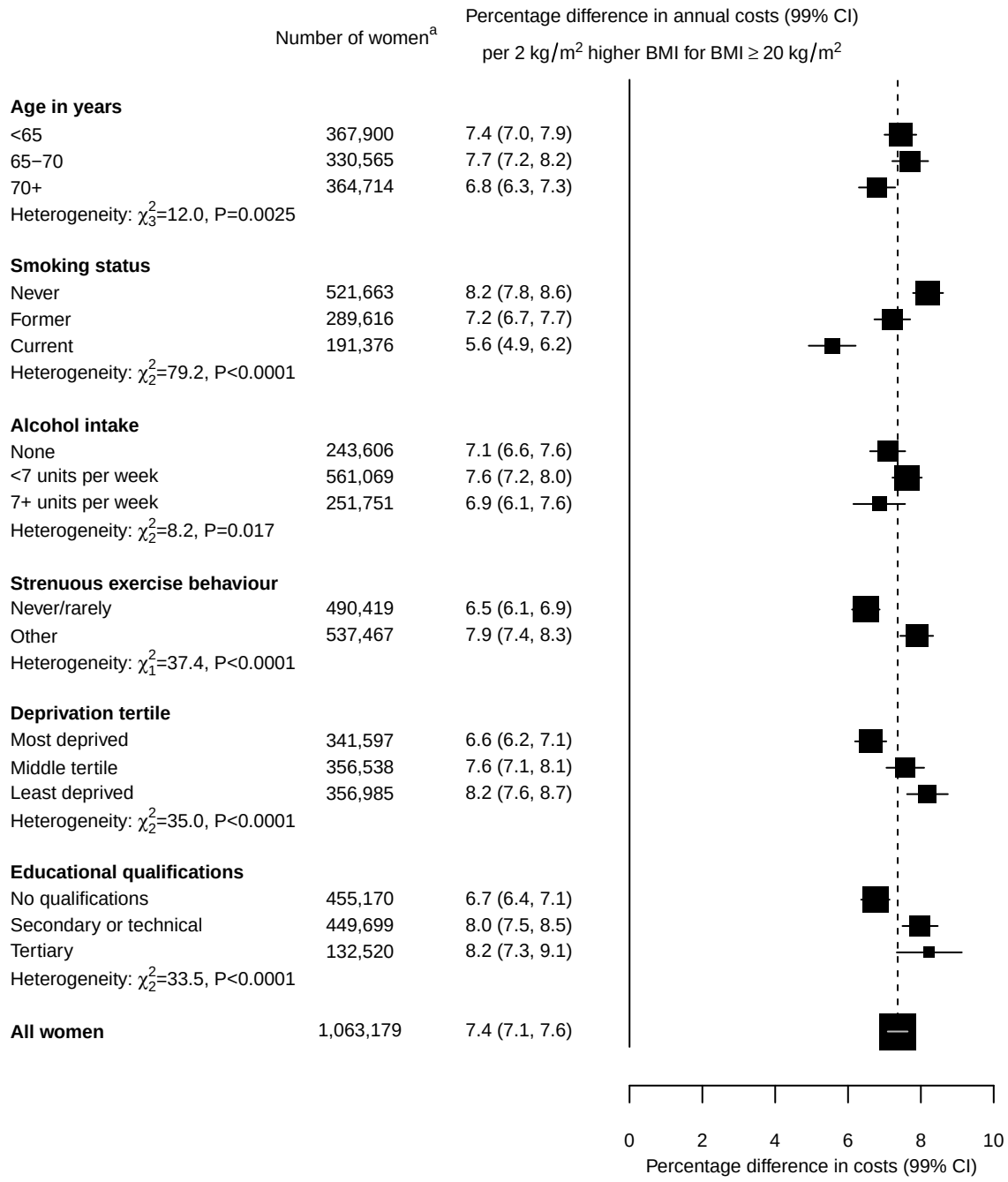
The percentage differences in annual hospital costs per 2 kg/m^2 higher BMI for BMI >20 kg/m^2 showed some statistical heterogeneity between subgroups of women defined by age, smoking status, alcohol use, exercise behaviour, socioeconomic deprivation, and educational attainment (**Figure 5.4**). Lower estimates of relative cost differences were observed for individuals with poorer health behaviours (smoking, exercise, alcohol consumption), with indicators of lower socioeconomic status (deprivation tertiles, educational attainment), and for older adults; however, these differences were small in magnitude.

Table 5.3: Estimation of annual hospital costs in relation to body mass index under various sensitivity analyses

	Body mass index (BMI) category (kg/m^2)								
	18.5-19.9	20-22.4	22.5-24.9	25-27.4	27.5-29.9	30-34.9	35-39.9	≥ 40	Trend[a]
Base case analysis	12.4 (7.9, 17.0)	0.0 (-1.7, 1.7)	4.6 (3.3, 5.9)	13.2 (11.8, 14.7)	26.1 (24.3, 28.0)	42.5 (40.4, 44.7)	73.3 (68.9, 77.8)	115.3 (106.8, 124.2)	7.4 (7.1, 7.6)
Including pre-existing cancer	11.8 (7.5, 16.3)	0.0 (-1.7, 1.7)	4.2 (2.9, 5.5)	13.0 (11.6, 14.4)	25.6 (23.8, 27.5)	41.8 (39.8, 43.9)	72 (67.7, 76.4)	111.8 (103.6, 120.4)	7.3 (7.0, 7.5)
Using data from all years of follow-up	12.0 (8.6, 15.6)	0.0 (-1.4, 1.4)	3.3 (2.3, 4.3)	11.7 (10.6, 12.8)	24.8 (23.3, 26.2)	41.7 (40.0, 43.3)	70.9 (67.5, 74.4)	101.6 (95.3, 108.2)	7.1 (6.9, 7.3)
Excluding BMI > 50 kg/m^2	12.4 (7.9, 17.0)	0.0 (-1.7, 1.7)	4.6 (3.3, 5.9)	13.2 (11.8, 14.6)	26.1 (24.3, 28.0)	42.5 (40.4, 44.7)	73.3 (68.9, 77.8)	112.6 (103.9, 121.7)	7.4 (7.2, 7.7)
Never smokers only	8.4 (1.4, 15.8)	0.0 (-2.6, 2.7)	7.6 (5.6, 9.6)	18.0 (15.9, 20.2)	32.8 (29.9, 35.8)	51.6 (48.3, 54.9)	84.6 (77.8, 91.6)	119.5 (106.5, 133.2)	7.9 (7.5, 8.3)
Excluding pre-existing heart disease & stroke	12.0 (7.4, 16.8)	0.0 (-1.8, 1.8)	4.6 (3.3, 6.0)	13.0 (11.5, 14.5)	25.9 (24.0, 27.9)	41.3 (39.1, 43.6)	71.3 (66.6, 76.1)	112.6 (103.4, 122.1)	7.2 (6.9, 7.5)
Exclude year fatal events and 2 preceding years	7.7 (3.3, 12.4)	0.0 (-1.8, 1.8)	6.0 (4.7, 7.4)	16.1 (14.6, 17.6)	30.1 (28.1, 32.0)	48.1 (45.9, 50.3)	79.4 (74.7, 84.2)	117.5 (108.6, 126.8)	7.7 (7.4, 8.0)
Mean measured BMI									7.2 (6.9, 7.4)

[a]Percentage difference in annual costs per 2 kg/m^2 higher BMI for BMI $\geq$20 kg/m^2.

Figure 5.4: Percentage differences in annual hospital costs per 2 kg/m^2 higher body mass index above 20 kg/m^2 by category of women



The area of each square is inversely proportional to the variance. The error bars show 99% confidence intervals. Participants with missing data on characteristics used to define subgroups were excluded.

[a]Numbers based on women with BMI $\geq$ 20 kg/m^2 only.

5.5.3 Projection of costs to all women aged 55 to 79 years in England

Total hospital costs

There were 6.6 million women aged between 55 and 79 years in England in 2013. 43% had a BMI below 25 kg/m^2, 34% were overweight but not obese, and 23% were obese (16% had grade 1 obesity, 5% grade 2 obesity, and 2% grade 3 obesity).

Total annual hospital costs among all 6.6 million women were projected to be £4.5 billion, of which 14.6% (£662 million) was estimated to be attributable to excess weight. Of the total excess weight attributable annual inpatient and day-case care costs, two-thirds were incurred among women who were overweight but not obese (31%) or who had grade 1 obesity (36%). Women with grades 2 or 3 obesity represented only 7% of the total population, but accounted for one-third of all overweight and obesity attributable costs. Within categories of BMI, the proportion of annual costs attributable to excess weight varied from 13% among women with BMI 25 to <30 kg/m^2, to 52% among women with BMI $\geq$ 40 kg/m^2 (**Table 5.4**).

Table 5.4: Annual inpatient and day case costs attributable to overweight and obesity among women aged 55 to 79 years in England

			Costs attributable to excess weight	
Body mass index (kg/m^2)	Total Population (million)	Total annual costs (£million)	Absolute annual costs (£million), 99% CI	Proportion costs attributable (%), 99% CI
<25	2.83	1,667	-	-
25 to <30	2.28	1,529	202 (200-205)	13 (13-13)
30 to <35	1.06	857	239 (234-243)	28 (28-28)
35 to <40	0.30	297	121 (115-125)	41 (40-41)
$\geq$ 40	0.16	192	100 (94-106)	52 (51-53)
$\geq$ 25	3.80	2,875	662 (643-679)	23 (23-23)

Hospital costs, by category of treated health condition

Mean standardised annual costs per person were higher for overweight and obese women than for women of healthy weight for most categories of health conditions (**Appendix Figure E.2**). Extrapolating these results to all women aged 55 to 79 years in England in 2013, excess weight was associated with elevated costs for all diagnostic categories except respiratory conditions and fractures (**Figure 5.5**; **Appendix Table E.2**). The diagnostic categories for which overweight and obesity accounted for the largest shares of total (condition-specific) annual costs were: diseases of the skin and subcutaneous system (ICD-10 chapter 12; 33% of all costs were estimated to be attributable to overweight and obesity), medical and surgical complications (ICD-10 chapter 19, ICD-10 T80-T88; 33%), endocrine, nutritional, and metabolic disorders (ICD-10 chapter 4; 29%), and musculoskeletal conditions (ICD-10 chapter 13; 28%).

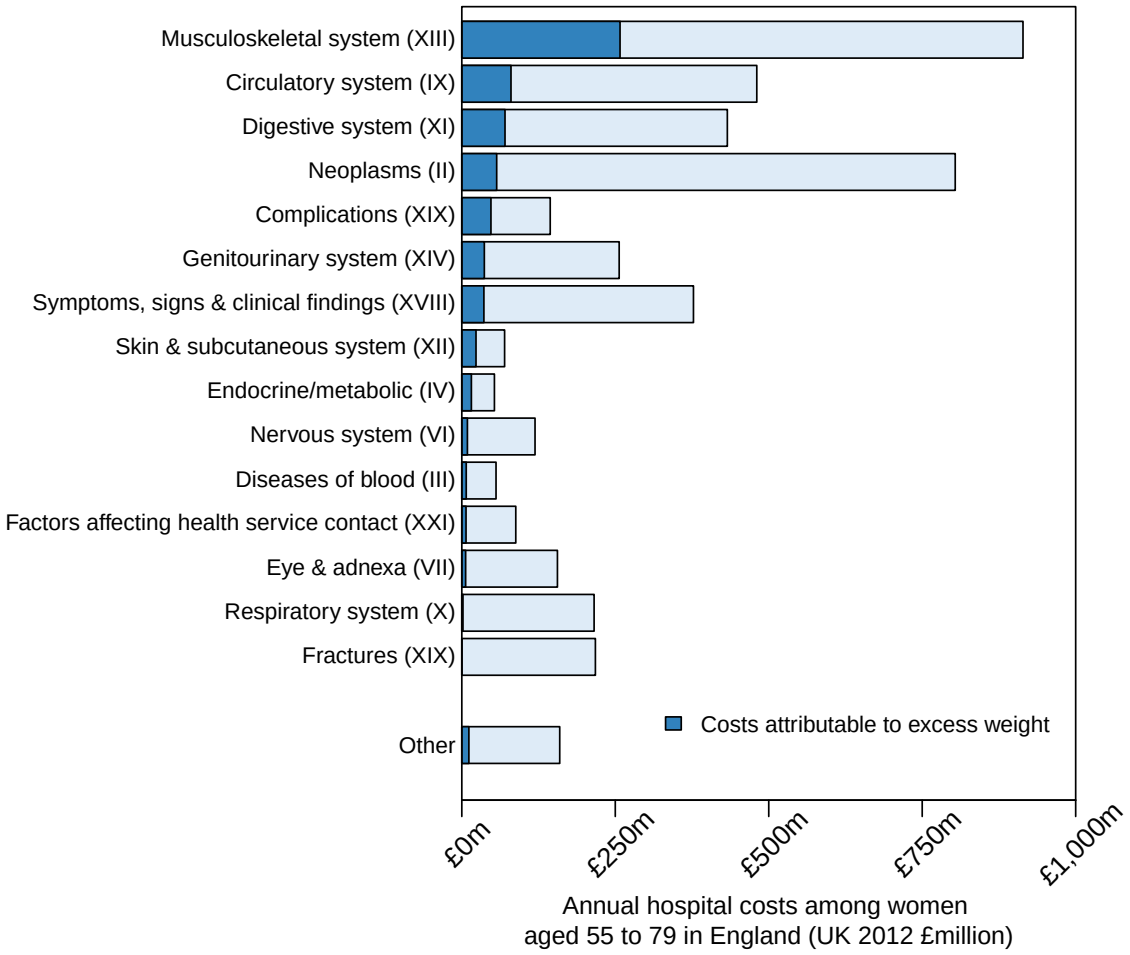
However, since there is substantial variation in total spending on different categories of health conditions, the ordering of categories of conditions by their contribution to total excess weight attributable costs is different. Of the £662 million total annual hospital costs attributed to excess weight among all women aged 55 to 79 years in England, £258 million (39%) was estimated to be due to musculoskeletal conditions (ICD-10 chapter 13), which was also the largest single category of hospital expenditure in this population. This was driven largely by arthropathies (excess costs of £224 million) and, in particular, knee replacements surgeries for women with osteoarthritis (£119 million) [**Figure 5.6**; **Appendix Table E.3**].

The next largest contributing ICD-10 chapter was diseases of the circulatory system (ICD-10 chapter 9), which accounted for around £80 million (12%) of all costs attributed to excess weight among women aged 55 to 79 years in England. Of these excess costs, around 34% was explained by ischaemic heart diseases (ICD-10: I20-I25), 35% by heart failure (I50), and 10% by cerebrovascular diseases (I60-I69).

Diseases of the digestive system (ICD-10 chapter 11) accounted for £70 million (11%) of total excess weight attributable costs; 45% of this was explained by diseases

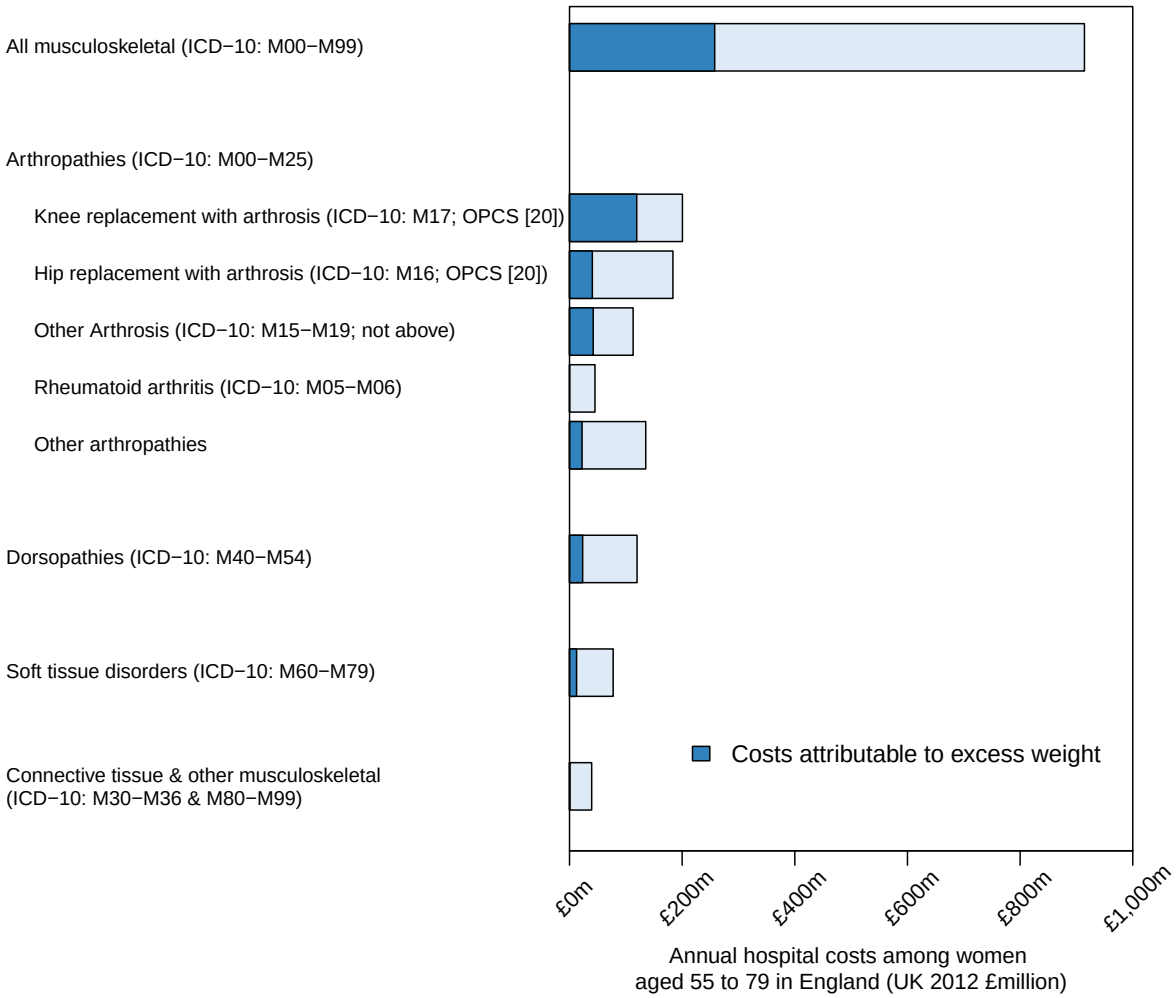
of the gallbladder, biliary tract, and pancreas (ICD-10: K80-K87). Neoplasms (ICD-10 chapter 2) accounted for £57 million (9%) of total excess weight attributable costs; 76% of this was jointly explained by malignant neoplasms of the digestive organs (ICD-10: C15-C26), breast (ICD-10: C50), and female genital organs (ICD-10: C51-C58).

Figure 5.5: Annual hospital costs attributable to excess weight by diagnostic category among women aged 55 to 79 years in England



Diagnostic categories are ordered here according to their contribution to overweight and obesity attributable costs.

Figure 5.6: Annual hospital costs attributable to excess weight by types of musculoskeletal conditions among women aged 55 to 79 years in England



5.5.4 Contribution of diabetes: an exploratory analysis

27,357 women (2.5%) self-reported diabetes at recruitment into the study. By the end of follow-up (31 March 2011), 69,748 women (6.4%) were identified as having diabetes, either by self-report or the presence of a diabetes code in hospital records. Using this information, the exploratory mediation analysis suggested that 39% of the excess costs of overweight and obesity were mediated by diabetes.

5.6 Discussion

5.6.1 Findings and interpretation of results

Overall summary

Based on hospital admissions over 5 years for 1.1 million middle-aged and older women in England, in this Chapter, I showed that higher BMI is strongly associated with higher annual rates and costs of hospital admissions: every 2 kg/m^2 higher BMI for BMI $\geq$20 kg/m^2 was associated with a 5.0% higher admission rate and 7.4% higher annual costs. 14.6% of total annual inpatient and day-case care costs among women aged 55 to 79 years in England were attributable to excess weight. Musculoskeletal conditions made the largest contribution to these excess costs, accounting for 39% of the total, due, in large part, to higher rates of knee replacement surgery among overweight and obese adults with osteoarthritis.

Total inpatient and day-case care costs

Across the 18 studies identified in the literature review (**Chapter 3**) that estimated inpatient care costs in relation to BMI, annual costs were on average 12% higher for overweight adults and 34% higher for obese adults, compared to adults at healthy weight.[9] The corresponding estimates derived from the analysis of the Million Women Study data reported in this Chapter were somewhat higher at 18% and 55%, respectively. These differences could have arisen for a large number of reasons, including differences in settings (most studies in the literature review were based on adults in the US), in characteristics of the sample populations, with many studies in the literature review based on general adult populations, while the Million Women Study included only middle-aged and older women, and differences in data quality and methods. Indeed, the estimates from the Million Women Study analysis were more similar to estimates from high-quality studies in women of similar age [29, 30]. In a study of 225,000 middle-aged and older individuals in the 45 and Up study in Australia, annual inpatient costs for obese women compared to those at healthy weight were 58% higher for women aged 45 to 64 years and 42% higher for women

[9]These are medians across studies of estimated mean percentage differences from each study.

aged 65 to 79 years [30]. Daviglus *et. al.* [29] reported 66% higher annual inpatient costs for obese women compared to women at healthy weight using data on 17,600 former industrial employees in the US aged 65 years or older.

Subgroup results

The association between higher BMI and annual costs was 8% lower for women aged ≥ 70 years or above compared to women aged <65 years, 20% lower for the most compared to the least deprived tertile, 18% for those with no formal educational qualification compared to those who completed tertiary education, 32% lower for current smokers compared to never smokers, and 18% lower for inactive compared to active women. The difference by age is consistent with the results reported from the literature review in **Chapter 3**. Socioeconomic differences may result from inequalities in access to healthcare [31]. Leading epidemiological studies have demonstrated that restricting analyses to never smokers increases estimated associations of BMI with mortality [15, 32]. Differences by smoking status are likely to reflect, at least in part, residual confounding by smoking. Alternatively, because smoking is associated with large increased risks of events like myocardial infarction that may require hospitalisation, the additional risks imparted by high body mass index may be reduced.

Inpatient and day-case care costs, by health condition

A key finding of this analysis was the large contribution of musculoskeletal conditions, particularly knee replacement surgery for women with osteoarthritis, to the costs attributable to excess weight in hospitals. This is a product of the substantially higher risk of arthrosis of the knee and knee replacement faced by adults with high BMI [33–36], and the high cost of a knee replacement procedure: in 2012, a knee replacement cost on average £6,000 [37].[10] Previous analysis of the Million Women Study data reported a ten-fold higher risk of knee replacement surgery for obese

[10]This was estimated from the 2011-12 NHS Reference Cost Schedule as the weighted average of costs for HRG codes HB21A-HB21C for elective inpatient care, where the weights are the number of knee replacements performed.

women compared to healthy weight women, and around a four-fold higher risk for overweight women [33]. Other studies have consistently reported elevated risks among overweight and obese adults for osteoarthritis and knee replacement with a primary osteoarthritis diagnosis, and quicker progression to knee replacement for people with osteoarthritis [34–36].

The next three categories of health conditions making the largest contributions to total excess weight attributable costs were diseases of the circulatory system, diseases of the digestive system, and neoplasms. These findings are consistent with evidence from leading observational studies and meta-analyses, which have reported higher incidence of coronary heart disease [38, 39], ischaemic stroke [40], heart failure [41], gallbladder disease [42], and certain cancers, including cancers of the colon, breast (postmenopausal), ovaries, kidney, pancreas, endometrium, and gallbladder [34, 43, 44] in adults with higher BMI. In addition, these conditions constitute a large share of total spending on hospital care (**Figures 5.2** and **5.5**).

The relationship between BMI and fracture risk is complex, with high BMI associated with an increased incidence of certain fractures like hip fracture, but reduced risks of other fractures, including most osteoporotic fractures and upper arm fracture [45]. Hence, the finding of no overall elevated or even lower costs of fractures in women with higher BMIs is not inconsistent with previous evidence, and may reflect several real effects operating in opposite directions.

At the population level, excess weight was not associated with elevated hospital costs for the treatment of respiratory conditions. This, however, masks important differences by weight status: compared to women at healthy weight, annual respiratory costs were higher for obese women but lower for women who were overweight but not obese. This result may be a consequence of confounding by pre-existing disease, which is likely to pose a particular issue for the estimation of respiratory disease costs, since certain respiratory conditions like chronic obstructive pulmonary disease (COPD) may both reduce weight and increase healthcare costs. The presence of COPD and other severe respiratory conditions were not recorded at baseline in the Million Women Study, and hence it was not possible to exclude

women with such conditions in this analysis. The exclusion of, on average, the first seven years of follow-up data may have alleviated this problem, because individuals with such conditions face a higher risk of mortality, but perhaps not completely eliminated it.

Seven studies estimated medical costs (usually inpatient and ambulatory care combined) in relation to BMI for different health conditions, defined by major diagnostic categories, and reported elevated costs among adults with higher BMI for most types of health conditions [29, 46–51]. Higher quality studies which estimated costs for a wide range of conditions, found both musculoskeletal and circulatory diseases to be the major contributors to total excess weight attributable costs, each accounting for between one-fifth and one-quarter of the total [47, 52]. These studies were based on employed adults in the US, and the lower contribution of musculoskeletal conditions to the total excess weight weight attributable costs than observed in the Million Women Study data, may be due to differences in the populations studied, with the Million Women Study consisting of only middle-aged and older women, among whom the incidence of osteoarthritis is higher [53].

5.6.2 Limitations

Categorisation of health conditions and exploratory diabetes analysis

Defining categories of disease using ICD-10 chapters provides tractable estimates and accords with the approach taken to programme budgeting by NHS England, thereby maximising the usefulness of the results to policy makers, and healthcare commissioners and providers. However, other classification systems would likely produce different results. BMI is strongly associated with diabetes [26], and diabetes with hospital costs [54], but the effects of diabetes on total hospital costs are likely to be distributed across several ICD-10 chapters, for example, in diseases of the circulatory system (ICD-10 chapter 9). As a consequence, the full impact of diabetes on costs and excess weight attributable costs will be underestimated in the main analysis by the estimate for the ICD-10 chapter in which it is classified (i.e. ICD-10 chapter 4: endocrine, metabolic, and nutritional disorders).

An exploratory mediation analysis using self-reported diabetes at recruitment and diagnosis codes for diabetes in hospital admission records, suggested that 39% of costs attributable to excess weight were mediated by diabetes. This estimate has important limitations. First, because BMI and diabetes are both influenced by fat mass and are highly collinear, controlling for diabetes in the estimation of the association between BMI and hospital costs may artificially reduce the impact of BMI because fat mass is implicitly controlled for.

Second, the prevalence of diabetes is underestimated using only hospital admission data, because those who develop diabetes during follow-up are only identified if it is recorded in their hospital admission records. Conversely, any diabetes identified in a hospital record is immediately associated with the cost assigned to that admission, and the likelihood that it is recorded at all may differ substantially between conditions and also by BMI. This could lead to overestimation of the contribution of diabetes to total excess weight attributable costs. Indeed, supplementing hospital admission data with information from the primary care records of 69,440 Million Women Study participants on clinical diagnoses, prescription items issued, and laboratory tests performed in order to more precisely identify diabetes, led to an estimated prevalence of diabetes of 12% at the end of study follow-up, in line with population statistics on type-2 diabetes prevalence [23, 55, 56], and a lower estimate of the total excess weight attributable hospital costs explained by diabetes of 25%.[11]

Estimating hospital costs

MWS participants were not linked to the Critical Care Minimum Dataset, which, since 2008 has contained information on critical care. By excluding critical care costs we are underestimating total inpatient care costs, and, if critical care costs follow a similar association with BMI as with other costs, then we may also underestimate the impact of excess weight on inpatient care costs. Similarly, we do not capture

[11]The estimate of 39% was reported in the manuscript on which this chapter is based [57] because, at the time of publication, no analysis using primary care data had been undertaken. The estimate of the proportion of total healthcare costs attributable to excess weight among the 69,440 women with primary care data was 13.5%, similar to that observed in the larger sample. Further details regarding the identification of diabetes using primary care records are provided in Chapter 6.

non-inpatient hospital activity like Accident and Emergency visits and outpatient appointments. The distribution of activity by health condition is also likely to differ by setting; for instance, many patients with fractures will be treated as outpatients.

Finally, we assume that in treating a hospitalised patient, the hospital incurs the cost as given in the NHS Reference Cost schedule. However, these include indirect and overhead costs, and so may not reflect the true marginal cost of treatment.

Subgroup analysis

The association between BMI and annual hospital costs from 2006 were estimated in participant subgroups by measures of socioeconomic status and behavioural risk factors at recruitment (on average in 1998). Follow-up questionnaires were sent to all surviving Million Women Study participants on average 8 years after recruitment (in 2006 on average). 54% of women included in the inpatient care cost analysis returned the questionnaire. Of these, $\approx$ 40% of smokers and $\approx$ 20% of users of alcohol at recruitment had quit at the 8 year follow-up; comparable data on exercise behaviour was not available. However, the response rate is low and it is likely to be a self-selecting and relatively healthy subset of the wider Million Women Study; annual hospital costs were $\approx$ 25% lower among those responding to the 8-year questionnaire compared to those who did not. A further limitation of using data at 8 years is that changes to health behaviours may have been prompted by adverse health events, and this may bias the estimated associations. At recruitment, attempts were made to address residual confounding by pre-existing disease using data exclusion techniques.

Generalisability of results

The results reported in this Chapter are based on data from middle-aged and older women in England who attended breast cancer screening. Women who attend breast cancer screening are less likely to come from the most deprived sections of the population [58], and may be, on average, in better health. These differences may render the absolute cost estimates generated in projecting costs from Million Women Study participants to all women aged 55 to 79 years in England somewhat inaccurate (most likely an underestimate), but they would not be expected to

change the qualitative conclusions, namely of the large impacts of excess weight on hospital costs, and the key contribution of musculoskeletal conditions to these excess costs. Overall annual rates of hospital admissions and costs in the Million Women Study data are consistent with national estimates [5, 6].

In addition, the extent to which costs in relation to BMI among middle-aged and older women in England apply to men, younger adults, and in different healthcare settings is uncertain, but previous evidence can offer some guidance as to the likely differences. Based on a systematic literature review of studies using individual participant data, reported in **Chapter 3**, percentage differences in total annual hospital costs for overweight and obese adults compared to adults at healthy weight, were found to be similar in women and men, and stronger in middle-aged than in either older or younger adults.

Differences in associations between BMI and costs by age and gender are likely to be even larger for specific health conditions because the incidence of many conditions, including cardiovascular disease, type-2 diabetes, and osteoarthritis, is strongly increasing with age and, in many cases, differs between men and women, with, for instance, a higher incidence of cardiovascular disease [59], but a lower incidence of osteoathritis [60], among men. In addition, there are age- and gender-differences in the the estimated associations between BMI and the incidence of many conditions, as described in **Chapter 2**.

In **Chapter 3**, I reported similar proportional associations between BMI and healthcare costs across countries with quite different healthcare systems, and the estimates derived from the Million Women Study data were similar to estimates from high-quality studies conducted among women of similar age in the US and Australia. Absolute differences in costs associated with excess weight are likely to show greater variation across countries because of different payment systems, different rates of technology adoption, differences in clinical practice, and differences in prices [3].

The results presented in this Chapter reflect clinical practice in England during the period of study follow-up, including clinical decisions on treatment that might be affected by weight status and comorbid conditions of obesity. For instance,

the Royal College of Surgeons in the UK reported that over a third of Clinical Commissioning Groups in England are restricting access to routine surgery such as hip and knee replacements until patients lose weight [61], even though is in contravention of national clinical guidelines [62–64]. Were decisions to perform elective surgeries (e.g. knee replacement surgery) in relation to weight to change in the future, then the relationship between excess weight and costs may also change. More generally, in other populations or at other times, the associations between BMI and costs might differ due to differences in clinical practice.

Limitations of observational data

The results presented in this Chapter were based on analysis of observational data, and so there is considerable potential for biases in the estimated associations arising from residual confounding, particularly by pre-existing disease (i.e. reverse causality) and smoking [65]. A variety of data exclusions in both the main and sensitivity analyses were undertaken to assess, and possibly reduce, the impact of these potential sources of bias. Although proportional estimates of annual costs in relation to BMI were found to be largely insensitive to different exclusion criteria, this does not preclude bias. Future research would benefit from the application of alternative methods, for example, instrumental variable regression using robust instruments such as genetic variants that explain population variation in BMI, to estimate causal associations between BMI and healthcare costs (i.e. Mendelian randomisation).

In this analysis, BMI derived from reported height and weight at recruitment was used, and efforts were made to control for influences on reported weight like pre-existing disease (diagnosed or not) that may bias associations between BMI and health-related outcomes. Updating BMI using reports of weight in follow-up MWS questionnaires is possible, but makes it harder to control for these potential biases using data exclusion methods. In addition, the response rates to follow-up questionnaires were low, with just around half of MWS participants completing the 8-year questionnaire, and, on average, respondents adopted healthier behaviours and were in better health than the general sample.

Using self-reported rather than measured anthropometric data may also impart bias into the analysis. However, as described in **Chapter 4**, BMI derived from self-reported height and weight at recruitment into the Million Women Study correlates very closely to BMI derived from measured values [66], even over almost a decade of follow-up [67], suggesting that BMI at recruitment is a robust measure of long-term exposure to excess weight. In addition, accounting for measurement error in BMI derived from self-reported height and weight did not change the estimated associations between BMI and annual hospital costs.

5.6.3 Conclusions

In this Chapter, I demonstrated that, in middle-aged and older women in England, higher BMI is associated with substantially higher rates of hospital admissions and higher annual hospital costs, in particular due to musculoskeletal conditions, but also diseases of the circulatory and digestive systems, and neoplasms. The majority of the impact of excess weight on inpatient and day-case care costs was among women who were overweight but not obese, or who had grade 1 obesity. This study provides novel estimates of hospital costs in relation to BMI in the UK, and is the largest study internationally. The detailed description of the incidence of the costs of excess weight on hospital care, by weight category, and for different health conditions, should be useful for the purposes of healthcare planning and commissioning, particularly in response to expectations about changes in the distribution of BMI within the population. Given the large increases in admission rates and hospital spending over recent years [6], these results underline the need for effective interventions to both reduce weight but also to prevent weight gain, in order to reduce or curtail the growing pressure on secondary care.

5.7 Summary

This chapter provided novel evidence on the impacts of excess weight on hospital admissions and associated costs among middle-aged and older women in England using data from the Million Women Study linked to Hospital Episode Statistics. In the next Chapter, I present similar analyses for primary care consultations, prescription medications, and diagnostic and monitoring tests using linked data from the Clinical Practice Research Datalink.

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6

Primary care costs in relation to body mass index

Summary

Linked data for primary care consultations, prescriptions, and monitoring and diagnostic tests were obtained from the Clinical Practice Research Datalink for 69,440 Million Women Study participants, aged 50 to 64 years at recruitment, who reported height and weight corresponding to a body mass index (BMI) of $\geq$18.5 kg/m^2, and who had no previous cancer at recruitment. Over an average of 6.0 years of follow-up from 1 April 2006 (11.1 years from recruitment), mean annual rates and costs (in UK 2016 prices) of consultations, prescription items, and tests were estimated in relation to BMI, overall and, for prescription items, by categories of therapeutic use. Associations of BMI with annual costs of consultations and prescriptions were projected to the 2013 population of women aged 55 to 79 years in England. Annual rates and mean costs of consultations (7.0 consultations, 99% CI 6.8 to 7.1; £288, 280 to 295) and of prescription items issued (27.0 items, 26.0 to 27.9; £227, 216 to 237) were lowest for women with a BMI of 20 to <22.5 kg/m^2. Every 2 kg/m^2 higher BMI beyond 20 kg/m^2 was associated with 5.2% (4.8 to 5.6) and 9.9% (9.2 to 10.6) higher annual consultation and prescription costs, respectively. Annual rates and mean costs of tests were similar for women at different BMIs. Among all women aged 55 to 79 years in England, 11% (£229 million/£2.2 billion) of all consultation costs and 20% (£384 million/£1.9 billion) of all prescription costs were attributable to excess weight (BMI $\geq$ 25 kg/m^2). 27% of the annual prescription costs attributable to excess weight were for diabetes drugs, 19% for circulatory system drugs, and 13% for analgesics.

6.1 Background

In the systematic literature review presented in **Chapter 3**, the proportional association between higher BMI and higher annual healthcare costs was strongest for medications and weakest for ambulatory care, which often included visits to primary care or family doctors. Six studies, with sample sizes ranging from 506 to 5,841 participants, separately reported costs for primary care [1–6]. Estimates ranged from 25% lower annual costs for obese compared to healthy weight adults [1] to 160% higher costs [2]. No breakdown of these costs by health conditions were identified. Similarly, few studies have separately estimated costs for monitoring and diagnostic tests in relation to BMI; those that have, reported marginally higher costs with higher BMI [1, 7].

Eighteen studies, with sample sizes ranging from 2,244 to 17,703, contributed to the estimated 18% and 64% higher mean annual medication costs for overweight and obese adults, respectively, compared to adults at healthy weight, presented in the literature review. Five studies estimated medication costs separately for different categories of therapeutic use, and reported the strongest proportional associations of higher BMI with higher costs for drugs used for the treatment of diabetes, cardiovascular disease, and pain, with cardiovascular medications accounting for the greatest share of the total excess weight attributable medication costs [5, 8–11].

Previous estimates of medication and primary care costs have been derived mostly from US data, with no reliable estimates pertaining directly to the UK, and were based on small-to-moderate numbers of participants. Given the large differences in pharmaceutical prices [12] and the major structural differences in healthcare delivery between the US and the UK, in particular with primary care in the UK playing a larger role in controlling access to specialist secondary care services [13–15], the estimated associations may not be expected to translate well to the UK. In addition, small numbers of participants limits the reliability of estimates of costs in relation to grades of obesity or for different health conditions. In addition, few studies have made a concerted effort to deal with potential reverse causality by pre-existing disease.

In this Chapter, I present estimates of annual rates and costs of primary care consultations, prescription items issued, overall and by categories of therapeutic use, and monitoring and diagnostic tests in relation to BMI among 69,440 middle-aged and older women in England from the Million Women Study, for whom linked data on use of primary healthcare services is available from the Clinical Practice Research Datalink. Prior to this, I further describe the use of, and expenditure on, primary healthcare and prescriptions in England, including variations over the life-cycle, by gender, and, where possible, across different health conditions.

6.2 Primary care in England

6.2.1 Primary care consultations

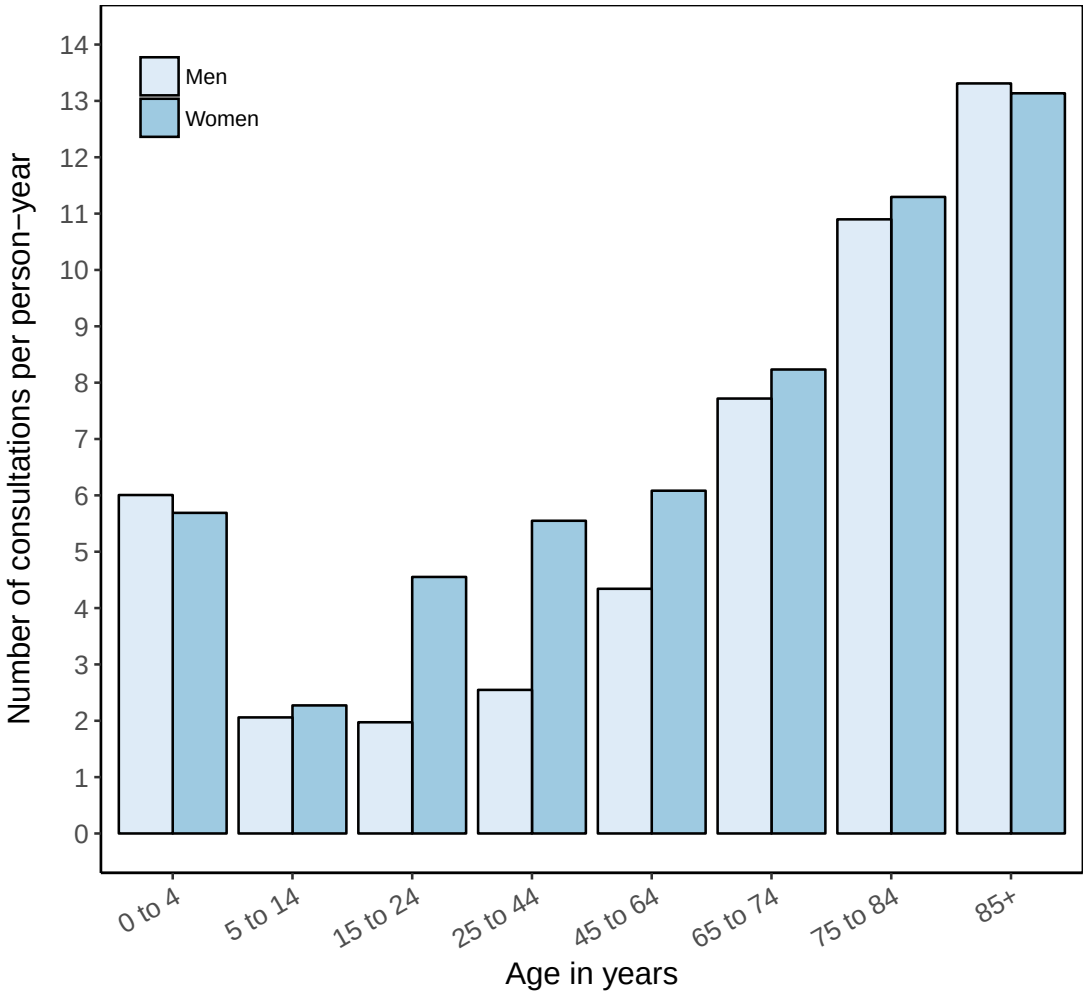
Primary care accounted for around 8% of government spending on healthcare in England in 2015 [16]. According to analysis of the Clinical Practice Research Datalink (CPRD), in 2013-14 the average adult in England had 5.2 contacts with their general practice, including 3.8 consultations (75% of all consultations) with their general practitioner (GP) and 1.4 consultations with nurses or other allied healthcare professionals [17].[1] 4.4 consultations (86%) were face-to-face contacts in the GP surgery, 0.1 (2%) were visits to the patient's home, and 0.6 (12%) were by telephone. Attaching costs per consultation from the Unit Costs of Health and Social Care annual report [20] to consultation rates reported in Hobbs *et. al.* [17], gives an estimate of annual consultation costs per person of £175 (in UK 2016 prices). Age- and sex-standardised rates of consultations increased by 10.5% between 2007-08 and 2013-14 [17]. This reflects increased rates of consultations with GPs, and increased rates of surgery and telephone consultations; rates of home visits fell over this period.

Consultation rates tended to be higher for women than men (6.1 versus 4.2 consultations per year); these differences were greatest among adults aged 65 years or less, and were more similar among older adults (**Figure 6.1**). Consultation rates were strongly increasing with age for both men and women, but most strongly for men: a man aged 45 to 64 years had on average 4.3 consultations per year compared to 10.9 for a 75 to 84 year old man; among women, the corresponding rates were 6.1 and 11.3 consultations per year. No decomposition of consultation rates or costs by health conditions has been identified.

No UK data on the rates of, or spending on, monitoring and diagnostic tests were identified.

[1] A separate analysis of data from the CPRD reported 13% fewer consultations per year in 2013-14 [18], and an analysis of a distinct primary care dataset, QResearch, reported an 18% higher rate of consultations per year [19]. Using QResearch it was estimated that only around two-thirds of consultations were with a GP.

Figure 6.1: Number of consultations per year in 2013-14 by age and sex



Source: based on data from Hobbs *et. al.* [17]

6.2.2 Prescription items

11% of government healthcare spending in England in 2015 was on pharmacy [16]. According to data from the Prescription Cost Analysis (PCA), 19.8 prescription items per person, at a cost of £169, were dispensed in England in 2015 [21]. Between 2005 and 2015, the rate of prescription items dispensed per person-year increased by 50% and the corresponding costs by 17%. Evidence on patterns of prescriptions issued by age, but not gender, is available for individuals aged 60 years or older for 2002 based on analysis of the QResearch database, which contains health records

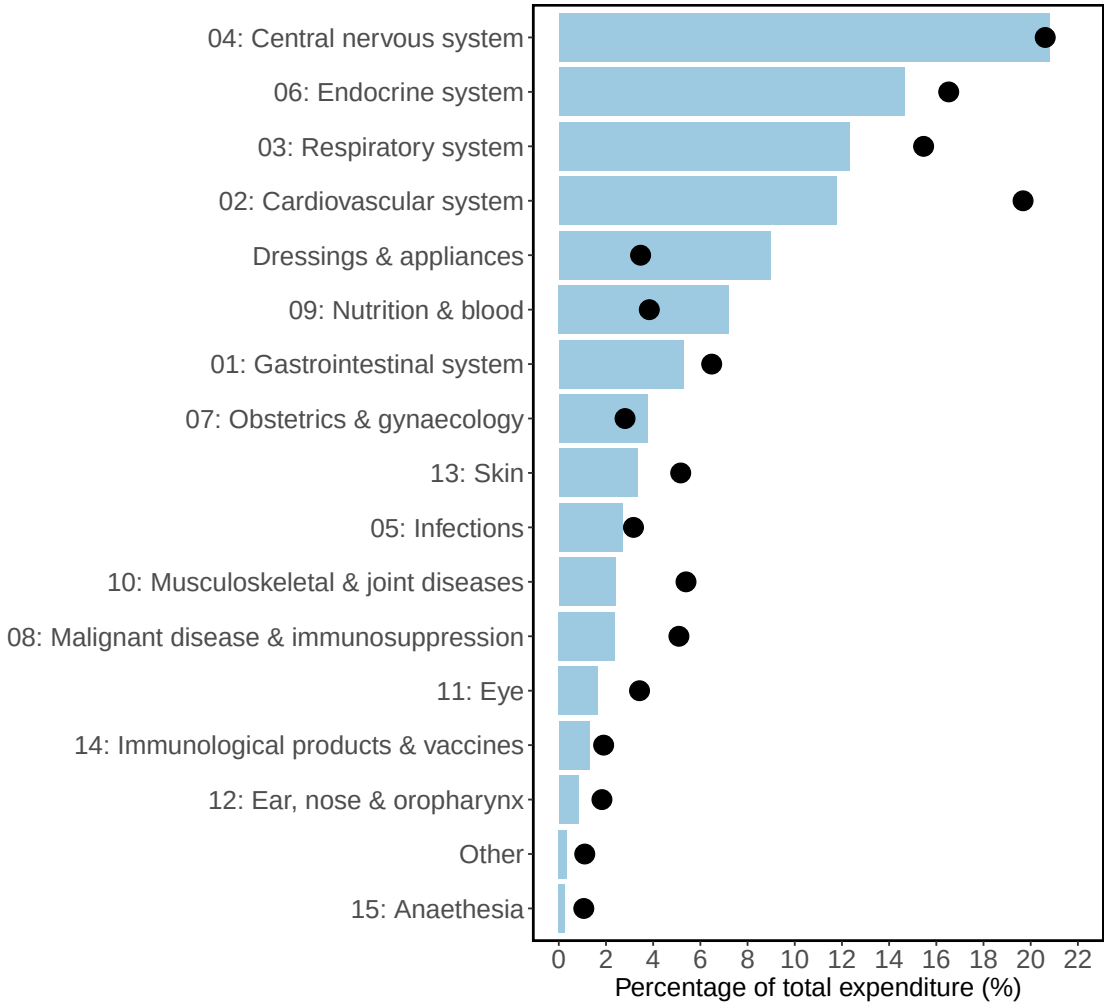
for over 24 million people in England from 1,500 primary care practices [19, 22].[2] Among adults aged 60 to 79 years, the average number of prescription items issued per year was 30.1 in 2002. The number of items issued was 80% higher among adults aged 75 to 79 years (40.0 items) compared to those aged 60 to 64 years (22.4 items). Attaching costs by British National Formulary[3] (BNF) chapter from the 2016 PCA [16] to data from QResearch [24], gives an annual cost per person aged 60 to 79 years of £227 (in UK 2016 prices).

Figure 6.2 shows the percentage of total prescription spending on each BNF chapter among all adults in England in 2013 from the PCA [21] and for adults aged 60 to 79 years from QResearch [24]. The largest categories of expenditure were for the central nervous system (which includes analgesics), the endocrine system (which includes diabetes), the respiratory system, and the cardiovascular system. Patterns of expenditure by BNF chapter among older adults were broadly similar to those in the general population; however, drugs for the endocrine system, the respiratory system, musculoskeletal and joint disease, and particularly the cardiovascular system accounted for somewhat larger proportions of total expenditure among older adults than in the general population.

[2]Estimates from QResearch are therefore not directly comparable to those based on analysis of PCA data, which were for 2015, and were based on all prescriptions dispensed in the community, rather than for only a non-representative sample of the population. Although sampling weights are used for QResearch analyses to control for selection on observables, namely list size and composition, and the geographical location of practices, this does not preclude selection based on unobserved characteristics.

[3]As described further in Chapter 4, the BNF is a pharmaceutical reference book in the UK which provides information on prescribing and pharmacology for medicines available on the NHS [23]. Medications can be categorised into one of fifteen chapters or therapeutic groups, describing the system of the body or the aspect of medical care to which they relate, and there are six pseudo-BNF chapters describing mainly dressings and appliances. Medications can also be summarised by section or paragraph, which are embedded within chapters.

Figure 6.2: Percentage of total spending on prescriptions by BNF chapter among the entire population of England and in adults aged 60 to 79 years



The blue bars represent estimates of expenditure across the entire population in England based on data from the Prescription Cost Analysis [21]; the black circles represent estimates for adults aged 60 to 79 years based on analysis of the QResearch database [24]. Categories of therapeutic use are presented in descending order of their contribution to total pharmacy expenditure in England.

6.3 Costing primary care

6.3.1 Primary care consultations and tests

Estimates of the costs of consultations with general practitioners, nurses, and other community healthcare professionals are reported in the Unit Costs of Health and Social Care, which are published annually by the Personal Social Services Research Unit at the University of Kent [20]. For nurses, these costs include salaries, salary oncosts, qualifications, overheads, and capital overheads. For GPs, they include net remuneration, practice expenses (administrative and clerical staff, office and general business, premises, other), pre-registration and post-graduate medical education, and capital costs. For certain healthcare professionals including speech therapists and physiotherapists, costs are not available from the Unit Costs of Health and Social Care report. Estimates of costs for many such professionals are reported in the NHS Reference Cost Schedule 2015-16 [25], along with costs for laboratory and other diagnostic tests. NHS Reference Costs, which are based on data provided by all hospitals in England, are calculated on a full absorption basis including direct, indirect, and overhead costs.[4]

6.3.2 Prescription items

Details of all prescription items dispensed in the community in England, including by community pharmacists, appliance contractors, dispensing doctors, and items personally administered by doctors,[5] are sent to the NHS Prescription Services, part of the NHS Business Services Authority, for payment. This information is collated and published monthly as the Prescription Cost Analysis [26]. It provides information, summarised by BNF code (including pseudo-BNF chapters), on the number of prescription items issued and the total costs of these items. Costs of each prescription item are given as net ingredient costs (NIC). The NIC refers to the cost of the drug before discounts and does not include any dispensing costs or

[4]See Chapter 5 for further details.

[5]PCA does not include items dispensed in hospital or on private prescriptions. Prescriptions written by dentists and hospital doctors are included only if they were dispensed in the community; though only a very small proportion are [13].

fees, or make any adjustment for income obtained where a prescription charge is paid at the time the prescription is dispensed or where the patient has purchased a pre-payment certificate. The cost of the drug is the basic price of the medicine, that is, the price listed in Part VIII or IX of the Drug Tariff [27] or, for drugs not listed in the Drug Tariff, the list price published by the manufacturer, wholesaler, or supplier. From the information in PCA, average costs per prescription item can be calculated at different levels of specificity, for example, the individual product, or the BNF chapter, section, or paragraph. Costs for each category are the weighted average of the NIC per prescription item and the number of items prescribed for each medication in that category.

6.4 Methods

6.4.1 Participants and follow-up

CPRD defines records as being of sufficient quality for research for both individuals, which depends on their registration status (most records that are flagged as being of poor quality are because the patient is only temporarily registered in a practice), recording of events in the patient record, and valid age and gender, and for practices, which depends on the continuity of data recording and the number of recorded deaths compared with an expected range. Women were excluded from analysis if they provided no data of sufficient quality for research beyond recruitment, or if they had gaps in registration of unknown duration. Women were further excluded from the main analysis if: there was missing information on height or weight; they were underweight (BMI <18.5 kg/m^2); they had a registration of cancer (other than non-melanoma skin cancer) before recruitment; or they contributed no data to CPRD beyond 31 March 2006 (**Appendix Figure F.1**).

Women with known cancer were excluded because cancer can cause severe weight loss and lead to high medical costs, thereby confounding the relationship between observed weight and costs [28]. Data prior to 1 April 2006 was excluded from the main analysis to reduce the influence of confounding by pre-existing disease (i.e. reverse causality), and because of the expansion of the Quality and Outcomes Framework (QOF) in this month (QOF is an annual reward and incentive programme for all GP surgeries in England, first introduced in 2004),[6] which may have influenced clinical practice [13].

Women contributed person-years of data from 1 April 2006 or, if later, the date at which the practice to which they belonged began to provide data of sufficient quality for analysis (as defined by CPRD), until the earliest of their date of death, emigration, or the end of follow-up in CPRD (31 January 2014).

[6]The QOF underwent a major revision in 2006 following the renewal of the General Medical Services contract, with the addition of clinical domains for dementia, depression, chronic kidney disease, atrial fibrilation, obesity, learning disabilities, and smoking, and with more than 10% of points being reassigned.

6.4.2 Categorisation and costing of healthcare services

All consultation records relating to a face-to-face surgery or clinic visit, home visit, out-of-hours visit, or telephone consultation, performed by a general practitioner (GP; a primary care doctor), a nurse, or allied health or social care professional were included (see **Appendix Table F.1** for lists of consultation and staff roles included). Records generated by staff with unknown roles were excluded from the main analysis (7%), and imputed in a sensitivity analysis (as described further below). Multiple consultations of the same type on a single day were considered to be duplicates and excluded (5%).[7] National unit costs (in UK 2016 prices) were used to estimate the cost of each consultation according to the role of the staff member recording the consultation and the type or location of the consultation (**Appendix Table F.2**).

Monitoring and diagnostic tests were costed using national unit costs (in UK 2016 prices; **Appendix Table F.3**). Tests that are routinely performed during standard consultations (e.g. blood pressure or forced expiratory volume tests) are excluded to avoid double-counting of costs: the costs of these tests will already be incorporated into the costs of the consultation in which they occurred. Duplicate records of a given test within a single consultation were excluded (1%).

Each prescription item was uniquely allocated to one of eighteen categories of 'therapeutic use'. These correspond to each of the fifteen standard BNF chapters, plus analgesics (BNF section 0407), drugs in diabetes (0601), and dressings and appliances (i.e. pseudo-BNF chapters). So that each medication is allocated to only one category, BNF chapter 04 (central nervous system) excludes analgesics, and chapter 06 (endocrine system) excludes drugs in diabetes. For circulatory system medications (chapter 02), medication use is further categorised as: diuretics (section 0202), beta-adrenoceptor blocking drugs (0204), hypertension and heart failure (0205), nitrates, calcium-channel blockers, and other antianginal drugs (0206), anticoagulants and protamine (0208), antiplatelet drugs (0209), lipid-regulating drugs (0212), and

[7] It is rare for an individual to have more than one consultation on a given day with the same healthcare professional in a primary care practice. In addition, based on discussions with a GP working in a CPRD practice, new records within a consultation may be generated each time a new health condition is discussed, and may therefore not reflect multiple consultations.

the remainder. Drugs for the circulatory system, diabetes, and analgesics were considered separately because previous evidence suggests they are major contributors to the costs of prescription medications associated with high BMI [5, 8–11]. The categorisation of prescription items by BNF chapter accords with the approach taken to programme budgeting in the UK, and therefore maximises the applicability of the results to policy makers, and healthcare commissioners and providers.

Costs per prescription item issued (in UK 2016 prices) at the BNF paragraph level were applied to each prescription item issued in CPRD using the BNF paragraph as recorded by the healthcare practitioner (**Appendix Table F.4**). Where BNF paragraph costs were not available (11.6% of prescription items), average costs by BNF section were applied, and where these were also unavailable (0.1%), average costs by BNF chapter were applied. Information is available on only the issuing of prescription items, and not whether the items were actually dispensed; dispensing rates are however very high (>98%) [29]. Therapies with unrecognised BNF codes in CPRD largely relate to pseudo-BNF chapters, and an average cost across all pseudo-chapters was applied to all such items. Costs do not include prescription charges.

6.4.3 Statistical analysis

Statistical models

Separate estimates of rates and mean annual costs of consultations, prescription items issued, and tests, by BMI category (18.5 to <20, 20 to <22.5, 22.5 to <25, 25 to <27.5, 27.5 to <30, 30 to <35, 35 to <40, and $\geq$40 kg/m^2), and percentage differences in rates and mean annual costs per 2 kg/m^2 higher BMI (a change in weight of approximately 5 kg for a woman of average height [162 cm] in England) in women with a BMI above 20 kg/m^2 (i.e. the range over which the relationship between BMI and total costs was approximately log-linear),[8] were calculated overall and, in the case of prescription items, by category of therapeutic use, with generalised linear models with a log-link function and Poisson-like variance. This model

[8]The estimates were similar regardless of the BMI range used in estimation.

specification was selected from a wider pool of candidate models using a range of common specification tests [30] and a comparison of model fit (see **Appendix D**).

Adjustment for confounders followed the same principles as described in greater detail in **Chapter 5**. In brief, all models were adjusted for age at the start of each annual period, and region of recruitment, socioeconomic status, parity, age at birth of first child, smoking, alcohol intake, and educational attainment at recruitment. Further adjustments were made for financial year and the proportion of each year with contributed data. Cluster-robust standard errors were used in all models to account for the lack of independence between outcomes for a given individual across years of follow-up. Variances for the estimate in each BMI category were derived from an estimate of the variance of the log risk specific to that category, and presented as group-specific 99% confidence intervals [31].

Standardised estimates of mean annual rates and costs

Standardised estimates of mean annual costs and number of consultations, prescription items issued, and tests per person for each BMI category were derived from the estimation models described above, using the method of recycled predictions (also known as predictive margins), using the methods described in **Chapter 5**. Standard errors around these estimates were given by the standard deviation of mean estimates based on 1,000 bootstrap replicates, and were used to construct 99% confidence intervals.

Sensitivity analyses

Sensitivity analyses were performed to assess the impact of model assumptions and data on estimated associations between BMI and total annual costs of primary care services. The reasons for these analysis are defined in **Chapter 5**. Associations were estimated: (i) including women with a history of cancer at baseline; (ii) including all years of follow-up from recruitment; (iii) restricting the analysis to never-smokers; (iv) excluding participants with self-reported heart disease or stroke at recruitment; (v) excluding women with BMI >50 kg/m^2; (vi) excluding the year of death and the preceding two years of observation for women who died during follow-up; and, in

estimates of percentage differences in total annual costs per 2 kg/m^2 higher BMI for BMI $\geq$ 20 kg/m^2, replacing self-reported BMI by mean measured BMI in categories of self-reported BMI from the Health Survey for England. For consultations, staff roles, where unknown, were imputed using the relative frequency of each staff role by category of consultation type among observed cases.

Subgroup analysis

Models of percentage differences in total annual costs per 2 kg/m^2 higher BMI for BMI $\geq$20 kg/m^2 were also estimated within subgroups defined by age at the start of each annual period (<65, 65 to <70, $\geq$70 years), and by smoking status (never, former, current), alcohol intake (rarely/never, <7 units per week, $\geq$ 7 units per week), strenuous exercise (never/rarely, other), tertiles of socioeconomic status [32], and educational attainment (none, secondary or technical, tertiary) at recruitment. Heterogeneity of percentage differences in annual costs per 2 kg/m^2 higher BMI for BMI $\geq$20 kg/m^2 between categories of each subgroup was assessed using a chi-squared test.

Projection of costs to all women aged 55 to 79 years in England in 2013

Costs attributable to each category of overweight and obesity and for overweight and obesity combined (i.e. excess weight; BMI $\geq$ 25 kg/m^2) were estimated for all women aged 55 to 79 years in England in 2013, for total consultation costs, total prescription costs, and prescription costs by category of therapeutic use, using the methods described in **Chapter 5**. Standard errors around these estimates were given by the standard deviation of mean estimates based on 1,000 bootstrap replicates, and were used to construct 99% confidence intervals.

Exploratory analysis of the mediating effect of diabetes on excess weight attributable costs

An exploratory analysis was undertaken to investigate the extent to which the primary care costs attributable to excess weight might be explained by diabetes, which is expected to be a leading contributor to these costs [33]. A similar mediation

analysis was used recently by the Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration to assess the extent to which the impact of BMI on coronary heart disease and stroke was mediated by glucose and diabetes [34].

The proportion of annual costs attributed to excess weight was estimated as described above but with diabetes status added as a covariate in the model. A woman was deemed to have diabetes in the annual period in which evidence for diabetes was first encountered and in all subsequent years. Evidence for diabetes was present if the individual self-reported diabetes at recruitment, had a hospital admission in which diabetes (ICD-10: E10-E14 except E12) was recorded in any diagnostic position, or using data from CPRD (not restricted only to data from April 2006), had a clinical diagnosis of diabetes, was prescribed a medication for diabetes, or had more than one HbA1c or glucose tolerance test result indicative of diabetes (see **Appendix Table F.5** for code lists). The date of onset of diabetes was considered as the earliest record of any of the above. The differences in estimated annual costs associated with excess weight between models with and without diabetes as a covariate was used to estimate the proportions of costs attributable to excess weight associated with diabetes.

6.5 Results

6.5.1 Participant characteristics at recruitment and details of follow-up

87,123 women recruited into the Million Women Study in England had high-quality follow-up in CPRD post-recruitment. I excluded 4,560 (5%) women with missing information on weight and/or height, 857 (1%) who were underweight (BMI <18.5 kg/m^2), 1,473 (2%) with a prior cancer registration, and 10,793 (14%) with no follow-up data in CPRD beyond 31 March 2006 (**Appendix Figure F.1**). The remaining 69,440 women were followed-up for an average of 6.0 years from 1 April 2006 (11.1 years from recruitment), during which time they had 3.1 million consultations, 3.7 million tests, and were issued 14.1 million prescription items (**Table 6.1**). Average age at recruitment was 56.0 years (standard deviation 4.8) and was relatively stable across BMI categories. 47% of women were at healthy weight, 36% were overweight, and 17% were obese. Overweight and obese women tended to live in more deprived areas and have a lower highest educational qualification, were less likely to perform strenuous exercise, drink alcohol, or be current smokers, but were more likely to be former smokers, and to report a prior health condition (one or more of: heart disease, stroke, diabetes, rheumatoid arthritis, osteoarthritis, osteoporosis, and depression/anxiety). Million Women Study participants with high-quality data in CPRD post recruitment were largely similar to those without, except they were slightly more likely to be from less deprived areas (**Table 6.2**).

Table 6.1: Baseline characteristics and details of follow-up by category of body mass index

	Body mass index category (kg/m^2)								
	18.5-19.9	20-22.4	22.5-24.9	25-27.4	27.5-29.9	30-34.9	35-39.9	≥ 40	All women
Number of women	1,950	11,254	19,303	14,996	9,866	8,591	2,575	905	69,440
Characteristics at recruitment									
Body mass index, median (IQR)	19.4 (0.6)	21.5 (1.1)	23.8 (1.3)	26.1 (1.3)	28.6 (1.2)	31.8 (2.3)	36.6 (2.3)	42.3 (3.9)	25.3 (5.4)
Age at recruitment, mean (SD)	55.8 (4.8)	55.6 (4.8)	55.9 (4.8)	56.3 (4.8)	56.3 (4.8)	56.3 (4.8)	55.8 (4.6)	55.7 (4.6)	56.0 (4.8)
Deprivaton tertile in study population (%)									
Least deprived	35.5	39.8	39.3	36.0	34.2	30.1	27.7	23.5	36.1
Most deprived	31.8	26.7	26.7	30.1	32.6	36.3	42.4	47.5	30.5
Highest educational attainment (%)									
None	36.0	33.5	38.1	42.7	46.8	50.6	53.6	57.1	41.9
Secondary or technical	45.4	48.6	47.0	44.5	41.6	39.4	38.3	34.7	44.5
Tertiary	18.5	17.8	14.9	12.8	11.6	10.0	8.0	8.2	13.6
Smoking status (%)									
Never	51.0	52.8	53.4	52.2	51.5	51.2	52.8	49.2	52.4
Former	19.8	25.3	27.9	29.1	31.1	32.9	34.1	37.7	28.9
Current	29.2	21.9	18.7	18.7	17.4	15.9	13.1	13.1	18.7
Current alcohol drinkers (%)	75.5	81.2	81.8	78.8	75.0	71.1	63.1	57.6	77.6
Exercise rarely or never (%)	17.3	14.4	15.8	19.1	23.5	28.9	33.1	41.6	20.0
With prior health conditions (%)[a]	21.2	18.8	20.5	24.3	28.3	33.7	39.7	46.5	24.9
Deatils of follow-up									
Years of follow-up (1,000s)	11.3	66.9	115.6	89.7	59.0	51.4	15.1	5.2	414.2
Total number of consultations (1,000s)	76	434	780	650	466	453	149	57	3,069
Total number of prescription items issued (1,000s)	309	1,631	3,144	2,926	2,296	2,479	881	383	14,051
Total number of diagnostic tests (1,000s)	100	570	996	832	547	478	141	56	3,723

Percentages exclude participants with missing data on characteristics; percentage of missing data is <3% for all characteristics except for smoking status (5%).

[a]Any of self-reported heart disease, stroke, diabetes, rheumatoid arthritis, osteoarthritis, osteoporosis or depression/anxiety.

Table 6.2: Baseline characteristics of Million Women Study participants with and without high-quality follow-up post recruitment in CPRD

	With high-quality follow-up in CPRD post recruitment?	
	No	Yes
Number of women	1,277,207	87,123
Body mass index, mean SD)	26.2 (4.7)	26.1 (4.6)
Age at recruitment, mean (SD)	56.2 (4.9)	56.1 (4.8)
Deprivation tertile in study population (%)		
Least deprived	33.3	35.6
Most deprived	33.5	31.1
Educational qualifications (%)		
No qualifications	43.9	42.1
Secondary or technical	42.9	44.2
Tertiary	13.1	13.7
Smoking status (%)		
Never	51.0	51.6
Former	28.5	28.9
Current	20.5	19.5
Current alcohol drinkers (%)	75.8	76.9
Exercise rarely or never (%)	49.0	47.0
With prior health conditions (%)[a]	26.5	25.6

[a]Any of self-reported heart disease, stroke, diabetes, rheumatoid arthritis, osteoarthritis, osteoporosis or depression/anxiety.

6.5.2 Estimates of annual rates and costs per person

Main analysis

Rates of primary care consultations per year were lowest for women with a BMI of 20 to <22.5 kg/m^2 at 7.0 consultations per year (99% CI 6.8 to 7.1), and rose steadily with higher BMI thereafter, reaching 11.1 consultations per year (10.3 to 11.9) for women with a BMI of $\geq$ 40 kg/m^2 (**Table 6.3**). Every 2 kg/m^2 higher BMI beyond 20 kg/m^2 was associated with a 4.9% (4.5 to 5.3) higher consultation rate. A similar pattern was observed for mean annual consultation costs (**Figure 6.3**). Annual costs rose from £288 (280 to 295) in women with a BMI of 20 to <22.5 kg/m^2 to £473 (441 to 506) in women with a BMI of $\geq$ 40 kg/m^2; a difference of 64.5% (53.5 to 76.3). Every 2 kg/m^2 higher BMI beyond 20 kg/m^2 was associated with 5.2% (4.8 to 5.6) higher annual consultation costs.

Rates of prescription items issued were also lowest for women with a BMI of 20 to <22.5 kg/m^2 at 27.0 items per year (99% CI 26.0 to 27.9), and rose steadily with higher BMI thereafter, reaching 69.2 items per year (63.6 to 74.8) for women with a BMI of $\geq$ 40 kg/m^2. Every 2 kg/m^2 higher BMI beyond 20 kg/m^2 was associated with a 10.0% (9.5 to 10.5) higher rate of prescription items issued. A

similar pattern was observed for mean annual prescription costs. Annual costs rose from £227 (216 to 237) in women with a BMI of 20 to <22.5 kg/m^2 to £587 (525 to 648) in women with a BMI of ≥40 kg/m^2; a difference of 158.7% (134.1 to 185.9). Every 2 kg/m^2 higher BMI beyond 20 kg/m^2 was associated with 9.9% (9.2 to 10.6) higher annual prescription costs.

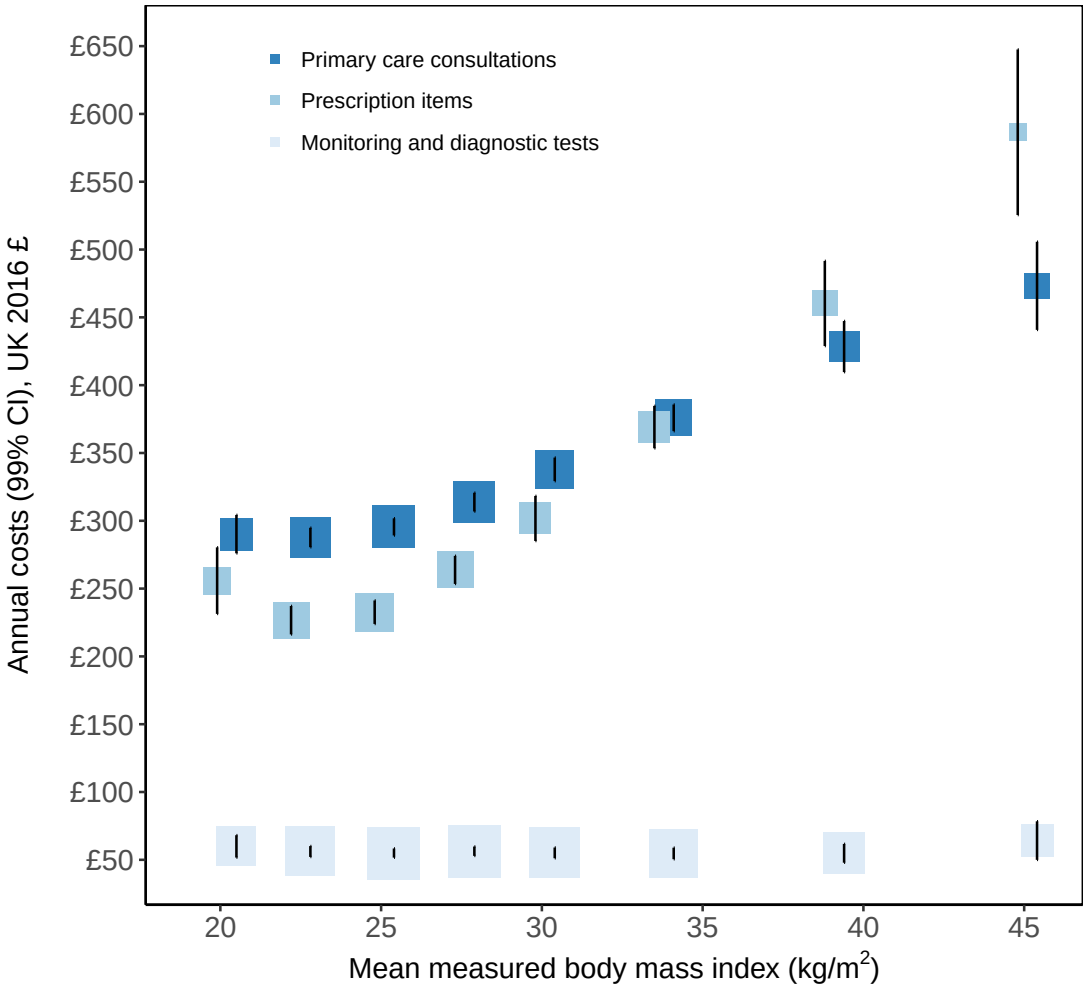
Each individual had on average 8.4 (standard deviation [SD] 23.0) monitoring and diagnostic tests per year at an annual cost of £53 (SD £166). There was no evidence of differences in annual rates or costs of tests across categories of BMI. Full regression results are presented in **Appendix Table F.6**.

Sensitivity analysis

Estimates of percentage differences in annual costs per 2 kg/m^2 higher BMI for BMI >20 kg/m^2 were very similar to the base-case results when including women with previous cancer, using data from all years of follow-up, excluding women with BMI >50 kg/m^2 or with previous heart disease or stroke, restricting analysis to only never-smokers, excluding up to the last three years of data for women who died, using imputed data to account for measurement error in BMI derived from self-reported height and weight, or, for annual consultation costs, imputing staff roles when unknown (**Figure 6.4**; **Appendix Tables F.7** to **F.9**).

Estimates of percentage differences in annual consultation and test costs for women in each BMI category compared to women with a BMI of 20 to 22.5 kg/m^2 were not materially different in any of the sensitivity analyses. For annual prescription costs, the percentage difference in costs for obese women were lower than in the base case analysis when not excluding data prior to April 2006 or when additionally excluding women with evidence of heart disease or stroke at recruitment, which suggests some impact of reverse causality due to pre-existing disease. In contrast, restriction of analysis to never-smokers increased the estimated associations for women with BMIs ≥35 kg/m^2, suggesting some residual confounding by smoking. These differences do not, however, attain statistical significance.

Figure 6.3: Annual costs of primary care consultations, prescription items, and diagnostic tests per person by category of body mass index



Standardised estimates of mean annual costs are plotted against mean measured BMI within categories of self-reported BMI from the Health Surveys for England. The area of each square is inversely proportional to the variance of the estimate. The error bars show 99% confidence intervals.

Subgroup analysis

The percentage differences in annual costs per 2 kg/m^2 higher BMI above 20 kg/m^2 were similar across subgroups of women defined by age, smoking status, alcohol use, exercise behaviour, socioeconomic deprivation, and educational attainment (**Figure 6.5**). For annual consultation and prescription costs there was some statistical heterogeneity in estimates between different age groups, with weaker associations between BMI and annual costs observed among older adults, and for prescription costs, the estimated association was significantly weaker among individuals who

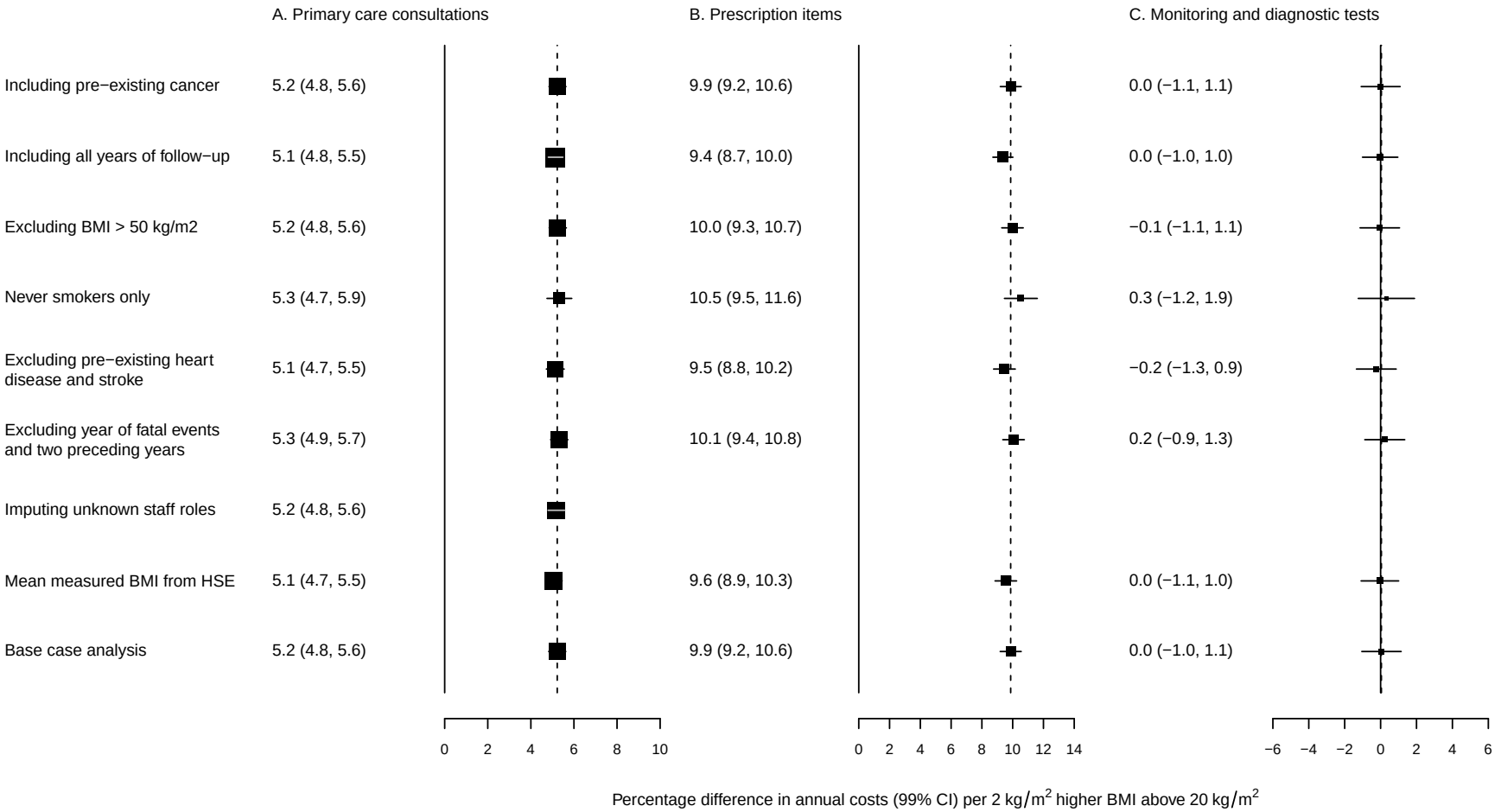
Table 6.3: Annual rates and costs of consultations, prescription items issued, and tests, by body mass index

BMI category (kg/m^2)	Rate per person-year		Annual costs per person	
	Number per year	Difference in rate (%)	Annual costs (2016 UK £)	Difference in costs (%)
Primary care consultations				
18.5 to <20	7.0 (6.7, 7.3)	0.4% (-4.2, 5.2)	£290 (276, 304)	0.9% (-3.8, 5.8)
20 to <22.5 (reference)	7.0 (6.8, 7.1)	0.0% (-2.0, 2.0)	£288 (280, 295)	0.0% (-2.0, 2.1)
22.5 to <25	7.1 (7.0, 7.3)	2.7% (1.1, 4.2)	£296 (289, 302)	2.7% (1.2, 4.3)
25 to <27.5	7.5 (7.4, 7.7)	8.4% (6.6, 10.1)	£314 (307, 321)	9.1% (7.3, 10.9)
27.5 to <30	8.1 (7.9, 8.3)	16.7% (14.4, 19.0)	£338 (329, 347)	17.5% (15.1, 19.8)
30 to <35	9.0 (8.7, 9.2)	28.8% (26.1, 31.6)	£376 (366, 386)	30.7% (27.8, 33.5)
35 to <40	10.1 (9.7, 10.5)	45.0% (39.3, 50.9)	£428 (410, 447)	48.9% (42.9, 55.3)
≥ 40	11.1 (10.3, 11.9)	59.2% (48.9, 70.3)	£473 (441, 506)	64.5% (53.5, 76.3)
Prescription items issued				
18.5 to <20	28.4 (26.2, 30.6)	5.4% (-2.2, 13.5)	£256 (231, 280)	12.9% (2.5, 24.3)
20 to <22.5 (reference)	27.0 (26.0, 27.9)	0.0% (-3.0, 3.1)	£227 (216, 237)	0.0% (-4.0, 4.2)
22.5 to <25	29.3 (28.5, 30.1)	8.7% (6.4, 11.1)	£233 (224, 241)	2.6% (-0.6, 5.8)
25 to <27.5	33.8 (32.8, 34.8)	25.4% (22.5, 28.3)	£264 (253, 274)	16.4% (12.7, 20.2)
27.5 to <30	39.2 (37.9, 40.5)	45.3% (41.4, 49.4)	£302 (285, 318)	33.1% (26.8, 39.7)
30 to <35	47.4 (45.9, 49.0)	76.0% (71.1, 81.0)	£369 (353, 385)	62.8% (56.7, 69.1)
35 to <40	57.0 (53.9, 60.1)	111.5% (100.4, 123.2)	£460 (429, 492)	103.0% (90.1, 116.9)
≥ 40	69.2 (63.6, 74.8)	156.5% (136.5, 178.3)	£587 (525, 648)	158.7% (134.1, 185.9)
Monitoring and diagnostic tests				
18.5 to <20	8.3 (7.2, 9.4)	3.3% (-9.5, 18.0)	£60 (52, 68)	6.7% (-6.0, 21.1)
20 to <22.5 (reference)	8.0 (7.5, 8.5)	0.0% (-5.8, 6.1)	£56 (52, 60)	0.0% (-5.4, 5.8)
22.5 to <25	8.1 (7.6, 8.5)	0.9% (-3.2, 5.2)	£55 (52, 58)	-2.0% (-6.0, 2.1)
25 to <27.5	8.6 (8.1, 9.1)	7.3% (2.4, 12.4)	£56 (53, 60)	0.4% (-4.2, 5.2)
27.5 to <30	8.6 (8.0, 9.1)	7.3% (1.3, 13.6)	£55 (51, 59)	-1.8% (-7.4, 4.1)
30 to <35	8.6 (8.0, 9.2)	7.0% (0.7, 13.8)	£55 (50, 59)	-2.6% (-8.6, 3.9)
35 to <40	8.6 (7.6, 9.6)	7.8% (-3.3, 20.2)	£55 (48, 62)	-2.4% (-13.1, 9.6)
≥ 40	10.0 (7.9, 12.2)	25.5% (1.3, 55.4)	£64 (50, 78)	14.4% (-8.0, 42.1)

BMI=body mass index. Values are means (99% confidence intervals), with floating confidence intervals for estimates of percentage differences in outcomes by BMI category.

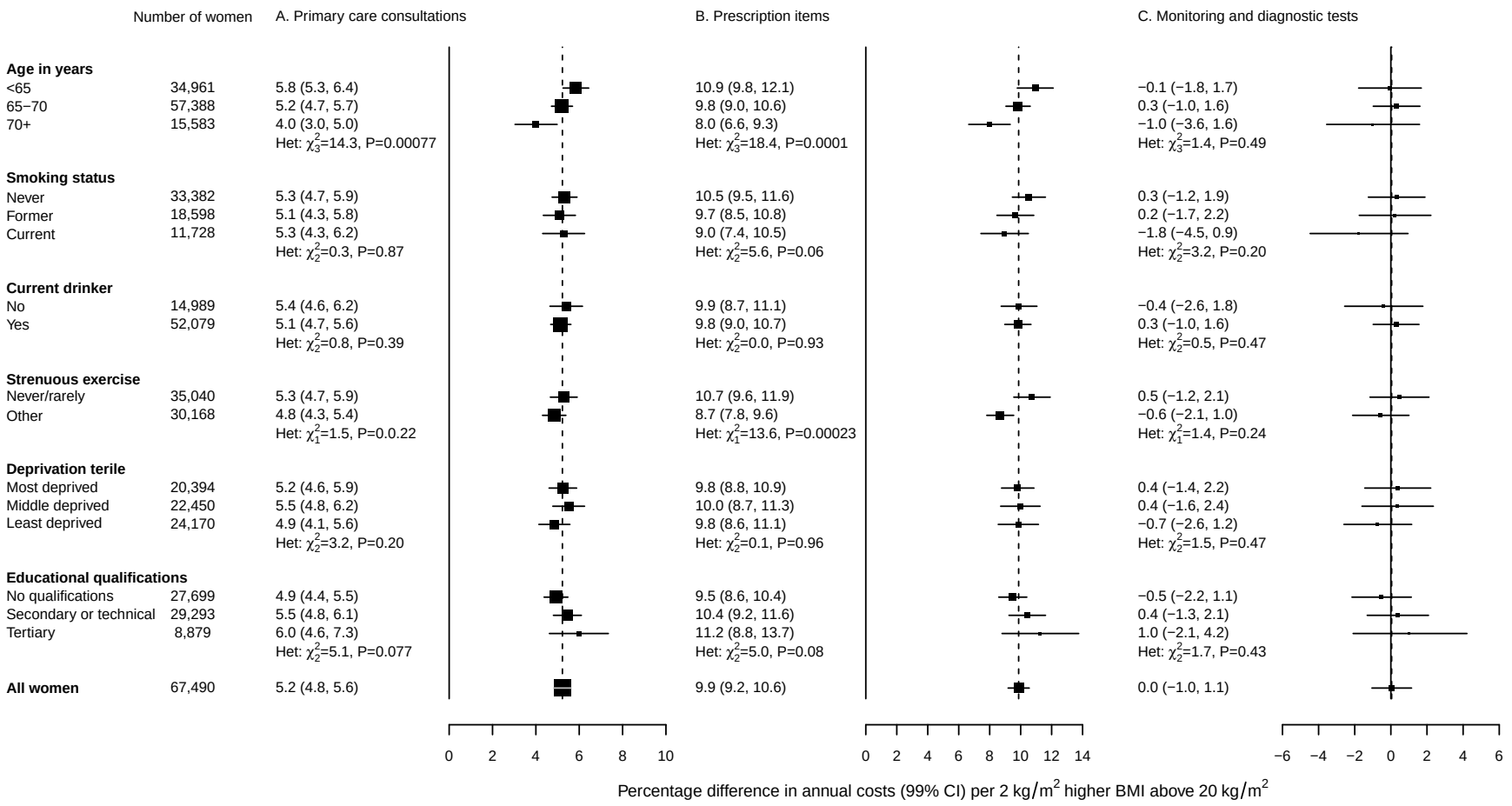
performed regular exercise than among those who rarely or never performed exercise; however, absolute differences in estimates were small.

Figure 6.4: Estimates of percentage differences in total annual consultation, prescription item, and test costs per 2 kg/m^2 higher body mass index beyond 20 kg/m^2 in sensitivity analyses



The area of each square is inversely proportional to the variance. The error bars show 99% confidence intervals.

Figure 6.5: Estimates of percentage differences in total annual consultation, prescription item, and test costs per 2 kg/m^2 higher body mass index beyond 20 kg/m^2, by category of women



The area of each square is inversely proportional to the variance.The error bars show 99% confidence intervals. Participants with missing data on characteristics used to define subgroups were excluded. Numbers of women are based on women with BMI $\geq$ 20 kg/m^2 only.

6.5.3 Projection of costs to all women aged 55 to 79 years in England

Number of women

There were 6.6 million women aged between 55 and 79 years in England in 2013. Of these, 43% had a BMI below 25 kg/m^2, 34% were overweight but not obese, and 23% were obese; 16% had grade 1 obesity, 5% grade 2 obesity, and 2% grade 3 obesity.

Monitoring and diagnostic tests

Among all 6.6 million women there were projected to be 56 million tests per year at a total cost of £370 million. There was no evidence of an association between BMI and rates or costs of tests, and therefore no excess weight attributable tests or costs of tests were projected.

Primary care consultations

Among all 6.6 million women, there were estimated to be 52.0 million consultations per year at a total cost of £2.2 billion. 10% of consultations (5.2 million) and 11% of total consultation costs (£229 million) were estimated to be attributable to excess weight (BMI $\geq$ 25 kg/m^2). Of the total excess weight attributable annual consultation costs, 70% were incurred among women who were overweight but not obese (31%) or who had grade 1 obesity (39%). Within categories of BMI, the proportion of annual costs attributable to excess weight rose from 10% among women with a BMI of 25 to <30 kg/m^2, to 38% among women with a BMI of $\geq$ 40 kg/m^2 (**Table 6.4**).

Prescription items, overall

It was estimated that 240 million prescription items were issued per year at a total cost of £1.9 billion among the 6.6 million women aged 55 to 79 years in England. 22% of prescription items (53 million items) and 20% of total prescription costs (£384 million) were estimated to be attributable to excess weight. Of the total excess weight attributable annual prescription costs, 67% was incurred among women who were overweight but not obese (29%) or had grade 1 obesity (38%).

Within categories of BMI, the proportion of annual costs attributable to excess weight rose from 18% among women with a BMI of 25 to <30 kg/m^2, to 61% among women with a BMI of ≥ 40 kg/m^2.

Table 6.4: Annual primary care consultation and prescription costs attributed to excess weight among women aged 55 to 79 years in England

Body mass index (kg/m^2)	Total population (million)	Total annual costs (£million)	Costs attributable to excess weight	
			Absolute annual costs (£ million), 99% CI	Proportion costs attributable (%), 99% CI
Primary care consultations				
<25	2.83	826	-	-
25 to <30	2.28	737	71 (69, 73)	10 (10, 10)
30 to <35	1.06	399	88 (85, 91)	22 (22, 22)
35 to <40	0.3	130	41 (37, 44)	32 (30, 33)
≥ 40	0.16	75	28 (24, 32)	38 (35, 41)
≥ 25 (all overweight and obesity)	3.8	1,340	229 (215, 241)	17 (17, 18)
Prescription items issued				
<25	2.83	661	-	-
25 to <30	2.28	636	112 (103, 119)	18 (17, 18)
30 to <35	1.06	392	147 (140, 153)	38 (37, 38)
35 to <40	0.3	139	70 (63, 75)	50 (48, 51)
≥ 40	0.16	92	56 (48, 63)	61 (58, 63)
≥ 25 (all overweight and obesity)	3.8	1,259	384 (353, 410)	31 (30, 31)

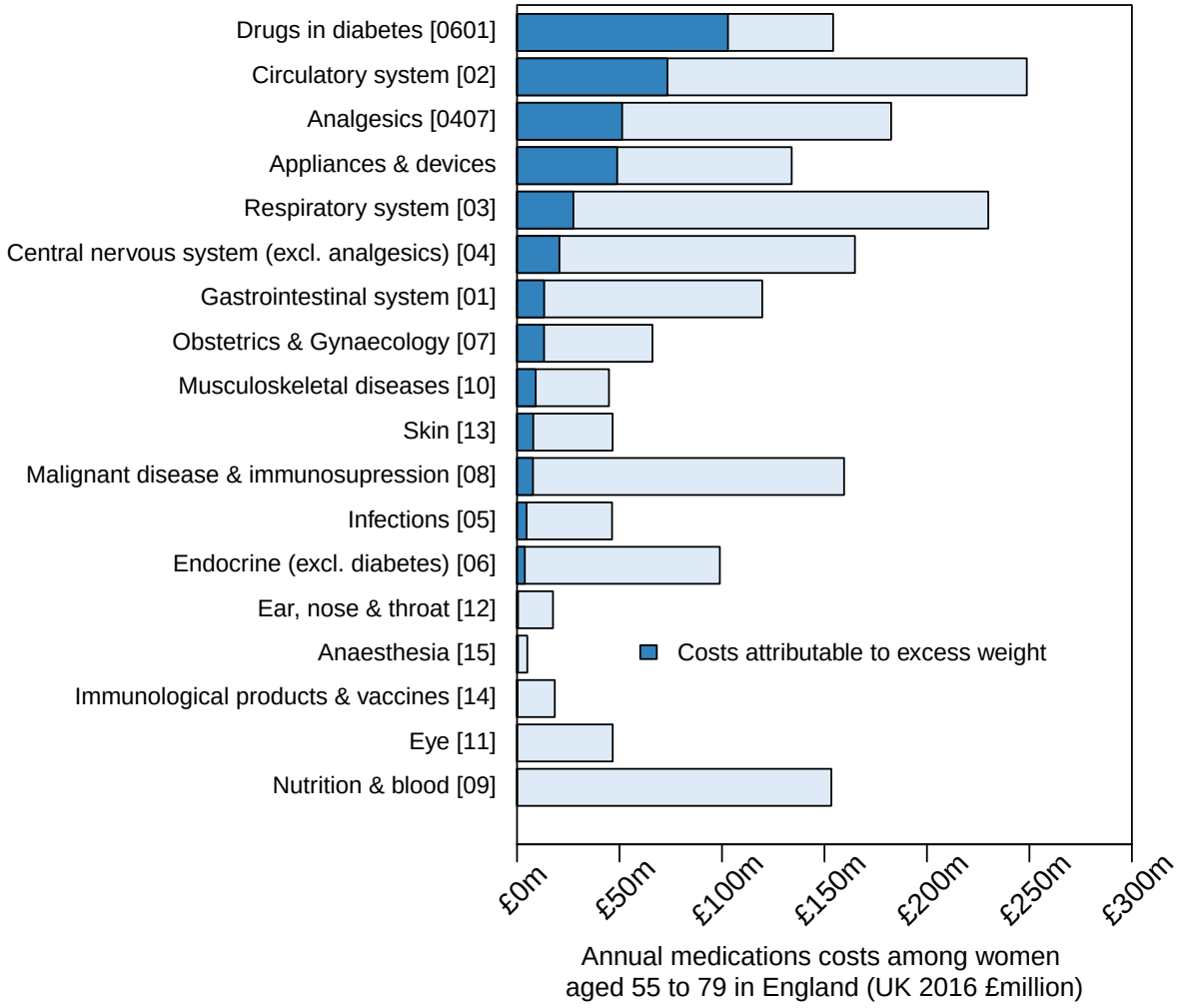
Prescription items, by category of therapeutic use

Mean standardised annual prescription costs per person were higher for overweight and obese women than for women of healthy weight for most categories of therapeutic use (**Appendix Figure F.2**). The strongest proportional associations between excess weight and annual costs were for drugs for diabetes (BNF section 0601), dressings and appliances, circulatory system medications (BNF chapter 02), and analgesics (BNF section 0407). Projecting estimates of annual costs per person to all women aged 55 to 79 years in England in 2013 (**Figure 6.6**; **Appendix Table F.10**), 67% of total spending on drugs for diabetes was explained by excess

weight, which compares to 36% of total spending on dressings and appliances, 30% on circulatory system medications, and 28% on analgesics.

Those categories of therapeutic use for which the proportional associations with excess weight were largest, include many commonly prescribed items, and are among the largest areas of pharmacy expenditure in the UK, particularly among older adults (**Figure 6.2**). Consequently, medications in these therapeutic areas account for almost three-quarters (£274 million; 72%) of total annual excess weight attributable prescription costs among women aged 55 to 79 years in England: £102 million (27% of total costs attributable to excess weight) was for drugs in diabetes, £73 million (19%) for circulatory system medications, £51 million (13%) for analgesics, and £48 million (13%) for dressings and appliances. Drugs for hypertension and heart failure (£14 million, BNF section 0205), anticoagulants and protamine (£17 million, BNF section 0208), and lipid-regulation (£15 million, BNF section 0212), each accounted for around 20% of the excess weight attributable costs for circulatory system medications.

Figure 6.6: Annual prescription costs attributable to overweight and obesity among women aged 55 to 79 years in England, by category of therapeutic use



Diagnostic categories are ordered here according to their contribution to overweight and obesity attributable costs.

6.5.4 Contribution of diabetes: an exploratory analysis

Diabetes was self-reported at recruitment into the study by 1,692 participants (3%). By the end of follow-up, 8,226 (12%) had some evidence of diabetes from primary care or hospital record data, which is in line with national diabetes prevalence statistics [29, 35, 36]. 22% of cases were identified by the Million Women Study questionnaire, of which 96% were also identified from medical records. Of those cases identified from medical records not reported in the recruitment questionnaire, 37% were identified from both hospital admission and primary care records, 7%

from only hospital admission records, and 56% from only primary care records. Based on this information, 37% of total consultation costs and 47% of prescription costs attributable to excess weight were estimated to be mediated by diabetes.

6.6 Discussion

6.6.1 Findings and interpretation of results

Overall summary

Using primary care data over 6 years for around 70,000 middle-aged and older women in England, in this Chapter, I showed that higher BMI was strongly associated with higher rates and costs of primary care consultations and prescription items issued, but not monitoring and diagnostic tests: every 2 kg/m^2 higher BMI above 20 kg/m^2 was associated with 5.2% higher annual consultation costs and 9.9% higher annual prescription costs. In total, 11% of annual consultation costs and 20% of annual prescription costs in women aged 55 to 79 years in England were attributable to excess weight. 27% of the excess weight attributable prescription costs were for drugs in diabetes, 19% for cardiovascular medications, and 13% for analgesics.

Primary care consultations and tests

In this Chapter, I estimated that annual consultation costs were 12% and 37% higher for overweight and obese women, respectively, compared to women at healthy weight. Corresponding estimates for annual ambulatory care costs, of which visits to primary care doctors are a subset, from the literature review reported in **Chapter 3**, were 4% and 26%. Few studies have separately estimated primary care consultation costs in relation to BMI [1–6]. Those that have were based on small numbers of participants (506 to 5,841 participants), and estimates of the costs for obese adults compared to adults at healthy weight varied from being 25% lower [1] to 160% higher [2].

Most studies of ambulatory care and primary care costs in relation to BMI used data from the US or countries where the structure of primary care differs substantially from that in the UK (e.g. Germany) [15]: in the UK, individuals cannot access specialist secondary care directly and must be referred by either a GP or a hospital department [14]. This and other differences, for example in the populations studied, and analytical methods used, limit the comparability of the estimates derived from analysis of the Million Women Study data and those from the systematic literature review. However, consistent with the results of the literature review, the estimated

proportional association between annual primary care consultation costs was weaker than the associations for both annual prescription and inpatient care costs.

The small number of studies that reported costs separately for monitoring and diagnostic tests reported marginally higher costs with higher BMI [1, 7].

Prescription medications

Based on analysis of the Million Women Study data, I showed that higher BMI was associated with higher annual prescription costs, overall and for many different categories of therapeutic use. Drugs for diabetes, cardiovascular disease, and analgesics together accounted for 30% of total prescription expenditure in women aged 55 to 79 years in England, based on extrapolation from the Million Women Study population, but for 70% of excess weight attributable costs. This is because, as described in **Chapter 2**, higher BMI is strongly associated with higher incidences of type-2 diabetes mellitus, ischaemic heart disease and stroke, hypertension, osteoarthritis, and lower back pain.

The literature review in **Chapter 3** identified eighteen studies that estimated prescription medication costs in relation to BMI, with samples sizes ranging from 2,244 to 17,703. Estimates of percentage cost differences compared to healthy weight adults were 18% for overweight adults and 64% for obese adults; the corresponding estimates from the Million Women Study were somewhat higher at 23% and 79%. The estimates derived from analysis of the Million Women Study data and those from the literature review are difficult to compare because differences could arise for a multitude of reasons including differences in healthcare settings, with pharmaceutical drugs tending to be more expensive in the US compared to the UK [12], and populations, with the Million Women Study consisting exclusively of middle-aged and older women, compared to the more general adult populations examined in the studies contributing to the literature review; and some differences may even operate in opposite directions, suggesting greater consistency of estimates than really exists.

Few studies estimated medication costs in relation to BMI by categories of therapeutic use [5, 8–11]. Those that did found the strongest proportional as-

sociations between costs and BMI for diabetes, cardiovascular medications, and medications for pain,[9] and these categories of therapeutic use contributed most to the prescription costs associated with excess weight, consistent with the analysis of the Million Women Study. Cardiovascular medications tended to contribute the most to overall excess weight attributable prescription medication costs. In contrast, analysis of the Million Women Study data identified diabetes as the largest contributor, followed by cardiovascular medications. Again, these differences may be due to differences in the populations studied or to differential costs by therapeutic category between the US and the UK [12, 37].

Subgroup results

Associations of primary care costs with BMI were mostly similar in population subgroups. There was some evidence of smaller associations among older adults, with each unit higher BMI associated with 45% and 36% higher annual consultation and prescription costs, respectively, in women aged less than 65 years compared to women 70 years or older. This is consistent with previous studies of associations between BMI and mortality and hospital admissions [28, 38]. This could be a result of changes to body composition in older adults, who tend to have less fat-free and muscle mass, or a consequence of reverse causality due to higher rates of comorbidities in older adults [39]. Associations were also about 20% smaller for physically active adults compared to inactive adults for prescription costs, although no difference was observed for consultation costs. It is possible that physical activity sometimes reflects a choice of lifestyle modifications over pharmacological treatment for conditions like diabetes or cardiovascular disease, but this cannot be assessed in these data.

[9] Medications for pain were categorised in various ways including non-steroidal anti-inflammatory drugs, osteoarthritis, and drugs for the central nervous system.

6.6.2 Limitations

Categorisation of health conditions

In order to understand the contributions of different health conditions to the overall excess weight attributable prescription costs, each prescription item was uniquely allocated to one category of therapeutic use, defined by the BNF chapter or section in which the medication appears. This accords with the approach taken to the categorisation of spending by health conditions in programme budgeting by NHS England [40], ensuring the usefulness of the results to policy makers, and healthcare commissioners and providers. This categorisation, however, differs from that used for hospital care, which impacts on the comparability of results. For instance, musculoskeletal conditions, particularly osteoarthritis, was the largest single contributor to excess inpatient care costs. For prescriptions, the impacts of musculskeletal problems are likely to be spread across different BNF chapters including musculoskeletal diseases (BNF chapter 10), central nervous system (BNF chapter4), and appliances and devices (BNF pseduo-chapters).

Due to the coding of clinical data in CPRD using version 2 READ codes, and the inherent nature of consultations, with a multitude of disparate health conditions potentially discussed within a single consultation, it was felt that there was no clear robust or systematic method of attributing consultations to specific health conditions, and so no breakdown of excess weight attributable primary care costs by health condition was undertaken. For similar reasons, no breakdown of spending on primary care by categories of health conditions is performed in NHS programme budgeting. However, since diabetes, cardiovascular disease, and pain are all known to be associated with increased use of primary care consultations [41–43], and the incidence of each is strongly increasing with higher BMI, it is likely that, as with medications and inpatient care (see **Chapter 5**), these conditions contribute considerably to the total excess weight attributable consultation costs.

Data quality in CPRD

Although CPRD data is now widely used for health research there remain important concerns about the integrity and interpretation of data: it has been shown, for example, that there is substantial between practice variation in the recording of data [44].[10] This is expected to be a particular problem for the estimation of rates of consultations in primary care.[11] Separate estimates of primary care workloads based on CPRD data on overlapping years have generated different estimates: the Nuffield Trust [18] estimated that there were 4.6 consultations per person in 2013-14, while Hobbs *et. al.* [17] reported 5.2 consultations per person. Disparities in estimates of workload were even greater when compared to estimated derived from other primary care datasets. Using QResearch it was estimated that there were on average 5.6 consultations per person in England in 2008-09 (the latest year of data available), compared to 4.8 using CPRD [17]; differences by type of consultation were even greater.

In contrast to hospital activity, where reliable national activity figures are available, there is no gold standard method of calculating activity data in primary care, and variations in data recording between practices, and in population coverage, limits the efficacy of data validation by reference to previous studies. Certainly, the overall estimates of the rates of consultations and prescription items issued based on analysis of the Million Women Study data presented in this Chapter are broadly in line with those reported by QResearch and previous analysis of CPRD data [17–19, 24].

Representativeness of the Million Women Study participants and the Clinical Practice Research Datalink

The results in this chapter are based on middle-aged and older women in England who attended breast cancer screening, and belonged to primary care practices

[10]For example, based on discussions with a GP based in a CPRD practice, some practices may generate a record for each consultation and record all conditions relevant to that consultation, while others will generate a new record every time a different condition is discussed.

[11]Data on prescriptions issued is expected to be of higher quality because the data is used to actually generate these prescriptions.

which were part of the CPRD data linkage scheme. Women who attend breast cancer screening are less likely to come from the most deprived sections of the population [45], and may be, on average, in better health. Similarly, although CPRD is said to be representative of the UK general population in terms of age, sex, and ethnicity [46], standardised mortality rates are considerably lower than in the general population [47], suggesting that those in CPRD are, on average, healthier. These differences may render the absolute cost estimates generated in projecting costs from Million Women Study participants to all women aged 55 to 79 years in England somewhat inaccurate (most likely an underestimate), but they would not be expected to change the qualitative conclusions, namely of the large impacts of excess weight on primary healthcare costs, and the key contributions of diabetes, cardiovascular disease, and pain to these excess costs. Overall rates of primary care consultations and prescription items issued estimated from the Million Women Study data are in line with national estimates [17, 19, 21].

Generalisability of results

The results presented in this Chapter were estimated among middle-aged and older women in England. The extent to which these results are informative for men, younger adults, and in other healthcare settings is not known, but previous evidence can offer some indication of likely differences. Consultation rates tend to be slightly higher in women than men, and are strongly increasing with age for both men and women (**Figure 6.1**), meaning that similar proportional associations between BMI and costs would lead to larger absolute impacts in women than in men and in older than in younger adults. There is however no clear evidence on differences in the association between BMI and primary care costs by age or sex. The contributions of different health conditions to excess weight attributable prescription costs would also be expected to differ in men and in younger adults because of differences in the prevalence of many conditions including diabetes, cardiovascular disease, and osteoarthritis, and differences in the BMI-disease risk associations by age and sex.

Although estimates of percentage differences in annual medication costs for overweight and obese adults compared to healthy weight adults in the Million Women Study analysis and in the literature review were comparable, this does not necessarily imply that the results are transferable to other countries. There are a large number of differences between these studies including in the healthcare settings and populations covered, and these effects may operate in opposite directions, i.e. the overall similarity of results may mask various important differences. Even if the proportional associations between BMI and costs are similar in different countries, absolute costs would be expected to differ to a much greater extent, because of the global variation in pharmaceutical prices. Prices tend to be much higher in the US, where most of the studies contributing to the literature review came from, than in the UK [12].

For primary healthcare contacts, the generalisability of results to different healthcare settings may be expected to be even more limited. This is because the delivery of primary healthcare varies considerably in different countries: in the UK, over 90% of patient contacts with the NHS are in primary care [48], and primary care doctors play a key role in controlling access to specialist secondary services [14]. In contrast, in other countries like the US and Germany, patients can directly access many specialist secondary care services [15].

The estimates of the use and costs of primary care services reported in this Chapter reflect clinical practice in England during the period of study follow-up, including clinical decisions and guidelines on which medications to prescribe. These are subject to variation over time in response to a wide number of factors including the appearance of novel drugs, the expiration of existing patents, and changes in medical evidence or clinician behaviour. For instance, reliable evidence on the efficacy of statin treatment for cardiovascular disease prevention [49], recommendations for statin treatment in clinical guidelines [50], and reductions in the prescribing costs of statins in the UK [51], have all contributed to the substantial increases in statin prescription rates from the early 2000s [52]. Similarly, concerns about potential side-effects of statins, even if unfounded, may partly account for

the reduction in statin initiation since 2006 [52]. In other healthcare settings or at other times, the estimated associations between BMI and costs might differ.

Within the time-frame of analysis here (2006-2014), annual age-standardised consultation rates were fairly stable, while the average number of items prescribed per year increased by about 25% over this period. Financial year is included as a covariate in the statistical models to account for this. In addition, we found similar relationships between BMI and annual primary care costs in exploratory analyses when splitting the data according to time-period, namely 2006-10 and 2011-14.

Exploratory diabetes analysis

High BMI explains a large proportion of the incidence of type-2 diabetes [53], which is associated with direct diabetes treatment costs, but also with increased costs due to increased risks of attendant events including cardiovascular disease [41]. An exploratory mediation analysis was undertaken to estimate the full contribution of diabetes to the total annual excess weight attributable consultation and prescription costs. This was done by comparing estimates of excess weight attributable costs from statistical models with and without time-updated diabetes status as a covariate. Diabetes was identified using the MWS recruitment questionnaire, hospital admission data, and primary care data. The estimated age-specific prevalence of type-2 diabetes at the end of follow-up was in line with national type-2 diabetes statistics [29, 35, 36]. However, because BMI and diabetes are both influenced by fat mass and are highly collinear, controlling for diabetes in the estimation of the association between BMI and hospital costs may artificially reduce the impact of BMI because fat mass is implicitly controlled for, and hence overestimate the contribution of diabetes.

Limitations of observational data

The results presented in this Chapter are based on analysis of observational data, and so there is considerable potential for biases in the estimated associations arising from residual confounding by pre-existing disease (i.e. reverse causality) and smoking [54]. A variety of data exclusions in both the main and sensitivity analyses were implemented to assess and possibly reduce the impact of these potential sources of

bias. Although proportional estimates of annual costs in relation to excess weight were found to be largely insensitive to different exclusion criteria, this does not preclude bias. Future research would benefit from the application of alternative methods, for example, instrumental variable regression using robust instruments such as genetic variants that explain population variation in BMI to estimate causal associations between BMI and healthcare costs (i.e. Mendelian randomisation). As described in **Chapter 4**, BMI derived from self-reported height and weight among Million Women Study participants correlates very closely to BMI derived from measured values even over almost a decade of follow-up [55]. In addition, accounting for measurement error in BMI derived from self-reported height and weight did not change the estimated associations between BMI and annual costs.

6.6.3 Conclusions

In this Chapter, I provided novel estimates of the impact of body mass index on the use and costs of primary healthcare services in England. I demonstrated that higher BMI exerted a significant influence on the demand for primary care healthcare services, with higher annual rates and costs of consultations and prescription items issued, in particular for diabetes, cardiovascular disease, and pain. The majority of the impact on primary care was among women who were overweight or had grade 1 obesity.

These results complement those in **Chapter 5**, which showed large increases in inpatient care costs with higher BMI, are the first reliable estimates on primary care costs in relation to BMI in the UK, and are based on by far the largest study internationally. The detailed description of the incidence of the costs of excess weight on primary health services should be useful for the purposes of healthcare planning and commissioning, particularly in responses to expectations about changes in the population weight distribution. The results underline the need for effective interventions to both reduce excess weight but also to prevent weight gain, in order to reduce the growing pressure on primary care [17].

6.7 Summary

In this Chapter I showed that excess weight was associated with increased use and costs of primary care consultations and prescription medications, but not diagnostic and monitoring tests, in middle-aged and older women in England.

In the final Chapter of this Thesis, I summarise the research presented in this Thesis, and interpret the results in relation to the existing literature. I discuss the potential implications of my research, and describe some of the limitations, before making recommendations for future research.

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7
Discussion

7.1 Findings and interpretation

7.1.1 Healthcare costs per person

Summary of results

At the outset of this Thesis, I summarised estimates of associations between BMI and healthcare costs from previous studies of individual participant data, and reported evidence of elevated annual healthcare costs among overweight and obese adults, compared to healthy weight adults, for total healthcare costs, and separately for inpatient care, ambulatory care, and medication costs (**Chapter 3**). Most of these studies were based on data from the US, with no reliable individual participant data pertaining directly to the UK, and were based on small-to-moderate numbers of participants, limiting their ability to estimate costs by grade of obesity or for different health conditions. In order to address these evidence gaps, I used data on over one million middle-aged and older women in England, followed-up for more than a decade, and reported that higher BMI was strongly associated with higher annual rates and costs of inpatient and day-case admissions (**Chapter 5**), primary care consultations, and prescription items issued, but not monitoring and diagnostic tests (**Chapter 6**).

The strongest proportional association between higher BMI and annual costs was for prescriptions, for which, every 2 kg/m^2 higher BMI beyond 20 kg/m^2 was associated with 9.9% higher annual costs, followed by inpatient care, with 7.4% higher annual costs per 2 kg/m^2 higher BMI, and the weakest association was with primary care consultations, for which annual costs were 4.5% higher per 2 kg/m^2 higher BMI.

Because spending on these different healthcare services differs substantially, the ordering of services by absolute differences in costs for overweight and obese individuals also differs. The largest absolute differences in costs for overweight, obese, and morbidly obese adults, compared to adults at healthy weight, were for inpatient and day-case care costs, with standardised differences in annual costs of £93, £318,

and £670 per person, respectively. Corresponding differences were £49, £179, and £356 for prescriptions, and £31, £104, and £181 for primary care consultations.

Subgroup results

We found consistent evidence across healthcare services that the association between BMI and annual costs was weaker among older compared to younger adults (within the age range of the sample). This is consistent with previous studies of associations between BMI and mortality [1], hospital admissions [2], and healthcare costs (see **Chapter 3**). This could be a result of changes to body composition in older adults, who tend to have less fat-free mass, or a consequence of reverse causality due to higher rates of comorbidities in older adults [3].

Associations by subgroups of the behavioural risk factors were less consistent across healthcare services. For inpatient care, weaker associations between BMI and total annual costs were observed for smokers compared to non-smokers, while there was no evidence of a difference for primary care consultations, and only weak evidence for prescription medications. The BMI-cost association was weaker in active versus non-active individuals for prescription medications, but stronger for inpatient care; for other healthcare services examined there was no evidence of a difference. While we would not necessarily expect such risk factors to affect costs of different healthcare services in the same way, because they differ substantially in terms of type and severity of conditions treated, accessibility, and electability of care, the precise reasons for these differences remain unclear.

The association between BMI and annual costs was stronger in women from less compared to more deprived backgrounds, but there were no differences in estimated associations by deprivation for primary care costs. A more consistent pattern is seen for highest educational qualification, with larger BMI-cost associations in more compared to less educated women. However, this did not attain statistical significance for primary care services. Previous studies have identified socioeconomic inequalities in access to certain secondary healthcare treatments like hip replacements [4].

Comparison with other studies

The ordering of healthcare services by the strength of the association between BMI and annual costs was the same in the literature review as in the Million Women Study data analysis: i.e. strongest for medications, followed by inpatient care, and then ambulatory care (in the literature review) or primary care (in the Million Women Study data).

However, the estimated percentage differences in costs for overweight and obese adults compared to adults at healthy weight from analysis of the Million Women Study data were generally somewhat higher than the median estimates presented in the literature review. For inpatient care, overweight and obese adults incurred 12% and 34% higher annual costs, respectively, compared to healthy weight adults, in the literature review, and 18% and 55% higher annual costs in the Million Women Study. For medications, 18% and 64% higher costs for overweight and obese adults, respectively, were reported in the literature review, versus 23% and 79% higher costs in the Million Women Study. Finally, ambulatory care costs were 4% higher for overweight adults and 26% higher for obese adults compared to healthy weight adults in the literature review, and 12% and 37% higher, respectively, for primary care consultation costs in the Million Women Study.

These differences could have arisen for a variety of reasons including in: the populations studied, with most studies in the literature review based on general adult populations, while the Million Women Study consisted of only middle-aged and older women, among whom the effects of excess weight on healthcare costs may be greatest; healthcare settings, with most studies in the literature review coming from the US; study design, e.g. whether the study was prospective; and the analytical methods used, for instance, in the confounding variables controlled for, or the approach taken to dealing with reverse causality by pre-existing disease. Indeed, the estimated proportional association between BMI and annual inpatient costs in the Million Women Study was more similar to corresponding estimates from high-quality studies of women of similar age [5, 6].

The few UK studies that have reported estimates of NHS costs in relation to BMI based on analysis of individual-participant data [7–9], reported higher costs with higher levels of BMI. However, comparability with the results presented in this Thesis is limited by differences in methodology and study objectives. All three studies identified BMI through routinely collected primary care records, and there is a major concern that the decision to measure weight is related to weight itself and to patient health status, which would bias estimated associations. Rudisill *et. al.* [9] estimated the direct impact of BMI on costs controlling for selected obesity-related conditions, whereas as here I am interested in the total impact of BMI on costs.

7.1.2 Projection of costs to the population

Excess weight attributable costs within different healthcare services

Projecting costs to all women aged 55 to 79 years in England in 2013, 15% of total annual inpatient and day-case care costs were attributed to excess weight, compared to 11% of total primary care consultation costs, and 20% of total prescription costs; no excess costs for monitoring and diagnostic tests were identified (**Figure 7.1**).

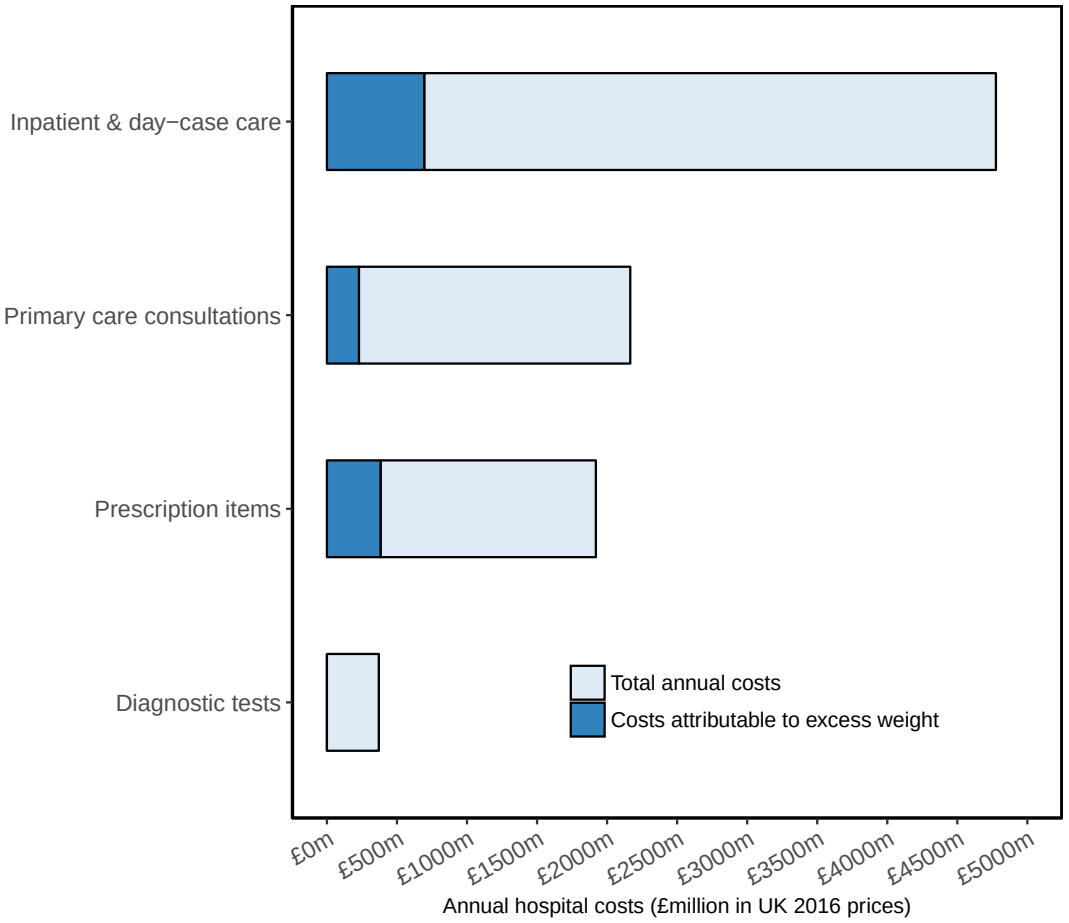
Distribution of excess weight attributable costs by healthcare service

Combining costs for these different health care services, total annual healthcare costs[1] were £9.2 billion,[2] of which £1.3 billion (14.2%) was attributable to overweight and obesity. Of the £1.3 billion total annual overweight and obesity attributable costs, 53% (£696 million) were incurred in an inpatient and day-case care setting, 17% (£229 million) was due to primary care consultations, and 29% (£384 million) to prescriptions. Within categories of BMI, the contributions of different services to excess weight attributable costs were similar.

[1] These do not, of course, include all healthcare services, as discussed further in this Chapter.

[2] In Chapter 5, inpatient and day-case costs are presented in UK 2012 prices, but here, for consistency with primary care costs, are inflated to 2016 prices using the hospital and community health services index [10]

Figure 7.1: Annual costs and costs attributable to overweight and obesity by type of healthcare service among women aged 55 to 79 years in England



Distribution of excess weight attributable costs by weight class

30% (£395 million) of the £1.3 billion total excess weight attributable costs was incurred among individuals who were overweight but not obese (BMI 25 to <30 kg/m^2), 37% (£487 million) among those with grade 1 obesity (30 to <35 kg/m^2), 18% (£238 million) among those with grade 2 obesity (35 to <40 kg/m^2), and 15% (£190 million) among those with grade 3 or morbid obesity ($\geq$ 40 kg/m^2). The contributions of each BMI category to overall excess weight attributable costs were similar for each type of healthcare service.

Distribution of excess weight attributable costs by health condition

One of the main contributions of this Thesis is to estimate the contributions of different treated health conditions to total excess weight attributable costs for inpatient care and prescription costs. Excess weight was associated with elevated costs for a large and diverse range of conditions. In the hospital setting, musculoskeletal problems were the main contributors to the direct costs of care attributable to excess weight (40% of total annual excess weight attributable costs), around half of which was due to knee replacements for women with osteoarthritis. Other major contributors to total excess weight attributable costs were diseases of the circulatory (accounting for 12% of the total) and digestive (11%) systems, and neoplasms (9%). For prescriptions, diabetes was the largest contributor to excess weight attributable costs (27% of the total), followed by circulatory diseases (19%), and pain requiring analgesics (13%).

In the hospital setting, diabetes is rarely the main condition treated or investigated, and so direct costs of diabetes are relatively low in this setting. However, because the type-2 diabetes is strongly associated with higher BMI, and diabetes is a risk factor for many conditions, including cardiovascular diseases like ischaemic heart disease and stroke, a sizeable proportion of the impact of excess weight on healthcare costs is expected to be mediated through type-2 diabetes. Exploratory analyses were performed for all types of healthcare services to estimate the full contribution of diabetes to excess weight attributable costs. Using detailed information on diabetes incidence from the Million Women Study recruitment questionnaire, hospital admission data, and primary care data, it was estimated that 25% of the inpatient care costs,[3] 37% of the primary care consultation costs, and 47% of the prescription costs attributed to excess weight were associated with diabetes.

[3]In Chapter 5, two estimates of this quantity were reported: 25% and 39%. The latter was reported in the corresponding published manuscript [11], and was estimated prior to the availability of the primary care data. The estimate of 25%, which utilises primary care data, is now considered the preferred estimate.

Comparisons with other studies

Few studies have estimated medical costs in relation to BMI for different health conditions [5, 12–17]. Higher quality studies which estimated costs for a wide range of conditions, found both musculoskeletal and circulatory diseases to be the major contributors to total excess weight attributable costs, each accounting for between one-fifth and one-quarter of the total [13, 17]. These studies were based on employed adults in the US, and the lower contribution of musculoskeletal conditions to the total excess weight weight attributable costs than observed in the Million Women Study data, may be due to differences in the populations studied; the Million Women Study includes only middle-aged and older women, among whom the incidence of osteoarthritis is higher [18].

Those studies which estimated prescription costs in relation to BMI for categories of therapeutic use [13, 19–22], reported the strongest proportional associations between annual costs and BMI for drugs in diabetes, cardiovascular medications, and medications for pain. These categories of therapeutic use also contributed most to the total prescription costs associated with excess weight, consistent with the analysis of Million Women Study data. However, in contrast to the Million Women Study data, in which diabetes was the largest contributor to total excess weight attributable costs, followed by cardiovascular medications, in these studies, cardiovascular medications tended to be by far the largest contributor to total excess weight attributable costs. These differences could have arisen for a multitude of reasons, including differences in the populations studied or to differential costs by therapeutic category between the US and UK [23, 24].

The key contributions of osteoarthritis, type-2 diabetes, and cardiovascular disease to the total annual excess weight attributable costs are also consistent with the epidemiological literature, which reports consistent evidence of strong associations between the incidence of such conditions and higher BMI [25–31], and the high costs of these conditions in both hospitals and pharmacy [32–37].

7.1.3 Contributions of Thesis

As shown in **Chapter 3**, most studies using individual participant data were based on adults in the US, were often of limited quality, and were typically based on small-to-moderate numbers of participants, limiting their ability to reliably estimate costs in relation to grades of obesity or for different health conditions. No reliable individual participant data pertaining directly to the UK was identified. Given differences between countries in terms of populations, payment systems, rates of technology adoption, treatment patterns, and variations in prices [24], it is important to collect data for different jurisdictions. In the UK, most evidence on the impact of excess weight on healthcare costs has come from population-attributable fraction studies [38]. These provide an estimate of the total share of healthcare spending due to overweight and/or obesity, but for the purposes of healthcare policy making, planning, and commissioning, a more detailed understanding of the incidence of excess weight attributable costs in different healthcare settings, for different health conditions, and by weight class, such as that provided in this Thesis, is valuable.

These evidence gaps were addressed in this Thesis in the context of middle-aged and older women in England using detailed and high-quality data from a large prospective cohort of over one million women in England, followed-up for more than a decade. The results provide novel estimates of healthcare costs in relation to BMI for the UK for this population group. It is also the largest study internationally, and enabled robust estimation of healthcare use and costs in relation to grades of obesity, for different health conditions, and across population subgroups. Though there are limits to the international transferability of results, the key findings of the widespread impact of excess weight on costs in different care settings and for many health conditions, the concentration of total excess weight attributable costs among people with moderate levels of excess weight, and the key contributions of osteoarthritis, type-2 diabetes, and cardiovascular disease to these costs, should be widely relevant.

7.2 Implications of results

Overview

The finding of large impacts of excess weight on healthcare costs, overall and across different care settings, underlines calls for further investment in programs designed to reduce excess weight or prevent weight gain, in order to curtail further increases in healthcare demand and expenditure. The detailed results concerning the incidence of excess weight attributable costs in different healthcare settings, for different health conditions, and by weight class, should also provide valuable information to governments, healthcare commissioners, primary care practices, and hospitals making investment and prioritisation decisions. The estimates of costs in relation to BMI can also be used in economic evaluations to estimate the cost-effectiveness of interventions.

Policy prioritisation: interventions to reduce excess weight or prevent weight gain?

The findings of large and diverse impacts of excess weight on healthcare use and costs, underline calls for greater investments in interventions to reduce excess weight or prevent weight gain. Estimates of the distribution of total excess weight attributable costs by overweight and obesity category could inform the nature of this investment. In particular, the findings that costs were higher with higher BMI beyond 20 kg/m^2, and that, although adults with severe obesity contributed disproportionately to total excess weight attributable costs, the bulk of the impact was among women who were overweight but not obese, or with only mild obesity (BMI 30 to <35 kg/m^2), raise important policy questions, including: should policy focus should shift further from treatment to prevention? Within treatment, should the emphasis be rebalanced towards people with low or moderate levels of excess weight and away from those who are very obese?

Weight management in England is based on a four tier approach [39]: tier 1 services include public health programmes like the promotion of healthy behaviours, and, in practice, are largely delivered by local and regional public health teams, but

also by primary care practices; tier 2 services are largely local community weight management services; tier 3 services consist of clinician led multidisciplinary teams providing a range of specialist services to obese patients, and are commissioned by Clinical Commissioning Groups; and tier 4 services are largely bariatric surgery.

The large contribution of individuals with moderate levels of excess weight to the total excess weight attributable costs, may support a shift in emphasis towards tier 1 and 2 services. This, of course, also depends on the costs that must be incurred to achieve weight loss or to prevent weight gain in these different domains. However, there is some evidence that many public health programs (tier 1 services) targeted at the population are cost-effective [40, 41]. Recent UK government strategic reports have emphasised the value of such programs in creating an environment to help individual's make healthy decisions [42, 43].

Referrals to community and commercial weight loss programs (tier 2 services) have been shown to be effective and cost-effective methods of tackling overweight and obesity [44–46], and are recommended in UK clinical guidelines [47]. However, because of a lack of funding and the non-mandated status of such activities, NHS referrals to such schemes are limited [48]. Generally, the NHS only refers individuals to such services if they are obese or have another serious medical condition such as diabetes. Consequently, those who are overweight but not obese, among whom the health burden and healthcare costs of excess weight are largest, may find it difficult to access such services. Many of the benefits of achieving weight loss accrue to the NHS, in the form of lower demand for healthcare services and cost savings; however, investment in tier 2 services is the responsibility of local authorities. Changes to the accountability for the provision of obesity services could lead to more appropriate levels of investment.

Bariatric surgery, a tier 4 service, has been shown to be a very effective and cost-effective intervention for reducing weight [49–52]. UK clinical guidelines recommend surgical interventions only for individuals with BMI $\geq$40 kg/m^2 or with a BMI of 35 to <40 kg/m^2 if they have another significant disease like diabetes [47]. Bariatric surgery is more costly to implement than many tier 2 services, and there are

difficulties in delivering such surgical interventions at scale to the large number of people who may benefit from them.

Healthcare planning and commissioning

The improved understanding provided by this Thesis of the impacts of excess weight on the demand for healthcare in different care settings are likely to be useful to governments, healthcare commissioners, including NHS England, in allocating its budget to nationally commissioned services including primary care and pharamcy and to Clinical Commissioning Groups (CCGs), who commission services including secondary care for their local populations, to the CCGs themselves, and to primary care practices and hospitals for the purposes of investment and prioritisation decisions, taking into account local needs, when used in conjunction with local obesity prevalence data [53], and expectations about changes to the distribution of BMI in the population.

Estimates of the distribution of inpatient and day-case care costs by health condition should be useful to CCGs when commissioning services from hospitals, and to hospitals themselves, in making investment decisions about staffing and equipment. For instance, rightward shifts in the BMI distribution of the population would be expected to increase total demand for hospital care, but disproportionately for knee replacement surgeries. The presentation of results by health conditions in different care settings using similar classifications to those used by NHS England for the purpose of programme budgeting should maximise the usefulness of these results to healthcare planners, commissioners, and providers.

7.3 Limitations

7.3.1 Healthcare services not included

Overview

In this Thesis, I estimated the impact of excess weight on the use and costs of inpatient and day-case care, primary care consultations, community prescriptions, and monitoring and diagnostic tests among middle-aged and older women in England. Together, these healthcare services account for just over half of all government healthcare spending in the UK. The remainder consists of other hospital services, namely outpatient care and accident and emergency services, non-hospital ambulatory care like home and dental care, and long-term residential and ambulatory care. Data on the use of these services for Million Women Study participants would have enabled the construction of total healthcare costs, and an even more detailed understanding of the full impact of excess weight on UK healthcare spending, and its distribution across care settings. However, data on outpatient and accident and emergency care from Hospital Episode Statistics was not linked to the Million Women Study, and for the other healthcare services, there are no databases containing appropriate individual level data. There are also wider economic costs associated with higher BMI, arising from higher rates of presenteeism, absenteeism, disability, and premature mortality, which may exceed the healthcare costs of high BMI [38], but a careful examination of these other costs is beyond the scope of this Thesis.

Outpatient and emergency care

Inpatient and day-case care together constitute around 70% of hospital spending in the UK. Most of the remainder is from outpatient care, with A&E accounting for only 2% of spending. Together outpatient and emergency care constitute around one-eigth of total governmental spending on healthcare. In the literature, I reported elevated costs for ambulatory care (which includes outpatient care) with higher BMI, though the association was weaker than for inpatient care. Although many studies in the literature review measured emergency department care costs, few presented cost estimates separately for these services. Those studies that did, tended to report

elevated costs in obese adults, but not overweight adults [7, 54–59]. Inpatient and day-case care account for about 70% of hospital spending but probably more than 80% of excess weight attributable hospital spending.[4]

Non-ambulatory healthcare services

Non-ambulatory healthcare services including home and dental care account for about one-sixth of total governmental healthcare spending. There is a lack of direct evidence on the association between excess weight and the use and costs of home healthcare and dental care services. However, the impact of obesity on mobility [60] may suggest an association between higher BMI and greater use of home healthcare services. Adult obesity has been linked with higher rates of periodontal disease [61] and tooth loss [62], suggesting that dental care costs may be somewhat elevated in obese adults. However the strength of the associations with costs, and hence the contribution of such services to total excess weight attributable costs, is unknown.

Long-term residential care

Long-term residential and ambulatory healthcare account for another eighth of governmental healthcare spending. Because obesity is associated with a range of disabling conditions, the need for nursing home care is greater in elderly obese adults: in the US, obese adults are twice as likely to be admitted to a nursing home as non-obese adults [63]. Obese patients are often more costly to treat than non-obese patients because they have, on average, more additional healthcare problems, including type-2 diabetes, which involve additional equipment, supplies, and staff costs. Long-term care costs are likely to be an important contributor to total excess weight attributable costs; however, there is a lack of direct evidence

[4] An estimate of 80% was derived using the associations between BMI and annual inpatient and ambulatory costs reported in the literature review, the mean inpatient costs from the Million Women Study analysis of inpatient care, the population distribution among women aged 55 to 79 years in England, and an assumed ratio of inpatient to outpatient cost of 70% to 30%. However, given that among older adults the ratio of inpatient to outpatient costs is even larger, inpatient care may constitute an even greater share of excess weight attributable hospital costs in this population.

on the effects of overweight and obesity on time to institutionalisation and the costs of institutionalisation, particularly in the UK.

7.3.2 Representativeness of participants in the Million Women Study

The projection of estimates of per person healthcare costs by category of BMI to the entire population of women aged 55 to 79 years in England, assumes that the distribution of characteristics of women within each BMI category is similar within the Million Women Study to the general population. While Million Women Study participants were representative of women who attended breast cancer screening [64], women who attended breast cancer screening were less likely to come from more deprived areas or from ethnic minorities, and were more likely to have a current prescription for hormone replacement therapy, but did not differ in terms of age or recent prescriptions for various other medications [65]. For analysis of primary care services, estimation was restricted to those women who were registered in a primary care practice that was part of the CPRD data linkage scheme during the follow-up period. Participants in CPRD are broadly representative of the UK population in terms of age, sex, and ethnicity [66, 67]. However age-standardised mortality rates are considerably lower for CPRD participants than the general population, and practice sizes are larger than average and differently geographically dispersed [68]. Million Women Study participants with CPRD data were similar to the broader Million Women Study population recruited in England. The differences between Million Women Study participants and the general population of women of similar age could result in a small biases to the projected estimates of absolute costs but would not be expected to substantially change the main findings of this research, namely of the large impacts of higher BMI on costs in different care settings and for different health conditions, and the key contributions of osteoarthritis, type-2 diabetes, and cardiovascular disease to total excess weight attributable costs.

7.3.3 Generalisability of results

The Million Women Study included only women of middle-age or older in England. It is important to consider the extent to which the associations between BMI and healthcare costs observed in this population, transfer to men and to younger individuals in England, to countries with different healthcare systems, and across time.

Generalisability to men and younger adults

In **Chapter 3**, there was no strong evidence that excess weight was more strongly associated with higher costs in women than in men. There is, however, evidence that the associations between excess weight and the incidence of some chronic diseases and acute events differ in men and women [28], and the incidence of conditions also differs: for instance, musculoskeletal problems are more common in women [69], and cardiovascular disease more common in men [70]. It follows that the distribution of conditions contributing to the overall excess weight attributable costs may also differ in similar ways between men and women. There is also some evidence that the effects of BMI are less pronounced in younger individuals, perhaps because some health conditions associated with higher BMI, including osteoarthritis and cardiovascular disease, take many years to develop and manifest. The costs attributable to excess weight may therefore be lower among younger individuals than for middle-aged and older woman, and the distribution of costs across health conditions would be expected to differ, reflecting the distribution of diseases in younger adults. There is also some evidence that health risks associated with obesity are lower for the very elderly [1, 71], and so excess weight attributable costs may also be lower.

Generalisability to other healthcare systems

Healthcare systems differ in a number of important respects which may influence the relationship between excess weight and the use and costs of healthcare services, including in the structure of healthcare delivery, the financing of healthcare, different rates of technology adoption, different treatment patterns, and, particularly in the case of pharmaceuticals, substantial global variations in prices [24]. There are,

however, reasons to think that the associations may be similar in spite of these differences. Healthcare use and costs are to a large extent determined by health events, and many of the effects of excess weight on health are thought to be transferable across different countries, particularly within Western populations [1], and thus we may expect to observe similar patterns of healthcare utilisation associated with excess weight. This hypothesis is consistent with the results of the literature review presented in **Chapter 3**, in which similar proportional associations between BMI and total healthcare costs were observed in the US and elsewhere.

Generalisability across time and place

Many of the healthcare costs associated with excess weight are a result of clinical decisions regarding whether and how to treat individuals. For instance, elective knee replacement surgeries among women with osteoarthritis are a key driver of hospital costs due to excess weight. In some healthcare systems, access to such treatments may be restricted based on weight status. Indeed, the Royal College of Surgeons reported that over a third of clinical commissioning groups in England are restricting access to routine surgery such as hip and knee replacements until patients lose weight [72], even though this is in contravention of national clinical guidelines [73–75]. Were decisions to perform elective surgeries (e.g. knee replacement surgery) in relation to weight to change in the future, then the relationship between excess weight and costs may also change. Similarly, in pharmacy, the use of statins has increased enormously since the early 2000s, at least in part in response to reliable evidence on the efficacy of statin treatment for cardiovascular disease prevention [76], recommendations for statin treatment in clinical guidelines [77], and reductions in the prescribing costs of statins in the UK [78]. The estimates of healthcare costs in relation to BMI reported in this Thesis reflect clinical practice in England during the period of study follow-up. In other healthcare settings, or at other times, the estimated associations between BMI and costs might differ.

7.3.4 Limitations of observational data

The research presented in this Thesis was based on analysis of observational data, and there is a risk of bias from residual confounding, by, for example, smoking or pre-existing disease (i.e. reverse causality) [1, 79], measurement error in BMI [80], or changes in BMI over time [81]. A variety of data exclusions in both the main and sensitivity analyses were undertaken to assess, and possibly reduce, the impact of these potential sources of bias. Although proportional estimates of annual costs in relation to BMI were found to be largely insensitive to different exclusion criteria, this does not preclude bias. There may be certain conditions, for instance chronic obstructive pulmonary disease, that can lead to both weight loss and high healthcare costs, but with which individuals live for many years, limiting the feasibility and effectiveness of data exclusion.

Data on measured height and weight among 541 participants around the time of recruitment, and in 3,999 participants, on average, 9 years later, demonstrated that BMI derived from self-reports and measurements of height and weight were similar, and that there was no evidence of attenuation bias, even at a decade after recruitment [82, 83]. In addition, imputing measured BMI by self-reported BMI categories did not change the estimated associations between BMI and annual healthcare costs.

7.3.5 Changes in body mass index over time

In this Thesis, I estimated the associations between body mass index, reported in middle-age, and future healthcare utilisation and costs. Weight can, however, change over time, and there is likely to be some degree of heterogeneity in the weight histories of women at a given BMI: some women will have been exposed to excess weight for many decades, some may always have been at healthy weight, while others will have more recently transitioned from a higher or a lower weight to their current weight. It is important to understand this heterogeneity in order to appropriately interpret the results, because the impact of long-term exposure to weight may differ from the effects of more recent changes in weight [84–86]; however, this an area which requires further research. We know from measurements of height

and weight in 3,999 Million Women Study participants on average 9 years after recruitment that BMI was stable in this population [83], with a mean difference of 1.4 kg/m^2 in BMI. Although this small overall difference will mask individual variation, it is reasonable to interpret BMI as an indication of long-term exposure to excess weight in the Million Women Study.

7.3.6 Healthcare costs as a measure of health burden

Epidemiological research has reliably demonstrated an impact of excess weight on mortality and a large range of non-fatal outcomes. Healthcare costs are a potential aggregate measure of individual health burden in that they account for a large range of different conditions and the clustering of these within individuals. However, the weights attached to health events or conditions reflect relative resource intensiveness of the resulting treatment, which may not always correlate well with the health impact, and deceased individuals do not incur healthcare costs. Preferred measures of the health burden include disability-adjusted life-years (DALYs) and quality-adjusted life-years (QALYs). Some modelling studies have generated estimates of the QALY impact of obesity [87] and the Global Burden of Disease project has generated DALY estimates [88–91]. A number of studies have estimated the association between BMI and measures of health related quality of life (HRQoL) such as EQ-5D or SF-12 using individual participant data (mostly cross-sectional), and tended to find negative impacts of obesity on HRQoL [92–101].

7.4 Future research

Estimation of costs for men and younger adults

The results presented in this Thesis are the most reliable estimates of healthcare costs in relation to BMI for the UK based on individual participant data. However, the study consisted of only middle-aged and older women, and the results may not translate well to men and younger adults. If data allows, similar analyses should be performed on general population samples, in order to gain a better understanding of heterogeneity in associations between BMI and healthcare costs by age and gender.

Estimation of total healthcare costs

Healthcare utilisation data was available for inpatient and day-case care, primary care consultations, prescriptions, and monitoring and diagnostic tests, which together constitute just over half of government healthcare spending. If a study were able additionally link to HES data on outpatients and emergency care, and identify reliable individual-level information on non-ambulatory and long-term care, then an estimate of total healthcare costs in relation to BMI could be made, and a more complete understanding of the distribution of the impacts of excess weight in different care settings provided.

Estimating causal associations

Estimates of the associations between BMI and health-related outcomes are potentially biased due to confounding by pre-existing disease (i.e. reverse causality) [79]. Previous studies have used instrumental variable regression[5] to try to identify causal associations between BMI and healthcare costs, using the weight of the oldest biological child aged between 11 and 20 years as an instrument for current BMI in adults [102, 103]. This instrument is limited in a number of respects, but most

[5]In instrumental variable regression, estimation follows a two-step process: the exposure is first modelled as a function of an instrument, the definition of which will follow, and then the outcome is modelled against the residuals from the first stage. A valid instrument must be correlated with both the exposure and outcome, but have no independent influence on the outcome, outwith its effect operating through the exposure.

obviously, in that it restricts estimation to a subsample consisting of only biological parents of particular age, severely compromising the generalisability of results.

A promising alternative comes from Mendelian randomisation, a specific form of instrumental variable modelling in which genetic variation forms the instrument. A number of recent papers have been published estimating the associations between BMI and a range of outcomes including type-2 diabetes [104, 105], coronary heart disease [105], socioeconomic status [106], breast cancer [107], and ovarian cancer [108] based on genetic score instruments formed from common genetic variants that have been shown to be associated with BMI [109]. Similar techniques could be used to address the research questions of interest in this Thesis, for example using data from the UK Biobank [110], which contains information on the genetic profiles of around 500,000 adults aged between 40 and 69 years (at recruitment) in the UK, and is linked to routine administrative health records.[6]

Effect of changes in weight

Although using information on the genetic variation in BMI may help overcome problems of reverse causation, the results would still largely reflect the impact of long-term exposure to excess weight on healthcare costs. However, when making investments decisions in programs designed to reduce excess weight or prevent weight gain, what is often important is the impact of weight loss or weight gain on healthcare use and costs. Such questions are extremely hard to address using observational data because changes in weight will often be the result of, potentially undiagnosed, health conditions, which confound estimates of the association between weight change and change in costs. One possibility to estimate the impact of weight change on healthcare use, would be to use data from trials of weight management programs, bariatric surgery, and/or pharmacological treatment. However, there are challenges here too: most trials tend to be small; many do not have linkage to administrative healthcare records, or did not collect resource use information from individuals; heterogeneity in the impacts by type of intervention would need

[6] At the time of writing, it was linked with hospital data, with linkage to primary care expected in late 2017.

to be accounted for; and individuals tend to regain substantial amounts of weight after initial weight loss [111].

Associations between objective measures of fat and healthcare costs

Throughout this Thesis, BMI was used to proxy excess weight or adiposity. Were information on objective measures of fat and its distribution to become routinely collected in large cohort studies, estimating the associations between these measures and healthcare resource use and costs would be valuable.

Better understanding mechanisms of effect

Overall, being overweight or obese was associated with higher hospital costs compared to being at healthy weight. This is likely to be driven by a number of factors, including differences by BMI in admission rates, in types of admission (for example, high cost knee replacements are considerably more common among obese women), in rates of complications and comorbidities, and in length of hospital stay. Given the approach to costing in this Thesis, it was not possible to reliably estimate the separate contributions of these factors to the overall association between higher BMI and higher hospital costs. Such information would however be valuable to hospitals in making treatment and planning decisions. Previous studies of specific conditions including myocardial infarction [112], gallbladder disease [113], and total knee arthroplasty [114], have reported higher costs of treating these conditions for adults at higher BMIs, but further research for these, and also for other conditions, is required.

7.5 Conclusions

In this Thesis, I demonstrated that, among middle-aged and older women in England, annual costs of inpatient and day-case care, primary care consultations, and prescriptions were strongly increasing in BMI, overall and for many different health conditions. The key drivers of excess weight attributable costs were osteoarthritis, type-2 diabetes, and cardiovascular disease. Although women with morbid obesity contribute disproportionately to total excess weight attributable costs, the majority of the impact is generated among those with relatively moderate levels of excess weight.

The results of this Thesis provide novel estimates of healthcare costs in relation to BMI using individual participant data for the UK, and is the largest study internationally, providing a level of detail not previously available. Although there are limits to the transferability of results, many of the qualitative conclusions, including the large and diverse effects of BMI on demand for healthcare, and the contribution of osteoarthritis, type-2 diabetes, and cardiovascular disease to this demand, should be informative in other healthcare settings.

The detailed understanding of the incidence of costs by level of excess weight, in different care settings, and for different health conditions, should be useful to governments, healthcare commissioners, and healthcare providers in making investment and prioritisation decisions. In addition, the results underline calls for greater investments in interventions designed to reduce weight and prevent weight gain in the population, in order to curtail the continuing increases in the demand for healthcare and healthcare spending seen in the UK.

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Appendices

A

Publications and presentations

Published manuscripts

Kent, S. *et al.* Hospital costs in relation to body-mass index in 1.1 million women in England: a prospective cohort study. *The Lancet Public Health* **2,** e214–e222 (2017)

Kent, S. *et al.* Body mass index and healthcare costs: a systematic literature review of individual participant data studies. *Obesity Reviews* **18,** 869–879 (2017)

Working papers

Kent, S. *et al.* Primary care costs in relation to body mass index in middle-aged and older women in England. *In preparation*

Oral presentations

Kent, S. *et al.* Primary care costs in relation to body mass index in middle-aged and older women in England. *Nuffield Department of Primary Care Health Sciences (Invited Seminar), University of Oxford, Oxford, July 2017.*

Kent, S. *et al.* Primary care costs in relation to body mass index in middle-aged and older women in England. *International Health Economics Association, Boston University, Boston, July 2017.*

Kent, S. *et al.* Healthcare costs in relation to body mass index in over 1.1 million women in England. *Nuffield Department of Population Health DPhil Seminar Series, University of Oxford, Oxford, January 2017.*

Kent, S. *et al.* Admitted patient care costs in relation to body mass index in over 1.1 million women in England. *Nuffield Department of Population Health DPhil Seminar Series, University of Oxford, Oxford, October 2016.*

Kent, S. *et al.* Admitted patient care costs in relation to body mass index in

over 1.1 million women in England. *Health Economic Research Centre Seminar Series, University of Oxford, Oxford, February 2016.*

Kent, S. *et al.* Admitted patient care costs in relation to body mass index in over 1.1 million women in England. *Health Economics Study Group, University of Manchester, Manchester, January 2016.*

Kent, S. *et al.* Admitted patient care costs in relation to body mass index in over 1.1 million women in England. *Nuffield Department of Population Health DPhil Seminar Series, University of Oxford, Oxford, January 2016.*

Kent, S. *et al.* Admitted patient care costs in relation to body mass index in over 1.1 million women in England. *International Health Economics Association, University Bocconi, Milan, July 2015.*

Kent, S. *et al.* Admitted patient care costs in relation to body mass index in over 1.1 million women in England. *Medical Sciences Division DPhil Day, University of Oxford, Oxford, July 2015.*

Kent, S. *et al.* Admitted patient care admission rates in relation to body mass index in over 1.1 million women in England. *Cancer Epidemiology Unit Seminar Series, University of Oxford, Oxford, January 2015.*

Poster presentations

Kent, S. *et al.* Admitted patient care costs in relation to body mass index in over 1.1 million women in England. *European Obesity Summit, Gothenburg, June 2016.*

Kent, S. *et al.* Admitted patient care costs in relation to body mass index in over 1.1 million women in England. *Nuffield Department of Population Health DPhil Poster Competition, University of Oxford, Oxford, October 2016.*

B

Systematic Literature Review

Table B.1: EMBASE search terms

1	health economics/
2	exp health care cost/
3	exp fee/
4	budget/
5	funding/
6	cost*.ti
7	economic*.ti
8	(expenditure* or charge*).ti
9	cost of illness/
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	exp obesity/
12	(obesity or obese).ti
13	(overweight or over-weight or over weight).ti
14	(bmi or body mass index or body mass).ti
15	11 or 12 or 13 or 14
16	10 and 15

Table B.2: MEDLINE search terms

1	economics/
2	exp “costs and cost analysis” /
3	exp economics, medical/
4	exp economics, hospital/
5	economics, nursing/
6	economics, pharmaceutical/
7	exp “fees and charges”/
8	cost*.ti
9	economic*.ti
10	(expenditure* or charge*).ti
11	exp “budgets”/
12	cost of illness/
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14	exp obesity/
15	exp overweight/
16	(obesity or obese).ti

Table B.3: National Heart, Lung and Blood Institute's quality assessment tool for cohort and cross-sectional studies

Criteria	**Yes**	**No**	**Other (CD, NR, NA)***
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Was the exposure(s) assessed more than once over time?			
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
12. Were the outcome assessors blinded to the exposure status of participants?			
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			

Two reviewers give an overall quality rating of good, fair, or poor

Table B.4: Summary of data characteristics of all included studies

Study	Country, year of cost reporting	Data source(s)	Population (at baseline)	Sample size	Mean years of follow-up (years outcome collection)	BMI assessment: measurement; timing	Type of outcome data	Cost reporting	Resource components included
Alter 2012 [9]	Canada, 2006	National Population Health Survey (Ontario)	<65 years	9,398	11.5 (1996-2006)	Self-reported; prospective	Administrative	Costs	All healthcare
An 2015 [10]	US, 2011	MEPS	≥18 years	125,955	2 (1998-2011)	Self-reported; prospective	Mixed	Expenditures	All healthcare
Anderson 2005 [11]	US, 1997	HealthPartners	≥40 years	4,674	4 (1996-1999)	Self-reported; prospective	Administrative	Charges	All healthcare excluding medications
Andreyeva 2004 [12]	US, 2002	Health and Retirement Study	54-69 years	7,971	2 (1996-2000)	Self-reported; retrospective	Self-reported	Expenditures	All healthcare
Arterburn 2005 [13]	US, 2000	MEPS	≥18 years	16,262	1 (2000)	Self-reported; prospective	Mixed	Expenditures	All healthcare
Atella 2015 [14]	Italy, unclear	Health Search/CD Patient Database	≥18 years	557,145	5 (2004-2010)	Measured; unclear	Administrative	Expenditures	All healthcare
Bell 2011 [15]	US, 2005	MEPS	≥6 years (81% ≥18 years)	65,271	2 (2000-2005)	Self-reported; prospective	Mixed	Expenditures	All healthcare
Bertakis 2005 [16]	US, unclear	UCSD Primary Care Center	≥18 years	506	1 (unclear)	Measured; unclear	Administrative	Charges	All healthcare excluding medications
Bhattacharya 2009 [17]	US, 2003	MEPS	20-50 years, employed	≈ 30,000	1 (2003)	Self-reported; prospective	Mixed	Expenditures	All healthcare
Borg 2005 [18]	Sweden, 2003	Malmo Prevention Project	25-60 years	32,710	15 (1974-1994)	Measured; prospective	Administrative	Costs	Inpatient
Brown 2008 [19]	Australia, 2001	Australian longitudinal study on women's health	50-55 years, women	7,004	1 (2001)	Self-reported; cross-sectional	Administrative	Costs	Ambulatory
Buchmueller 2015 [20]	Australia, 2009	45 and Up Study	≥45 years	241,635	3 (2006-2009)	Self-reported; prospective	Administrative	Costs	All healthcare
Bungum 2003 [21]	US, NK	US City Government (HMO)	18-64 years, employed	506	5 (1993-1998)	Self-reported; cross-sectional	Administrative	Charges	All healthcare

Table B.4 continued: Summary of data characteristics of all included studies

Study	Country, year of cost reporting	Data source(s)	Population (at baseline)	Sample size	Mean years of follow-up (years outcome collection)	BMI assessment: measurement; timing	Type of outcome data	Cost reporting	Resource components included
Burton 1998 [22]	US, 1996	First Chicago/Nationa Bank of Detriot	≥18 years, employed	843	3 (1989-1995)	Mixed; cross-sectional	Administrative	Charges	All healthcare
Cai 2010 [23]	US, 2000	NHANES I	35-55 years	5,043	30 (1991-2000)	Measured; prospective	Administrative	Charges	Inpatient, ambulatory
Cawley 2012 [24]	US, 2005	MEPS	20-64 years, parents	9,852	2 (2000-2005)	Self-reported; prospective	Mixed	Expenditures	All healthcare
Cecchini 2015 [25]	US, 2010	MEPS	Unclear	Unclear	2 (1997-2010)	Self-reported; prospective	Mixed	Expenditures	All healthcare
Chu 2010 [26]	Taiwan, 2001	NHIS (Taiwan)	20-85 years	12,283	1 (2001)	Self-reported; cross-sectional	Self-reported	Charges	Inpatient, ambulatory
Colagiuri 2010 [27]	Australia, 2005	Australian Diabetes, Obesity and Lifestyle Study	≥25 years	6,140	1 (2004-2005)	Measured; retrospective	Self-reported	Mixed	All healthcare
Counterweight 2008 [28]	UK, 2001	Counterweight Programme	18-75 years	3,400	1.5 (2000-2002)	Mixed; unclear	Administrative	Costs	Medications
Daviglus 2004 [29]	US, 2002	Centre for Medical Services, Chicago Heart Association	≥65 years	17,601	18 (1984-2002)	Measured; prospective	Administrative	Charges	Inpatient, ambulatory
Detournay 2000 [30]	France, 1992	Medical Care Household Survey	≥18 years	10,126	0.25 (1991-1992)	Self-reported; prospective	Self-reported	Mixed	All healthcare
DiBonaventura 2015 [31]	US, 2013	National Health and Welness Survey	≥18 years	71,530	0.5 (2013)	Self-reported; retrospective	Self-reported	Expenditures	Inpatient, ambulatory, emergency
Durden 2008 [32]	US, 2005	MarketScan Research	≥18 years, employed	88,984	1 (2003-2005)	Self-reported; cross-sectional	Administrative	Expenditures	All healthcare
Esposti 2006 [33]	Italy, 2002	General practices in Ravenna	≥18 years	2,622	1 (2001-2002)	Measured; retrospective	Administrative	Costs	Medications
Finkelstein 2001 [34]	Canada, 2006	National Population Health Survey (Ontario)	40-79 years	2,170	1 (1994-1996)	Self-reported; retrospective	Administrative	Charges	Ambulatory

Table B.4 continued: Summary of data characteristics of all included studies

Study	Country, year of cost reporting	Data source(s)	Population (at baseline)	Sample size	Mean years of follow-up (years outcome collection)	BMI assessment: measurement; timing	Type of outcome data	Cost reporting	Resource components included
Finkelstein 2003 [35]	US, 1998	MEPS	≥18 years	9,867	1 (1998)	Self-reported; prospective	Mixed	Expenditures	All healthcare
Finkelstein 2005 [36]	US, 2004	MEPS	18-64 years, employed	20,329	1 (2000-2001)	Self-reported; prospective	Mixed	Expenditures	All healthcare
Finkelstein 2008 [37]	US, 2004	MEPS	≥18 years	66,161	2 (2001-2004)	Self-reported; prospective	Mixed	Expenditures	All healthcare
Finkelstein 2009 [38]	US, 2008	MEPS	≥18 years	21,877	1 (2006)	Self-reported; retrospective	Mixed	Expenditures	All healthcare
Heithoff 1997 [39]	US, 1993	MEPS	18-65 years, employed	16,217	1 (1987)	Self-reported; retrospective	Self-reported	Expenditures	All healthcare
Hu 2008 [40]	Taiwan, 2004	NHIS (Taiwan)	≥18 years	12,520	3 (2002-2004)	Self-reported; prospective	Self-reported	Expenditures	All healthcare
Janssen 2009 [41]	Canada, 2003	Canadian Community Health Survey	≥18 years	25,038	2 (2002-2003)	Self-reported; cross-sectional	Administrative	Costs	Ambulatory
Kleinman 2014 [42]	US, 2012	Human Capital Management Services Research Reference Database	≥18 years, employed	72,778	1 (2001-2012)	Self-reported; prospective	Administrative	Expenditures	All healthcare
Konig 2015 [43]	Germany, 2009	ESTHER	50-74 years	2,642	0.25 (2008-2010)	Self-reported; retospective	Self-reported	Costs	All healthcare
Korda 2015 [44]	Australia, 2010	45 and Up Study	≥45 years	224,254	3.2 (2006-2011)	Self-reported; prospective	Administrative	Costs	Inpatient
Kuriyama 2002 [45]	Japan, 1998	Ohsaki National Health Insurance beneficiaries cohort study	40-79 years	41,967	4 (1995-1998)	Self-reported; prospective	Administrative	Expenditures	All healthcare
Lakdawalla 2005 [46]	US, 1998	MCBS	70 years	2,757	1 (1991)	Self-reported; cross-sectional	Mixed	Expenditures	All healthcare
Li 2015 [47]	US, 2013	Geisinger Health System	≥18 years	60,955	5 (2004-2013)	Measured; cross-sectional	Administrative	Costs	All healthcare
Lynch 2005 [48]	Japan, 2000	Electronics company	≥18 years, employed	4,961	1 (2000-2001)	Measured; cross-sectional	Administrative	Expenditures	All healthcare

Table B.4 continued: Summary of data characteristics of all included studies

Study	Country, year of cost reporting	Data source(s)	Population (at baseline)	Sample size	Mean years of follow-up (years outcome collection)	BMI assessment: measurement; timing	Type of outcome data	Cost reporting	Resource components included
Martin 2009 [49]	US, 2005	National transportation logistics company data	≥18 years, employed	2,950	1 (2004-2005)	Measured; prospective	Administrative	Charges	All healthcare
McHugh 2015 [50]	Ireland, 2013	Irish Longitudinal Study on Ageing	≥50 years	5,841	1 (2009-2011)	Measured; retrospective	Self-reported	Costs	All healthcare
Mora 2015 [51]	Spain, 2010	Primary care centres and 2 hospitals in Northwest Barcelona	≥16 years	NS (452,108 observations)	7 (2004-2010)	Measured; unclear	Administrative	Costs	All healthcare
Moriarty 2012 [52]	US, 2007	Mayo clinic	≥18 years	30,529	7 (2001-2007)	Measured; unclear	Administrative	Charges	All healthcare
Nakamura 2007 [53]	Japan, 2006	National Health Insurance (Shija)	40-69 years	4,502	10 (1991-2001)	Measured; prospective	Administrative	Expenditures	All healthcare
Narbro 2002 [54]	Sweden, 1997	SOS obesity intervention study	37-60 years	2,244	0.25 (1987)	Measured; cross-sectional	Self-reported	Costs	Medications
Onwudiwe 2012 [55]	US, 2002	MCBS	≥65 years	7,706	1 (2002)	Self-reported; cross-sectional	Administrative	Charges	All healthcare
Ostbye 2014 [56]	US, 2011	Duke Health and Safety Surveillance System	≥18 years, employed	17,703	10 (2001-2011)	Self-reported; cross-sectional	Administrative	Charges	All healthcare
Pan 2012 [57]	Taiwan, 2007	MJ Health Screening Centres	≥20 years	111,949	11 (1996-2007)	Measured; prospective	Administrative	Expenditures	All healthcare
Peterson 2015 [58]	US, 2013	MEPS	≥18 years	215,107	1 (2002-2011)	Self-reported; unclear	Mixed	Expenditures	All healthcare
Pronk 1999a [59]	US, 1996	HealthPartners	≥40 years	5,689	1.5 (1995-1996)	Self-reported; prospective	Administrative	Charges	All healthcare excluding medications

Table B.4 continued: Summary of data characteristics of all included studies

Study	Country, year of cost reporting	Data source(s)	Population (at baseline)	Sample size	Mean years of follow-up (years outcome collection)	BMI assessment: measurement; timing	Type of outcome data	Cost reporting	Resource components included
Pronk 1999b [60]	US, 1996	HealthPartners	18-64 years, employed	8,822	3 (1993-1996)	Self-reported; cross-sectional	Administrative	Charges	All healthcare
Qin 2016 [61]	China, 2009	China Health and Nutrition Surveys	$\geq$18 years	14,615	0.08 (2000-2009)	Self-reported; retrospective	Self-reported	Expenditure	All healthcare
Quesenberry 1998 [62]	US, 1994	Kaiser Permanente Medical Care, Nothern California	$\geq$20 years	17,118	1 (1993-1994)	Self-reported; cross-sectional	Administrative	Costs	All healthcare
Raebel 2004 [63]	US, 1999	Obese: LOSE Weight Study; control: Kaiser Permanente Colorado	$\geq$21 years	1,764	1 (1998-2000)	Mixed; unclear	Administrative	Mixed	All healthcare
Rudisill 2016 [64]	UK, 2013	CPRD	$\geq$20 years	250,046	3.5 (2008-2013)	Mixed; unclear	Administrative	Costs	All healthcare
Stuart 2008 [65]	US, 2003	MCBS	$\geq$65 years	8,473	1 (2003)	Self-reported; cross-sectional	Administrative	Expenditures	Medications
Sturm 2002 [66]	US, 1998	Healthcare for communities	18-65 years, employed	$\approx 10,000$	1 (1997-1998)	Self-reported; retrospective	Self-reported	Expenditures	All healthcare
Sturm 2013 [67]	South Africa, 2010	Vitality health promotion programme	$\geq$18 years	69,380	1 (2010)	Self-reported; cross-sectional	Administrative	Expenditures	All healthcare
Tarride 2012 [68]	Canada, 2002	Canadian Community Health Survey	$\geq$18 years	28,797	1 (2000-2002)	Self-reported; cross-sectional	Administrative	Costs	Inpatient, ambulatory
Terry 1998 [69]	US, 1993	HealthPartners	$\geq$18 years	5,780	1 (1992-1993)	Self-reported; prospective	Administrative	Charges	All healthcare
Teuner 2013 [70]	Germany, 2005	MONICA & KORA	25-75 years	2,946	0.02 (2004-2005)	Measured; prospective	Self-reported	Expenditures	Medications
Thompson 2001 [71]	US, 1998	Kaiser Permanente Northwest Division	35-64 years, employed	1,286	7 (1990-1998)	Self-reported; prospective	Administrative	Mixed	All healthcare
Thorpe 2004 [72]	US, 2001	MEPS	$\geq$19 years	21,460	1 (2001)	Self-reported; prospective	Mixed	Expenditures	All healthcare

Table B.4 continued: Summary of data characteristics of all included studies

Study	Country, year of cost reporting	Data source(s)	Population (at baseline)	Sample size	Mean years of follow-up (years outcome collection)	BMI assessment: measurement; timing	Type of outcome data	Cost reporting	Resource components included
Tigbe 2013 [73]	UK, 2003	Counterweight Programme	≥18 years	3,324	1.5 (2002-2003)	Mixed; unclear	Administrative	Costs	All healthcare
Tucker 2002 [74]	US, 1995	Technology company	≥18 years, employed	982	1 (1994-1995)	Measured; prospective	Administrative	Expenditures	All healthcare
Van Nuys 2014 [75]	US, 2011	MarketScan Research	≥18 years	29,699	3 (2006-2008)	Self-reported; cross-sectional	Administrative	Expenditures	All healthcare
Veiga 2008 [76]	Portugal, 1999	National Health Survey (Portugal)	≥18 years	22,831	0.04 (1998-1999)	Self-reported; retrospective	Self-reported	Expenditures	All healthcare
von Lengerke 2010 [77]	Germany, 2001	KORA S4	25-74 years	947	0.5 (1999-2001)	Measured; prospective	Self-reported	Costs	All healthcare
Wang 2004 [78]	US, 2002	General Motors Corporation & UWA	18-65 years, employed	23,490	2 (1996-1997)	Self-reported; cross-sectional	Administrative	Expenditures	All healthcare
Wang 2005 [79]	US, 2002	General Motors Corporation & UWA	≥65 years	42,520	2 (2001-2002)	Self-reported; cross-sectional	Administrative	Expenditures	All healthcare
Wee 2005 [80]	US, 2003	MEPS	≥18 years	10,860	1 (1998)	Self-reported; prospective	Mixed	Expenditures	All healthcare
Wolfenstetter 2012 [81]	Germany, 2005	MONICA & KORA	25-75 years	2,581	1 (2003-2005)	Measured; prospective	Self-reported	Costs	Inpatient, ambulatory
Yang 2008 [82]	US, 2001	MCBS	≥65 years	28,906	2 (1992-2001)	Self-reported; cross-sectional	Mixed	Expenditures	All healthcare
Yen 2006 [83]	US, 2002	Midwest utility company	≥18 years, employed	2,082	2 (2001-2002)	Self-reported; cross-sectional	Administrative	Expenditures	All healthcare

CPRD=Clinical Practice Research Datalink; ESTHER=Epidemiolgishe Studie zu Chancen der Verheutung Frueherkennung und optimieren Therapie vhronischer Erkrankungen in der aelteren Bevoelkerung; KORA=German cooperative health research agency in the region of Augsburg; MCBS=Medicare Current Beneficiary Survey; MEPS=Medical Expenditure Panel Survey; MONICA=Monitoring of trends in cardiovascular diseases; NHANES=National Health and Nutrition Examination Survey; NHIS=National Health Interview Survey; UCSD=University of California San Diego; UK=United Kingdom; US=United States; UWA=Internation Union, United Automobile, Aerospace and Agricultural Implement Workers of America.

Table B.5: Characteristics of the methods of included studies

Study	Cost outcome	Subcategories of costs for results	Subgroups for results	Statistical model	BMI modelling	Covariates	Exclusions
Alter 2012 [9]	11.5 years	Inpatient, ambulatory, medications	Smoking, physical activity, stress	Propensity score matching	Categorised: 18.5-25, 25-30, 30+	Age, gender, smoking, physical activity, deprivation, comorbidities, psychosocial stress	Pre-existing heart disease
An 2015 [10]	Annual	Inpatient, ambulatory, emergency department, medications	Age, gender, race/ethnicity	Two-part log link gamma variance GLM	Categorised: <30, 30+	Age, gender, race/ethnicity, smoking, alcohol use, education, income, health insurance, region, survey wave	Pregnant women
Anderson 2005 [11]	Annual	None	Age	Log-linear regression	Categorised: <25, 25-30, 30+	Age, gender, smoking status, chronic disease	Non-white
Andreyeva 2004 [12]	Annual	None	Gender	Log-linear regression	Categorised: 18.5-25, 25-30, 30-35, 35-40, 40+	Age, race/ethnicity, smoking, alcohol use, education, income, health insurance, marital status, region, survey wave; stratified by gender	Individuals with weight changes >10% between survey waves
Arterburn 2005 [13]	Annual	None	None	Two-part log-linear regression	Categorised: <18.5, 18.5-25, 25-30, 30-35, 35-40, 40+	Age, gender, race/ethnicity, smoking, household income, education, marital status, health insurance, region	Pregnant women
Atella 2015 [14]	Annual	Ambulatory/medications health conditions	Age	Multi-equation recursive model within seemingly unrelated regression estimator approach	Categorised: 18.5-25, 25-30, 30-35, 35-40, 40+	Age, gender, region, year, General Practitioner behaviour	None
Bell 2011 [15]	Annual	Inpatient, ambulatory, medications	Age, gender	Two-part log-linear regression	Categorised: 18.5-25, 25-30, 30+	Age, race/ethnicity, insurance status, education, family income, region, survey year; stratified by gender	Pregnant women
Bertakis 2005 [16]	Annual	Inpatient, ambulatory, emergency department, other	None	Unclear	Categorised: <30, 30+	Age, gender, education, income, depression, physical functioning	None

Table B.5 continued: Characteristics of the methods of included studies

Study	Cost outcome	Subcategories of costs for results	Subgroups for results	Statistical model	BMI modelling	Covariates	Exclusions
Bhattacharya 2009 [17]	Annual	None	Age, gender, insurance type	Unclear	Categorised: not obese, obese	Unclear	Pregnant women
Borg 2005 [18]	15 years	None	Age, gender	Two part log-linear regression cost model; combined with survival estimates	Categorised: 18.5-25, 25-30, 30+	Age, gender	None
Brown 2008 [19]	Annual	None	Physical activity level	None	Categorised: 18.5-25, 25-30, 30+	None	Serious illness or disability
Buchmueller 2015 [20]	Annual	Inpatient, emergency department, ambulatory, medications	Age, gender	Two-part linear regression	Categorised: <18.5, 18.5-25, 25-30, 30-35, 35+	Age, marital status, country of birth, skin colour, language, education, smoking status, eligibility for healthcare subsidies, income, labour force participation, private health insurance, geographic area	None
Bungum 2003 [21]	Annual	None	None	None	Categorised: <25, 25-30, 30+	None	None
Burton 1998 [22]	3 years	Major diagnostic categories	Gender	None	Categorised: <19, 19-22, 23-24, 25-Risk, Risk-30, 30+; Risk: >27.8 for men and >27.3 for women	Stratified by gender	None
Cai 2010 [23]	Lifetime	None	Gender	Log link gamma variance GLM; combined with survival estimates	Categorised: 18.5-25, 25-30, 30+	Age, sex, race, smoking status, time-to-death	Became underweight over 10 years follow-up
Cawley 2012 [24]	Annual	Inpatient, ambulatory, medications, other	Gender, race/ethnicity, health insurance	Two-part log link gamma variance GLM instrumental variable regression	Categorised: <30, 30+; continuous	Age, gender, race/ethnicity, education, census region, household composition, survey information self-reported or proxy -reported, employment status, gender oldest child, age oldest child, MEPS year	Pregnant women; No biological child aged 11 to 20 at survey

Table B.5 continued: Characteristics of the methods of included studies

Study	Cost outcome	Subcategories of costs for results	Subgroups for results	Statistical model	BMI modelling	Covariates	Exclusions
Cecchini 2015 [25]	Annual	Inpatient, outpatient, medications; health conditions	None	Two-part log link gamma variance GLM	Continuous	Age, gender, survey year, education, family income, insurance coverage, marital status, region of residence	None
Chu 2010 [26]	Annual	Inpatient, ambulatory	Gender	Censored Tobit model	Categorised: <18.5, 18.5-24, 24-27, 27+	Age, smoking, alcohol use, obesity-related disorders; stratified by gender	None
Colagiuri 2010 [27]	Annual	None	None	None	Categorised: 18.5-25, 25-30, 30+	None	None
Counterweight 2008 [28]	Annual	None	Gender	Two-part linear regression	Continuous	Age; stratified by gender	None
Daviglus 2004 [29]	Annual	Cardiovascular disease- and diabetes-related	Gender	General linear model	Categorised: 18.5-25, 25-30, 30-35, 35+	Age, race, education, smoking; stratified by gender	CHD, diabetes mellitus or major electrocardiographic abnormality
Detournay 2000 [30]	Annual	Inpatient, ambulatory	None	Matching obese: healthy weight 1:2	Categorised: 18.5-25, 30+	Age, gender, education	Pregnant women
DiBonaventura 2015 [31]	Annual	None	Diabetes	GLM with negative binomial distribution and log link	Categorised: 18.5-25, 25-30, 30-35, 35-40, 40+	Age, gender, race, marital status, education, income, exercise, smoking, alcohol use, charlson comorbidity index	None
Durden 2008 [32]	Annual	Inpatient, ambulatory, emergency department, medications	None	Two-part log link gamma variance GLM	Categorised: <18.5, 18.5-25, 25-30, 30-35, 35+	Age, gender, region, wage rate, union status, industry type, health plan type, year	Extreme height, weight or BMI
Esposti 2006 [33]	Annual	Therapeutic use	None	Log-linear regression	Categorised: 18.5-25, 25-30, 30+	Age	Serious illness
Finkelstein 2001 [34]	Annual	None	Smoking	Linear regression	Categorised: <20, 20-25, 25-30, 30-35, 35+; continuous	Age, gender, household income, smoking	None
Finkelstein 2003 [35]	Annual	None	None	Two-part log-linear regression	Categorised: 18.5-25, 25-30, 30+	Age, gender, race/ethnicity, region, household income, education, marital status	None

Table B.5 continued: Characteristics of the methods of included studies

Study	Cost outcome	Subcategories of costs for results	Subgroups for results	Statistical model	BMI modelling	Covariates	Exclusions
Finkelstein 2005 [36]	Annual	None	Gender	Two-part log-linear regression	Categorised: 18.5-25, 25, 25-30, 30-35, 35-40, 40+	Age, race/ethnicity, education, income, census region, smoking status; stratified by gender	Pregnant women
Finkelstein 2008 [37]	Lifetime	None	Age, gender, race/ethnicity	Two-part log link gamma variance GLM ; combined with survival estimates	Categorised: <18.5, 18.5-20, 20-25, 25-30, 30-35, 35+	Age (interacted with BMI), education, smoking, insurance status, marital status, census region, population density; stratified by gender and race/ethnicity	Hispanic
Finkelstein 2009 [38]	Annual	Inpatient, ambulatory, medications	None	Two-part log link gamma variance GLM	Categorised: 18.5-25, 30+	Age, gender, race/ethnicity, region, household income, education, marital status	None
Heithoff 1997 [39]	Annual	Inpatient, ambulatory, medications	Gender	Piecewise log-linear regression	Continuous	Age, race, income, smoking status, insurance status; stratified by gender	None
Hu 2008 [40]	Annual	Inpatient, ambulatory	Age, gender, education, income	Two-part log-linear regression	Categorised: <18.5, 18.5-23, 23-25, 25-30, 30+	Age, ethnicity, smoking, alcohol use, education, household income, chronic diseases; stratified by gender	Catastrophic illnesses
Janssen 2009 [41]	Annual	None	Age, gender	Two-part log link gamma variance GLM	Categorised: <18.5, 18.5-25, 25-30, 30+	Smoking, physical activity, income; stratified by age and gender	Extreme BMI, extreme costs, pregnant women
Kleinman 2014 [42]	Annual	Medical, medications	Gender, disease history	Two-part log link gamma variance GLM	Categorised: <27, 27-30, 30+	Age, gender, marital status, race, salary, zip code regions, exempt status, year of index date	Pregnant women
Konig 2015 [43]	3 months	Inpatient, ambulatory/medications, nursing care	None	Linear regression	Categorised: 18.5-25, 25-30, 30-35, 35+	Age, gender, marital status, education, income, health insurance	None

Table B.5 continued: Characteristics of the methods of included studies

Study	Cost outcome	Subcategories of costs for results	Subgroups for results	Statistical model	BMI modelling	Covariates	Exclusions
Korda 2015 [44]	Annual	None	Age and gender	Log link gamma variance GLM	Categorised: 15-18.5, 18.5-20, 20-22.5, 22.5-25, 25-27.5, 27.5-30, 30-32.5, 32.5-35, 35-40, 40-50	Age, area of residence, education, household income, smoking, alcohol intake, private health insurance; stratified by age and sex	Pre-existing cancer
Kuriyama 2002 [45]	Monthly	Inpatient, ambulatory	None	Analysis of covariance	Categorised: <18.5, 18.5-21, 21-23, 23-25, 25-30, 30+	Age, gender, smoking, alcohol use, physical functioning status	Extreme BMI; died in year 1; cancer, myocardial infarction, stroke or kidney disease
Lakdawalla 2005 [46]	Lifetime	Medicare only	None	Linear regression; applied to Future Elderly Model	Categorised:<20, 20-25, 25-30, 30+	Diabetes, cancer (excl. skin), heart disease, osteoarthritis, limitations in activities of daily living	HMO enrolees
Li 2015 [47]	Annual	Inpatient, ambulatory, medications	Glycemic stage	Log link gamma variance GLM	Categorised: 18.5-25, 25-30, 30-35, 35-40, 40+	Age, gender, race, smoking, employment, insurance type, year	Selected health conditions including malignancy, HIV; abnormal weight gain or loss
Lynch 2005 [48]	Annual	Inpatient, ambulatory	Age, gender	Two-part log link GLM	Categorical: <25, 25+	Age, sex, smoking, alcohol use, exercise, nutrition, stress, blood pressure	None
Martin 2009 [49]	Annual	Inpatient, ambulatory, medications	None	Linear regression	Categorised: 18.5-25, 25-30, 30+	Age, race, region of country, driver type, driver tenure	Women
McHugh 2015 [50]	Annual	Inpatient, outpatient, allied health services	None	Seemingly unrelated probit regression model	Categorised: 18.5-25, 25-30, 30-35, 35-40, 40+	Age, sex, marital status, education, health insurance, self-rated health, depression, health conditions	None
Mora 2015 [51]	Annual	None	Gender	Two-part log link gamma variance random effects GLM	Categorised: <18.5-25, 25-30, 30-35, 35+	Age, gender, immigration status, employment status, lifestyles, public health insurance, language	None
Moriarty 2012 [52]	Annual	None	Retirement status; presence comorbidities	Log link gamma variance general estimating equation	Categorised: <18, 18-25, 25-30, 30-35, 35-40, 40+	None	None

Table B.5 continued: Characteristics of the methods of included studies

Study	Cost outcome	Subcategories of costs for results	Subgroups for results	Statistical model	BMI modelling	Covariates	Exclusions
Nakamura 2007 [53]	Monthly	Inpatient, ambulatory	None	Analysis of covariance on log costs (total, ambulatory); Wilcoxon's rank sum test log costs (inpatient)	Categorised: <18.5, 18.5-25, 25+	Age, gender, smoking, alcohol use (total, outpatient); none (inpatient)	Died in first 5 years of follow up
Narbro 2002 [54]	Annual	None	None	None	Categorised: 'general population', 'obese'	None	Cancer, myocardial infarction, other severe illnesses; other trial exclusion criteria
Onwudiwe 2012 [55]	Annual	None	None	Log link gamma variance GLM	Categorised: <18.5-25, 25-30, 30-35, 35+	Age, gender, race/ethnicity, smoking, marital status, education, income, private insurance, medicaid coverage	None
Ostbye 2014 [56]	Annual	Medical (major diagnostic categories), medications (therapeutic use)	Gender	Negative-binomial generalized estimation equations	Categorised: 19-25, 25-30, 30-35, 35-40, 40+	Age, gender, race/ethnicity, calendar time period; stratified by gender	None
Pan 2012 [57]	Annual	Cause-specific (ICD-9-CM codes)	Age and gender	None	Categorised: <18.5, 18.5-24, 24-27, 27+	stratified by age and gender	Died in first 5 years of follow up
Peterson 2015 [58]	Annual	None	Physicial disabilities.	Log link gamma variance GLM	Categorised: 18.5-25, 25-30, 30+	Age, gender, race/ethnicity, marital status, education, income, health insurance, geographical location, self-rated health, mental health, physical disabilities	None
Pronk 1999a [59]	Annual	None	Chronic disease	Two-part log-linear regression	Continuous	Age, gender, race, smoking, physical activity, diabetes, heart disease	None

Table B.5 continued: Characteristics of the methods of included studies

Study	Cost outcome	Subcategories of costs for results	Subgroups for results	Statistical model	BMI modelling	Covariates	Exclusions
Pronk 1999b [60]	Annual	Inpatient, ambulatory	None	Log-linear regression	Categorised: 'low risk', 'high risk'; risk threshold is 27.8 for men and 27.3 for women	Age, gender, exercise, asthma, history of cancer, diabetes, heart disease, high cholesterol, high blood pressure, debilitating back pain, and lung disease	None
Qin 2016 [61]	Single event	None	None	Two-part random-effects log link gamma variance GLM instrumental variable regression	Categorised: 18.5-25, 25+	Age, gender, education, residential type, employment status, household size, marriage status, household income.	Pregnant women
Quesenberry 1998 [62]	Annual	Inpatient, ambulatory	Age	Log transformed linear regression	Categorised: 20-25, 25-30, 30-35, 35+	Age, gender	Pregnant women
Raebel 2004 [63]	Annual	Inpatient, ambulatory, medications	None	Matching with two-part linear mixed models	Categorised: 18.5-25, 25+; continuous	Age, sex, primary outpatient medical office, absence of selected diagnoses, chronic disease score	Extreme costs; LOSE Weight study inclusion criteria
Rudisill 2016 [64]	Annual	None	Gender, disease status	Two-part log link gamma variance GLM	Categorised: 18.5-25, 25-30, 30-35, 35-40, 40+	Age, gender, comorbidity (any of type-2 diabetes, cancer, stroke, coronary heart disease), depression	Received bariatric surgery
Stuart 2008 [65]	Annual	Therapeutic use	None	Log link gamma variance GLM	Categorised: <18.5, 18.5-25, 25-30, 30-35, 35-40, 40+	Age, gender, race/ethnicity, marital status, education, income, drug coverage, census region	Long-term care
Sturm 2002 [66]	Annual	Medical, medications	None	None	Categorised: <25, 25-30, 30+	None	None
Sturm 2013 [67]	Annual	Inpatient, ambulatory	Age	Linear regression	Categorised: 20-25, 25-30, 30-35, 35+	Age, gender, smoking, alcohol use	Pregnant women
Tarride 2012 [68]	Annual	Inpatient, ambulatory	Age, gender	Two-part log link gamma variance GLM	Categorised: <18.5, 18.5-25, 25-30, 30+	Age, gender, physical activity, smoking, income; stratified by age and gender	Pregnant women; extreme costs
Terry 1998 [69]	Annual	None	Age	Linear regression	Categorised: not obese, obese	Age, gender, general health status	None

Table B.5 continued: Characteristics of the methods of included studies

Study	Cost outcome	Subcategories of costs for results	Subgroups for results	Statistical model	BMI modelling	Covariates	Exclusions
Teuner 2013 [70]	Annual	Therapeutic use	None	Two-part log link gamma variance GLM	Categorised: 18.5-25, 25-30, 30-35, 25+	Age, gender, socioeconomic status	None
Thompson 2001 [71]	Annual	Inpatient, ambulatory, medications (therapeutic use)	None	Linear regression	Categorised: 18.5-25, 25-30, 30-35, 35+	Age, gender	Smokers; recent history of CHD, stroke, HIV or cancer
Thorpe 2004 [72]	Annual	Health conditions: diabetes, hyperlipidaemia, heart disease	None	Two-part log transformed linear regression	Categorised: <18.5, 18.5-20, 20-25, 25-30, 30+	Age, gender, race/ethnicity, smoking, education, health insurance status, income, marital status, region	None
Tigbe 2013 [73]	Annual	Inpatient, ambulatory, emergency department, prescriptions	Gender	Linear regression	Continuous	Age, gender, lifestyle factors	None
Tucker 2002 [74]	Annual	Major disease categories	None	Linear regression	Categorised: <27, >27	Age, gender, wellness, exercise, stress	None
Van Nuys 2014 [75]	Annual	Payer	None	Spline regression	Categorised: 15-18.5-25, 25-30, 30-35, 35-40, 40-48; continuous	Age, gender, industry, state of residence, comorbidities	Pregnant women
Veiga 2008 [76]	Annual	None	None	Two-part log-linear regression	Categorised: 18.5-25, 25-30, 30+	Age, gender, smoking, alcohol use, education, family income, employment status, marital status, type health insurance, region	None
von Lengerke 2010 [77]	Annual	None	Socioeconomic status	GLM with mixed poisson-gamma distribution	Categorised: <18.5, 18.5-20, 20-25, 25-30, 30-35, 35+	Age, gender, sickness fund type, place of residence, socioeconomic status	None
Wang 2004 [78]	Annual	Medical, medications; major diagnostic code categories	Physical activity level	Log link gamma variance GLM	Categorised: 18.5-25, 25-30, 30+	Age, gender, chronic diseases, overall health risk status, physical activity	Existing health conditions (heart problems, cancer, diabetes, stroke, chronic bronchitis/emphysema); extreme values height, weight, activity

Table B.5 continued: Characteristics of the methods of included studies

Study	Cost outcome	Subcategories of costs for results	Subgroups for results	Statistical model	BMI modelling	Covariates	Exclusions
Wang 2005 [79]	Annual	Inpatient, ambulatory, medications	Physical activity level	Log link gamma variance GLM	Categorised: 18.5-25, 25-30, 30+	Age, gender, major diseases, chronic diseases, overall health risk status, physical activity	Extreme BMI
Wee 2005 [80]	Annual	Inpatient, ambulatory, emergency department, medications	Age, gender, race/ethnicity	Two-part log-linear regression	Categorised: <18.5, 18.5-25, 25-30, 30-35, 35-40, 40+	Age, gender, race/ethnicity, education, insurance, region, rural/urban residence	None
Wolfenstetter 2012 [81]	Annual	Inpatient, ambulatory	None	Two-part log link gamma variance GLM	Categorised: 18.5-25, 25-30, 30+	Age, gender, socioeconomic status	None
Yang 2008 [82]	Lifetime	Inpatient, ambulatory, medications, long term nursing	Gender	Two-part log-linear regression; as part of simultaneous equations framework	Categorised: <18.5, 18.5-25, 25-30, 30+; continuous	Age, gender, race, marital status, education, income, urban/rural residence, smoking, functional status, existing chronic diseases, acute medical events	None
Yen 2006 [83]	Annual	None	None	Unclear	Categorised: low BMI, high BMI	Unclear	None

GLM=Generalized linear model; BMI=Body mass index

Table B.6: Quality assessment results

Study	Overall quality	Q1	Q2	Q3	Q4	Q6	Q7	Q8	Q9	Q10	Q12	Q14
Alter 2012 [9]	Good											
An 2015 [10]	Fair											
Anderson 2005 [11]	Fair											
Andreyeva 2004 [12]	Fair											
Arterburn 2005 [13]	Good											
Atella 2015 [14]	Fair											
Bell 2011 [15]	Good											
Bertakis 2005 [16]	Poor											
Bhattacharya 2009 [17]	Poor											
Borg 2005 [18]	Fair											
Brown 2008 [19]	Poor											
Buchmueller 2015 [20]	Good											
Bungum 2003 [21]	Poor											
Burton 1998 [22]	Poor											
Cai 2010 [23]	Good											
Cawley 2012 [24]	Good											
Cecchini 2015 [25]	Fair											
Chu 2010 [26]	Fair											
Colagiuri 2010 [27]	Poor											
Counterweight 2008 [28]	Poor											
Daviglus 2004 [29]	Good											
Detournay 2000 [30]	Good											
DiBonaventura 2015 [31]	Poor											
Durden 2008 [32]	Poor											
Esposti 2006 [33]	Poor											
Finkelstein 2001 [34]	Fair											
Finkelstein 2003 [35]	Good											
Finkelstein 2005 [36]	Good											
Finkelstein 2008 [37]	Good											
Finkelstein 2009 [38]	Fair											
Heithoff 1997 [39]	Fair											
Hu 2008 [40]	Good											
Janssen 2009 [41]	Fair											
Kleinman 2014 [42]	Fair											
Konig 2015 [43]	Poor											
Korda 2015 [44]	Good											
Kuriyama 2002 [45]	Good											
Lakdawalla 2005 [46]	Fair											
Li 2015 [47]	Good											
Lynch 2005 [48]	Fair											
Martin 2009 [49]	Fair											
McHugh 2015 [50]	Poor											
Mora 2015 [51]	Fair											
Moriarty 2012 [52]	Poor											
Nakamura 2007 [53]	Good											
Narbro 2002 [54]	Poor											
Onwudiwe 2012 [55]	Fair											
Ostbye 2014 [56]	Good											
Pan 2012 [57]	Fair											
Peterson 2015 [58]	Poor											
Pronk 1999a [59]	Good											

Table B.6 continued: Quality assessment results

Study	Overall quality	Q1	Q2	Q3	Q4	Q6	Q7	Q8	Q9	Q10	Q12	Q14
Pronk 1999b [60]	Fair			■				■				■
Qin 2016 [61]	Poor					■	■	■		■		
Quesenberry 1998 [62]	Fair					■						
Raebel 2004 [63]	Poor		■			■			■			■
Rudisill 2016 [64]	Poor					■			■			■
Stuart 2008 [65]	Fair					■						
Sturm 2002 [66]	Poor			■	■	■		■		■		■
Sturm 2013 [67]	Poor		■	■	■	■						
Tarride 2012 [68]	Fair					■						
Terry 1998 [69]	Fair							■				■
Teuner 2013 [70]	Good									■		
Thompson 2001 [71]	Good											
Thorpe 2004 [72]	Good											
Tigbe 2013 [73]	Poor				■	■			■			
Tucker 2002 [74]	Poor		■					■				■
Van Nuys 2014 [75]	Fair			■		■						■
Veiga 2008 [76]	Poor			■		■	■			■		
von Lengerke 2010 [77]	Fair						■			■		
Wang 2004 [78]	Fair			■		■						■
Wang 2005 [79]	Fair			■		■						■
Wee 2005 [80]	Good											
Wolfenstetter 2012 [81]	Good									■		
Yang 2008 [82]	Fair					■						■
Yen 2006 [83]	Poor			■		■		■				■

Overall quality was independently assessed by two reviewers (Seamus Kent [SK] and Francesco Fusco) using the National Heart, Lung, and Blood Institute's (NHLBI) quality assessment tool for observational cohort and cross-sectional studies. Disagreements regarding overall quality scores were resolved through discussion. Assessment of individual quality criteria presented here are those from SK only. The shaded boxes indicate that the study is considered not to have met the quality criteria for the specified questions (see Table B.3). Question 5, 11, and 13 are not reported here as they were considered less relevant to studies of this type and were consistent across all studies. There is no formal mechanism for converting results for each question into an overall quality score using the NHLBI tool. Within each question, studies vary in the extent to which the criteria were or were not met, and so also in the risk of bias. As such, studies with the same profile may have different scores.

Table B.7: List of studies contributing and not contributing (with reasons) to the quantitative summaries

Studies contributing to quantitative summary of results
Andreyeva 2004 [12], Atella 2015 [14], Bell 2011 [15], Brown 2008 [19], Buchmueller 2015 [20], Bungum 2003 [21], Chu 2010 [26], Colagiuri 2010 [27], Daviglus 2004 [29], Di Bonaventura 2015 [31], Durden 2008 [32], Esposti 2006 [33], Finkelstein 2003 [35], Finkelstein 2009 [38], Hu 2008 [40], Konig 2015 [43], Li 2015 [47], Martin 2009 [49], Mora 2015 [51], Nakamura 2007 [53], Onwudiwe 2012 [55], Ostbye 2014 [56], Pan 2012 [57], Quesenberry 1998 [62], Stuart 2008 [65], Sturm 2002 [66], Tarride 2012 [68], Teuner 2013 [70], Thompson 2001 [71], Veiga 2008 [76], von Lengerke 2010 [77], Wang 2004 [78], Wang 2005 [79], Wolfenstetter 2012 [81]

Partial duplicates[a]
Arterburn 2005 [13], Janssen 2009 [41], Korda 2015 [44], Peterson 2015 [58], Thorpe 2004 [72]

Studies not contributing to quantitative summary of results

Estimates of relative costs by BMI category could not be reliably derived:
Estimates per unit BMI or for each integer of BMI: Counterweight 2008 [28], Finkelstein 2001 [34], Heithoff 1997 [39], Pronk1999a [59], Raebel 2004 [63] *Results presented only graphically:* Burton 1998 [22], Finkelstein 2005 [36], Finkelstein 2008 [37], Moriarty 2012 [52], Tigbe 2013 [73], Van Nuys 2014 [75], Wee 2005 [80] *Only absolute additional costs presented:* Sturm 2013 [67] *Relative effects could not be extracted from reported regression models:* Rudisill 2016 [64] *Relevant results not presented in any format:* Cecchini 2015 [25], McHugh 2015 [50]

Non-healthy weight reference group used: An 2015 [10], Bertakis 2005 [16], Bhattacharya 2009 [17], Cawley 2012 [24], Detournay 2000 [30], Kleinman 2014 [42], Narbro 2002 [54], Pronk 1999b [59], Terry 1998 [69], Tucker 2002 [74], Yen 2006 [83]

Costs presented over more than 1 year: Alter 2012 [9], Borg 2005 [18], Cai 2010 [23], Lakdawalla 2005 [46], Yang 2008 [82]

Overweight and obesity categories combined: Lynch 2005 [48], Qin 2016 [61]

Geometric mean costs by BMI category presented: Kuriyama 2002 [45]

Results for only combined cost categories (but not total): Anderson 2005 [11]

[a]Uses same data source and methods as an included study with some overlap of data years.

Table B.8: Characteristics of studies contributing and not contributing results to the quantitative summary

	Contributing	Not contributing
Number of studies	39	36
Overall quality rating		
Good/Fair	29 (74)	22 (61)
Poor	10 (26)	14 (39)
Region		
United States	21 (54)	23 (64)
Europe	8 (21)	7 (19)
Asia	4 (10)	3 (8)
Other[a]	6 (15)	3 (8)
Study population		
All adults	19 (49)	14 (39)
Working age adults	10 (26)	14 (39)
Middle-aged or elderly	10 (26)	8 (22)
Sample size		
Median (IQR)	17118 (6572, 51738)	9398 (3362, 29303)
$\geq 10,000$ participants	23 (59)	16 (46)
$< 10,000$ participants	16 (41)	19 (54)
Body mass index reporting		
Measured	12 (31)	8 (22)
Self-reported	27 (69)	23 (64)
Mixed[b]	0 (0)	5 (14)
Prospective study		
Yes	15 (38)	16 (44)
No	24 (62)	20 (56)
Outcome data		
Administrative records	22 (56)	22 (61)
Self-reported	11 (28)	5 (14)
Mixed	6 (15)	9 (25)
Length of outcome data collection period		
$>$ 1 year	18 (46)	18 (50)
$\leq$ 1 year	21 (54)	18 (50)

[a]Canada, Australia, and South Africa.

[b]Two studies used mostly measured weight but mostly self-reported height; three studies measured height and weight for some, but not all, participants.

Table B.9: Results of included studies by type of healthcare service

Study	Quality score	BMI group	All health-care	Inpatient	Ambulatory	Medications
Alter 2012 [9]	Good	18.5-25	R	R	R	R
		25-30	1.04	1.07	0.97	0.91
		30+	1.13	1.16	1.04	0.9
An 2015 [10][A]	Fair	<30	R	R	R	R
		30+	1.27*	1.25*	1.24*	1.43*
Anderson 2005 [11][B]	Fair	<25		R		
		25-30		1.31		
		30+		1.54*		
Andreyeva 2004 [12][C]	Fair	18.5-25	R			
		25-30	1.13*			
		30-35	1.24*			
		35-40	1.49*			
		40+	2.10*			
		30+	1.35*			
Arterburn 2005 [13][B]	Good	<18.5	1.05			
		18.5-25	R			
		25-30	1.1			
		30-35	1.23*			
		35-40	1.45*			
		40+	1.81*			
		30+[D]	1.36*			
Atella 2015 [14]	Fair	<18.5	1.13*		1.01*	
		18.5-25	R		R	
		25-30	1.03*		1.10*	
		30-35	1.18*		1.25*	
		35-40	1.41*		1.39*	
		40+	1.50*		1.51*	
		30+[D]	1.25*		1.30*	
Bell 2011 [15][C]	Good	18.5-25	R	R	R	R
		25-30	1.18*	1.1	1.30*	1.24*
		30+	1.50*	1.01	1.43*	1.68*
Bertakis 2005 [16][E]	Poor	<30	R	R	R	
		30+	1.61*	1.73*	1.47*	
Bhattacharya 2009 [17][C]	Poor	not obese	R			
		obese	1.23#			
Borg 2005 [18][C]	Fair	18.5-25	R			
		25-30	1.15*			
		30+	1.71*			
Brown 2008 [19]	Poor	18.5-25			R	
		25-30			1.01#	
		30+			1.17#	
Buchmueller 2015 [20][A,C]	Good	<18.5	1.34*	1.56#	1.10*	1.07
		18.5-25	R	R	R	R
		25-30	1.04*	1.03	1.04*	1.15*
		30-35	1.20*	1.19*	1.14*	1.39*

Table B.9 continued: Results of included studies by type of healthcare service

Study	Quality score	BMI group	All health-care	Inpatient	Ambulatory	Medications
		35+	1.53*	1.61*	1.29*	1.79*
		30+[D]	1.30*	1.31*	1.18*	1.51*
Bungum 2003 [21]	Poor	<25	R			
		25-30	5.03*			
		30+	5.44*			
Burton 1998 [22]	Poor	Results by BMI categories could not be reliably extracted				
Cai 2010 [23]	Good	18.5-25	R			
		25-30	1.1			
		30+	1.39*			
Cawley 2012 [24][A]	Good	<30	R			
		30+	2.55*			
Cecchini 2015 [25]	Fair	Results by BMI categories could not be reliably extracted				
Chu 2010 [26][F]	Fair	<18.5	1.15#	1.55	0.65*	
		18.5-24	R	R	R	
		24-27	1.65#	1.27	2.13*	
		27+	1.84#	1.12	2.76*	
Colagiuri 2010 [27][B]	Poor	18.5-25	R			
		25-30	1.19			
		30+	1.54*			
Counterweight 2008 [28]	Poor	Results by BMI categories could not be reliably extracted				
Daviglus 2004 [29][C]	Good	18.5-25	R			
		25-30	1.24#			
		30-35	1.51			
		35+	1.96#			
		30+[D]	1.59#			
Detournay 2000 [30]	Good	<30	R	R	R	
		30+	1.12	0.99#	1.23#	
DiBonaventura 2015 [31]	Poor	18.5-25	R			
		25-30	1.06*			
		30-35	1.13*			
		35-40	1.21*			
		40+	1.45*			
		30+[D]	1.21*			
Durden 2008 [32][E]	Poor	<18.5	1.13#	1.50#	0.99#	1.10#
		18.5-25	R	R	R	R
		25-30	1.05#	0.95#	0.97#	1.04#
		30-35	1.22#	1.29#	1.16#	1.32#
		35+	1.61#	2.10#	1.58#	1.84#
		30+[D]	1.36#	1.59#	1.31#	1.52#
Esposti 2006 [33]	Poor	18.5-25				R
		25-30				1.19*
		30+				1.69*
Finkelstein 2001 [34]	Fair	continuous	$8.9 per unit higher BMI			

Table B.9 continued: Results of included studies by type of healthcare service

Study	Quality score	BMI group	All health-care	Inpatient	Ambulatory	Medications
Finkelstein 2003 [35]	Good	18.5-25	R			
		25-30	1.15			
		30+	1.37*			
Finkelstein 2005 [36]	Good	Results by BMI categories could not be reliably extracted				
Finkelstein 2008 [37]	Good	Results by BMI categories could not be reliably extracted				
Finkelstein 2009 [38]	Fair	18.5-25	R	R	R	R
		30+	1.42*	1.46*	1.27*	1.80*
Heithoff 1997 [39]	Fair	Results by BMI categories could not be reliably extracted				
Hu 2008 [40][B,G]	Good	<18.5	0.91	0.95	0.88	
		18.5-23	R	R	R	
		23-25	1.26#	1.27	1.25*	
		25-30	1.37*	1.30*	1.40*	
		30+	1.54*	1.35*	1.70*	
		25+[D]	1.39*	1.45	1.29	
Janssen 2009 [41][C]	Fair	<18.5			0.87	
		18.5-25			R	
		25-30			1.03	
		30+			1.15*	
Kleinman 2014 [42][G]	Fair	<27	R	R		R
		27-30	1.15*	1.15*		1.17*
		30+	1.51*	1.51*		1.48*
Konig 2015 [43][A]	Poor	18.5-25	R	R	R	
		25-30	1.15	1.28	1.13	
		30-35	1.08	1.04	1.19*	
		35+	1.50*	1.7	1.40*	
		30+[D]	1.20#	1.22	1.25*	
Korda 2015 [44][C]	Good	15-18.5		1.43*		
		18.5-20		1.07#		
		20-22.5		0.99		
		22.5-25		R		
		25-27.5		1.03#		
		27.5-30		1.10#		
		30-32.5		1.13#		
		32.5-35		1.18#		
		35-40		1.25#		
		40+		1.36#		
		30+[D]		1.20#		
Kuriyama 2002 [45][H]	Good	<18.5	1.16	1.44*	0.99	
		18.5-21	1.03			
		21-23	R	R	R	
		23-25	1.02			
		25-30	1.10*			
		30+	1.22*	1.12	1.29*	
		25+[D]	1.11*			

Table B.9 continued: Results of included studies by type of healthcare service

Study	Quality score	BMI group	All health-care	Inpatient	Ambulatory	Medications
Lakdawalla 2005 [46]	Fair	<20	1.04			
		20-25	R			
		25-30	1.07*			
		30+	1.21*			
Li 2015 [47]^{C}	Good	18.5-25	R	R	R	R
		25-30	1.09#	1.12#	1.06#	1.16#
		30-35	1.22#	1.28#	1.16*	1.31#
		35-40	1.25#	1.32#	1.22#	1.36*
		40+	1.48*	1.85#	1.28*	1.47*
		30+^{D}	1.28#	1.39#	1.19#	1.35#
Lynch 2005 [48]	Fair	<25	R			
		25+	1.00			
Martin 2009 [49]	Fair	18.5-25	R	R	R	R
		25-30	1.38*	1.27	1.75#	2.28*
		30+	1.58*	1.32	1.76#	3.76*
McHugh 2015 [50]	Poor	Results by BMI categories could not be reliably extracted				
Mora 2015 [51]	Fair	18.5-25	R			
		25-30	1.09*			
		30-35	1.17*			
		35+	1.27*			
		30+^{D}	1.19*			
Moriarty 2012 [52]	Poor	Results by BMI categories could not be reliably extracted				
Nakamura 2007 [53]	Good	<18.5	1.16	1.75	1.02	
		18.5-25	R	R	R	
		25+	1.30*	1.13	1.26*	
Narbro 2002 [54]	Poor	general population				R
		obese				1.62#
Onwudiwe 2012 [55]^{C}	Fair	<18.5	1.51			
		18.5-25	R			
		25-30	1.03			
		30-35	1.21			
		35+	1.44			
		30+^{D}	1.28			
Ostbye 2014 [56]^{G}	Good	19-25	R	R		R
		25-30	1.22#	1.24#		1.15#
		30-35	1.39#	1.64#		1.48#
		35-40	1.64#	1.92#		1.72#
		40+	1.77#	2.06#		1.98#
		30+^{D}	1.54#	1.76#		1.60#
Pan 2012 [57]^{C}	Fair	<18.5	0.81#			
		18.5-24	R			
		24-27	1.45#			
		27+	2.01#			
Peterson 2015 [58]	Poor	18.5-25	R	R		

Table B.9 continued: Results of included studies by type of healthcare service

Study	Quality score	BMI group	All health-care	Inpatient	Ambulatory	Medications
		25-30	1.03			
		30+	1.13*			
Pronk 1999a [59]	Good	continuous		$1.02* per unit higher BMI		
Pronk 1999b [60]	Fair	<27	R			
		27+	1.08*			
Qin 2016 [61]	Poor	18.5-25	R			
		25+	1.06*			
Quesenberry 1998 [62]	Fair	20-25	R	R	R	
		25-30	0.95	0.83	0.99	
		30-35	1.25*	1.33*	1.21*	
		35+	1.44*	1.70*	1.37*	
		30+[D]	1.31*	1.44*	1.26*	
Raebel 2004 [63]	Poor	continuous		$1.02* per unit higher BMI		
Rudisill 2016 [64]	Poor	Results by BMI categories could not be reliably extracted				
textbfStuart 2008 [65][A]	Fair	<18.5				0.89
		18.5-25				R
		25-30				1.10*
		30-35				1.33*
		35-40				1.43*
		40+				1.40*
		30+[D]				1.36*
Sturm 2002 [66]	Poor	<25		R		R
		25-30		1.11#		
		30+		1.36#		1.77#
Sturm 2013 [67]	Poor	20-25	R	R	R	
		25-30	+$140	-$220	+$360	
		30-35	+$2,238*	+$537*	+$1,700*	
		35+	+$4,425*	+$1,909*	+$2,515*	
Tarride 2012 [68]	Fair	<18.5	1.05	1.16	1.02	
		18.5-25	R	R	R	
		25-30	0.98	1.01	0.97	
		30+	1.25*	1.34*	1.23*	
Terry 1998 [69][C]	Fair	not obese	R			
		obese	+$1#			
Teuner 2013 [70]	Good	18.5-25				R
		25-30				1.18
		30-35				1.65*
		35+				1.79*
		30+[D]				1.68
Thompson 2001 [71]	Good	18.5-25	R	R	R	R
		25-30	1.1	1.2	0.96	1.37*
		30+	1.36*	1.38	1.14	2.05*
Thorpe 2004 [72]	Good	<18.5	1.12*			
		18.5-25	R			
		25-30	1.12*			
		30+	1.37*			
Tigbe 2013 [73]	Poor	Results by BMI categories could not be reliably extracted				

Table B.9 continued: Results of included studies by type of healthcare service

Study	Quality score	BMI group	All health-care	Inpatient	Ambulatory	Medications
Tucker 2002 [74]	Poor	<27	R			
		27+	1.72*			
Van Nuys 2014 [75][E]	Fair	Results by BMI categories could not be reliably extracted				
Veiga 2008 [76][I]	Poor	18.5-25	R			
		25-30	1.08*			
		30+	1.13*			
von Lengerke 2010 [77][C]	Fair	18.5-25	R			
		25-30	0.87			
		30-35	1.22			
		35+	3.31*			
		30+[D]	1.76#			
Wang 2004 [78]	Fair	18.5-25	R	R		R
		25-30	1.08*	1.07*		1.17*
		30+	1.22*	1.19*		1.39*
Wang 2005 [79]	Fair	18.5-25	R	R	R	R
		25-30	1.03#	1.03	1	1.08#
		30+	1.07#	1.12*	0.97	1.20#
Wee 2005 [80]	Good	Results by BMI categories could not be reliably extracted				
Wolfenstetter 2012 [81]	Good	18.5-25	R			
		25-30	1.24*			
		30+	1.25*			
Yang 2008 [82][B,C]	Fair	<18.5	0.84*	0.82	0.79	0.71
		18.5-25	R	R	R	R
		25-30	1.08#	1.08	1.12	1.21
		30+	1.15*	1.15	1.2	1.39#
Yen 2006 [83]	Poor	low BMI	R	R		R
		high BMI	+$1,420	+$810		+$263

R=reference group (healthy weight). Records marked in bold contribute to the quantitative summary of results. Colour shaded areas indicate that estimates of relative costs are based on combined healthcare service type categories.

*=Significant at 5% level; #=unknown significance; the absence of a symbol means not significant at the 5% level.

[A]Relative costs calculated by adding adjusted incremental absolute costs to unadjusted costs for the reference group.

[B]Significance inferred from non-overlapping confidence intervals.

[C]Relative costs derived from weighted average by demographic characteristics (usually age and/or gender). Results are considered significant if significant for all groups, non-sigificant if non-significant for all, and otherwise unknown.

[D]This 'all obese' category was derived by combining results for subcategories of obesity.

[E]Adjusted results for all categories could not be extracted; reported costs for certain categories of cost are therefore not adjusted.

[F]Significance derived using multiple two-sample t-tests for comparisons of means.

[G]Relative costs calculated by adding costs of component parts. Results are considered significant if significant for all, non-sigificant if non-significant for all, and otherwise unknown.

[H]Results given as relative geometric means for total and outpatient costs.

[I]Both parts of two-part model were significant.

Table B.10: Median (interquartile range) percentage change in costs for sensitivity analyses

	Base case analysis	Excluding poor quality studies	Excluding studies using non-standard BMI cut-offs	Including partial duplicate studies	Excluding studies assessing costs over less than one year
All healthcare costs					
Underweight	13% (5, 16)	14% (1, 21)	13% (7, 29)	13% (5, 16)	13% (1, 20)
Overweight	12% (5, 24)	12% (4, 24)	10% (5, 20)	10% (5, 22)	10% (5, 24)
Obese	36% (25, 54)	36% (28, 53)	35% (25, 50)	36% (25, 52)	36% (26, 54)
Inpatient care costs					
Underweight	53% (25, 56)	55% (16, 56)	33% (11, 52)	50% (30, 56)	50% (16, 55)
Overweight	12% (2, 27)	12% (2, 27)	11% (2, 25)	11% (3, 27)	11% (2, 25)
Obese	34% (22, 44)	34% (22, 42)	38% (32, 45)	33% (21, 43)	38% (32, 45)
Ambulatory care costs					
Underweight	0% (-10, 2)	2% (-14, 2)	0% (-4, 4)	-1% (-14, 2)	-1% (-14, 2)
Overweight	4% (-2, 28)	6% (-1, 30)	3% (-3, 20)	4% (-2, 26)	4% (-2, 28)
Obese	26% (19, 31)	26% (21, 36)	26% (19, 30)	26% (18, 31)	27% (19, 34)
Medication costs					
Underweight	7% (-3, 9)	-3% (-8, 2)	7% (-3, 9)	7% (-3, 9)	7% (-3, 9)
Overweight	18% (15, 27)	17% (15, 24)	18% (15, 27)	18% (15, 27)	18% (15, 27)
Obese	68% (51, 77)	64% (42, 77)	68% (51, 77)	68% (51, 77)	68% (51, 77)

Table B.11: Results of included studies by gender

Study	BMI group	Males	Females
Andreyeva 2004 [12]^{A,B}	18.5-25	R	R
	25-30	1.17*	1.09*
	30-35	1.21*	1.27*
	35-40	1.58*	1.43*
	40+	2.05*	2.11*
	30+^{C}	1.30*	1.41*
Bell 2011 [15]^{A}	18.5-25	R	R
	25-30	1.25*	1.24*
	30+	1.50*	1.52*
Bhattacharya 2009 [17]	not obese	R	R
	obese	1.09	1.33*
Borg 2005 [18]^{A}	18.5-25	R	R
	25-30	1.14*	1.20*
	30+	1.64*	1.75*
Brown 2008 [19]	18.5-25		R
	25-30		1.01 #
	30+		1.17 #
Cai 2010 [23]	18.5-25	R	R
	25-30	1.16	1.16
	30+	1.47*	1.37*
Cawley 2012 [24]^{D}	<30	R	R
	30+	1.7	2.87*
Chu 2010 [26]^{E}	<18.5	2.11#	0.88#
	18.5-24	R	R
	24-27	1.32#	2.12#
	27+	1.23#	3.04#
Daviglus 2004 [29]^{A}	18.5-25	R	R
	25-30	1.16*	1.23
	30-35	1.41*	1.54
	35+	1.90*	1.98*
	30+^{C}	1.47*	1.66#
Hu 2008 [40]^{B,F}	<18.5	0.99	0.83*
	18.5-23	R	R
	23-25	1.25*	1.40*
	25-30	1.39*	1.53*
	30+	1.45*	1.66*
Janssen 2009 [41]^{A}	<18.5	0.87	0.96
	18.5-25	R	R
	25-30	1.03	1
	30+	1.15*	1.18*
Kleinman 2014 [42]^{F}	<27	R	R

Table B.11 continued: Results of included studies by gender

Study	BMI group	Males	Females
	27-30	1.18*	1.11#
	30+	1.51*	1.53*
Korda 2015 [44]^{A}	15-18.5	1.58#	1.06#
	18.5-20	1.33#	0.84
	20-22.5	1.1	0.87
	22.5-25	1	1
	25-27.5	0.96#	1.11*
	27.5-30	1.00*	1.20*
	30-32.5	1.05*	1.18*
	32.5-35	1.11*	1.19*
	35-40	1.18*	1.14*
	40+	1.30*	1.22*
	30+^{C}	1.10*	1.18*
Mora 2015 [51]	18.5-25	R	R
	30-35	1.20*	1.14*
	35+	1.29*	1.24*
	30+^{C}	1.21*	1.17*
Ostbye 2014 [56]^{F}	19-24	R	R
	25-29	1.22#	1.27#
	30-34	1.60#	1.33#
	35-39	1.86#	1.56#
	40+	2.04#	1.66#
	30+^{C}	1.71#	1.47#
Pan 2012 [57]^{A}	<18.5	0.93#	0.77#
	18.5-24	R	R
	24-27	1.30#	1.62#
	27+	1.82#	2.19#
Tarride 2012 [68]	<18.5	1.15	1.01
	18.5-25	R	R
	25-30	0.9	1.04
	30+	1.12	1.38*
Yang 2008 [82]^{B}	<18.5	0.84*	0.84*
	18.5-25	R	R
	25-30	1.06	1.11*
	30+	1.13*	1.17*

R=Reference group (healthy weight). *=Significant at 5% level; #=unknown significance; the absence of a symbol means not significant at the 5% level.
^{A}Relative costs derived from weighted average by demographic characteristics (usually age and/or gender). Results are considered significant if significant for all groups, non-significant if non-significant for all, and otherwise unknown.
^{B}Significance inferred from non-overlapping confidence intervals.

Table B.11 continued: Results of included studies by gender

Study	BMI group	Males	Females

[C]This 'all obese' category was derived by combining results for subcategories of obesity.
[D]Relative costs calculated by adding adjusted incremental absolute costs to unadjusted costs for the reference group.
[E]Significance derived using multiple two-sample t-tests for comparisons of means.
[F]Relative costs calculated by adding costs of component parts. Results are considered significant if significant for all, non-significant if non-significant for all, and otherwise unknown.

Table B.12: Results of included studies by age categories

Study	BMI group	Age group 1	Age group 2	Age group 3	Age group 4	Age group 5	Age group 6	Age group 7
Atella 2015 [14]	*Age group (years)*	18-45	45-65	65+				
	<18.5	1.16*	1.14*	1.11*				
	18.5-25	R	R	R				
	25-30	1.06*	1.10*	1.03*				
	30-35	1.18*	1.27*	1.14*				
	35-40	1.39*	1.52*	1.33*				
	40+	1.75*	1.68*	1.36*				
	30+[A]	1.26*	1.35*	1.19*				
Borg 2005 [18][B]	*Age group (years)*	30	35	40	45	50	55	60
	18.5-25	R	R	R	R	R	R	R
	25-30	1.11*	1.10*	1.10*	1.09*	1.08*	1.08*	1.08*
	30+	1.59*	1.57*	1.56*	1.52*	1.50*	1.50*	1.47*
Hu 2008 [40][A,B]	*Age group (years)*	18-35	35-50	50-65	65+			
	<18.5	1.04	0.99	0.88	1.09			
	18.5-23	R	R	R	R			
	23-25	0.91	1.03	1.1	1.24			
	25-30	0.91	1.17	1.19	1.46*			
	30+	1.15	1.63*	1.84*	1.22			
Janssen 2009 [41][D]	*Age group (years)*	18-40	40-60	60+				
	<18.5	1.14	1.15	0.94				
	18.5-25	R	R	R				
	25-30	0.91	0.93	1.05				
	30+	1.05	1.07	1.28*				

Table B.12 continued: Results of included studies by age categories

Study	BMI group	Age group 1	Age group 2	Age group 3	Age group 4	Age group 5	Age group 6	Age group 7
Korda 2015 [44][D]	*Age group (years)*	45-65	65-80	80+				
	15-18.5	1.16#	1.28*	1.1				
	18.5-20	0.9	1.11#	1.03				
	20-22.5	0.93	1	1.04				
	22.5-25	R	R	R				
	25-27.5	1.11*	1.05#	1.03				
	27.5-30	1.26*	1.17*	1.08				
	30-32.5	1.34*	1.29*	1.11				
	32.5-35	1.48*	1.39*	1.06				
	35-40	1.70*	1.52*	1.14				
	40+	2.03*	1.71*	1.12				
	30+[A]	1.51*	1.38*	1.1				
Pan 2012 [57][D]	*Age group (years)*	20-40	40-60	60+				
	<18.5	1.12#	0.91#	0.94#				
	18.5-24	R	R	R				
	24-27	1.08#	1.20#	1.08#				
	27+	1.37#	1.80#	1.25#				
Quesenberry 1998 [62]	*Age group (years)*	20-40	40-60	60-75	75+			
	20-25	R	R	R	R			
	25-30	1.1	1.03	0.99	0.77			
	30-35	1.24*	1.59*	1.18	1.04			
	35+	1.48*	1.72*	1.38*	0.53			
Tarride 2012 [68]	*Age group (years)*	20-40	40-60	60+				

Table B.12 continued: Results of included studies by age categories

Study	BMI group	Age group 1	Age group 2	Age group 3	Age group 4	Age group 5	Age group 6	Age group 7
	<18.5	0.95	1.2	0.98				
	18.5-25	R	R	R				
	25-30	1.03	0.92	1.04				
	30+	1.19*	1.36*	1.20*				

R=reference group (healthy weight). *=Significant at 5% level; #=unknown significance; the absence of a symbol means not significant at the 5% level.

[A]This 'all obese' category was derived by combining results for subcategories of obesity.

[B]Relative costs derived from weighted average by demographic characteristics (usually age and/or gender). Results are considered significant if significant for all groups, non-significant if non-significant for all, and otherwise unknown.

[C]Relative costs calculated by adding costs of component parts. Results are considered significant if significant for all, non-significant if non-significant for all, and otherwise unknown.

[D]Significance inferred from non-overlapping confidence intervals.

C

Million Women Study recruitment questionnaire

The recruitment questionnaire was completed by all participants between 1996 and 2001. I had no involvement in the design of the questionnaire.

THE MILLION WOMEN STUDY

A national survey of women invited for breast screening

We need one million women to help us in research that will benefit women all over the world.
Would you become one of these special women?

More and more women are taking hormone replacement therapy (HRT) so it is vital that we find out as much as possible about its benefits and any possible side effects. We have a unique opportunity through the NHS Breast Screening Programme to learn about the way different types of HRT and other lifestyle factors affect a woman's health, particularly her breasts. Britain is the only country in the world that can carry out this study because it is the only one with the combination of a large population and a comprehensive national breast screening programme.

The NHS Breast Screening Programme, the Imperial Cancer Research Fund and the Medical Research Council have joined together to organise The Million Women Study. If one million women answer this questionnaire over the next three years we could have some of the answers to our most important questions about HRT within five years or so.

We would be very grateful if you could set aside some time to answer these questions. It should not take more than 10-15 minutes. You do not have to answer this questionnaire and if you decide not to you will still have your screening done in the normal way.

Please answer every question and do not leave blanks as all the information that you give us is very useful. If you are not sure about exact dates or ages an approximate answer is better than none. If you have any questions you can ring us on freephone **0800 262 872.**

Even if you are not taking HRT it is just as important that you fill in the questionnaire.
Please bring this questionnaire to your breast screening appointment

To help us read your answers please write as clearly as possible and be sure to complete the questionnaire as shown:

Please put a cross in the appropriate box(es) ☒ ☐ ☐

OR put numbers in the appropriate box e.g. *23rd April 1946* 2 3 / 0 4 / 4 6 *age* 4 4 *years*

GENERAL QUESTIONS ABOUT YOU

1. What is your date of birth? *(please put day/month/year)*

☐☐ / ☐☐ / ☐☐

2. How old are you? ☐☐ years

3. How tall are you? *(please give to the nearest inch)*

☐ feet ☐☐ inches

4. About how much do you weigh?

☐☐ stone ☐☐ lbs

5. How old were you when you finished full time schooling? *(please cross one box)*

- ☐ did not go to school
- ☐ 13 or younger
- ☐ 14
- ☐ 15
- ☐ 16
- ☐ 17 or older

6. What qualification(s) do you have from school, college or the equivalent?
(please put a cross in the most appropriate box(es))

- ☐ clerical or commercial qualifications *(eg secretarial, hairdressing etc)*
- ☐ nursing or teaching
- ☐ "O" level *(or equivalent)*
- ☐ "A" level *(or equivalent)*
- ☐ college/university degree *(or equivalent)*
- ☐ none of these

7. About how many cigarettes do you smoke on average *each day*, now? *(please cross one box)*

- ☐ none
- ☐ less than 5
- ☐ 5-9
- ☐ 10-14
- ☐ 15-19
- ☐ 20-24
- ☐ 25 or more

8. Are you an ex-smoker? ☐ No ☐ Yes

9. About how much wine, beer or spirits do you drink on average *each week*? *(please cross one box for each type)*

Wine (glasses per week)	**Lager/Cider/Beer** (half pints per week)	**Spirits** (tots per week)
☐ none	☐ none	☐ none
☐ less than 1	☐ less than1	☐ less than1
☐ 1-3	☐ 1-3	☐ 1-3
☐ 4-6	☐ 4-6	☐ 4-6
☐ 7-10	☐ 7-10	☐ 7-10
☐ 11-15	☐ 11-15	☐ 11-15
☐ 16-20	☐ 16-20	☐ 16-20
☐ 21+	☐ 21+	☐ 21+

If you drink **wine** is it

- ☐ mostly red
- ☐ mostly white
- ☐ about the same amount of red and white?

10. How often do you do *any* exercise?

- ☐ rarely/never
- ☐ less than once a week
- ☐ once a week
- ☐ 2-3 times a week
- ☐ 4-6 times a week
- ☐ every day

11. How often do you do *strenuous* exercise?

(that is, enough to cause sweating or a fast heart beat.)

- ☐ rarely/never
- ☐ less than once a week
- ☐ once a week
- ☐ 2-3 times a week
- ☐ 4-6 times a week
- ☐ every day

QUESTIONS ABOUT YOU AND YOUR FAMILY

12. Have you ever had any children? ☐ No ☐ Yes

- if No, please go on to question 15

13. How many children have you had? ☐☐

(please include stillbirths; it is not necessary to include miscarriages)

14. When was each child born, and for how many months did you breastfeed each child, if at all?

	DATE OF BIRTH (If you had twins or triplets please repeat the same date for each child) day / month / year	BREASTFEEDING (Months that you breastfed each child; put "0" if you did not breastfeed that child and "1" if you breastfed for a month or less)
1st child	☐☐ / ☐☐ / ☐☐	☐☐ months
2nd child	☐☐ / ☐☐ / ☐☐	☐☐ months
3rd child	☐☐ / ☐☐ / ☐☐	☐☐ months
4th child	☐☐ / ☐☐ / ☐☐	☐☐ months
5th child	☐☐ / ☐☐ / ☐☐	☐☐ months
6th child	☐☐ / ☐☐ / ☐☐	☐☐ months
7th child	☐☐ / ☐☐ / ☐☐	☐☐ months
8th child	☐☐ / ☐☐ / ☐☐	☐☐ months
9th child	☐☐ / ☐☐ / ☐☐	☐☐ months
10th child	☐☐ / ☐☐ / ☐☐	☐☐ months

15. Have you ever been for breast screening before?

- ☐ No
- ☐ Yes- If **Yes**, about how many years ago was your last screen? ☐☐ years ago

16. Have you ever had a breast lump removed or any operations on your breast(s)?

- ☐ No
- ☐ Yes- If **Yes**, how old were you? ☐☐ years

(If you have had more than one operation please write your age at the first operation)

17. Have you ever had breast cancer diagnosed?

- ☐ No
- ☐ Yes- If **Yes**, how old were you when the cancer was first diagnosed? ☐☐ years

18. Has your mother ever had breast cancer diagnosed?

- ☐ No ☐ Don't know
- ☐ Yes- If **Yes**, how old was she when the cancer was first diagnosed? ☐☐ years

19. How many sisters do you have? ☐☐ sisters

(put"0" if you do not have any sisters, please include any sisters who have died)

20. Have any of your sisters ever had breast cancer diagnosed?

- ☐ No/No sisters ☐ Don't know
- ☐ Yes- If **Yes**, how old were they when the cancer was first diagnosed?

1st sister ☐☐ years **2nd sister** ☐☐ years

QUESTIONS ABOUT YOUR HEALTH

21. Have you ever had any other cancer?

☐ Yes ☐ No

Please describe

22. Have you EVER had:

(please cross "Yes" or "No" for each condition)

High blood pressure - when pregnant	☐ Yes	☐ No
High blood pressure - when not pregnant	☐ Yes	☐ No
Heart disease *(eg heart attack/angina)*	☐ Yes	☐ No
Stroke	☐ Yes	☐ No
Diabetes	☐ Yes	☐ No
High blood cholesterol	☐ Yes	☐ No
Blood clot *(thrombosis)*	☐ Yes	☐ No

23. Are you NOW being treated for:

High blood pressure *(hypertension)*	☐ Yes	☐ No
Heart disease	☐ Yes	☐ No
Diabetes	☐ Yes	☐ No
High blood cholesterol	☐ Yes	☐ No
Varicose veins	☐ Yes	☐ No
Clotting problems	☐ Yes	☐ No
Asthma	☐ Yes	☐ No
Rheumatoid arthritis	☐ Yes	☐ No
Osteoarthritis	☐ Yes	☐ No
Thyroid problems	☐ Yes	☐ No
Osteoporosis	☐ Yes	☐ No
Depression/Anxiety	☐ Yes	☐ No

24. Are you *NOW* being treated for any other *serious* illness?

☐ Yes ☐ No

Please describe this illness

Please describe the treatment

QUESTIONS ABOUT PAST OPERATIONS

25. Have you had a hysterectomy?

☐ No

☐ Yes- If **Yes**, how old were you? ☐☐ years

26. Have you had BOTH ovaries removed?

☐ No ☐ Not sure

☐ Yes- If **Yes**, how old were you? ☐☐ years

27. Have you been sterilised *(had your tubes tied)***?**

☐ No

☐ Yes- If **Yes**, how old were you? ☐☐ years

QUESTIONS ABOUT YOUR USE OF THE PILL

28. Have you ever used the pill *(oral contraceptive)*?

☐ Yes

☐ No ***- if No, please go to question 32***

29. About how old were you when you *first went on* the pill? ☐☐ years

30. About how old were you when you *last came off* the pill? ☐☐ years

31. For how many years *in total* did you take the pill?

☐☐ years

(Add together the years and months when you actually took the pill -do not count the years and months when you were not taking it. Please write "0" if you used the pill for less than a year in total)

QUESTIONS ABOUT YOUR USE OF HORMONE REPLACEMENT THERAPY (HRT)

32. Have you ever used hormone replacement therapy (HRT)? ☐ No ***- if No - please go to question 39***

☐ Yes

33. How old were you when you *first started* using HRT?

☐☐ years

34. Had your periods stopped before you started using HRT? *(Cross "Yes" if you had a hysterectomy before starting HRT)*

☐ No

☐ Yes **- if Yes**, how old were you when your periods stopped? ☐☐ years

35. For about how many years *in total* have you used HRT? ☐☐ years

(Add together the years and months when you used HRT - do not count the years and months when you were not using HRT. Please write "0" if you used HRT for less than a year in total)

36. Are you *now* using HRT?

☐ Yes

☐ No **- if No**, how old were you when you **last** used HRT? ☐☐ years

37. What is the name of the most RECENT HRT you have used?

☐ Prempak C 0.625mg	☐ Premarin 0.625mg
☐ Prempak C 1.25mg	☐ Premarin 1.25mg
☐ Tridestra	☐ Evorel 25mcg/50mcg
☐ Trisequens	☐ Evorel 75mcg/100mcg
☐ Trisequens Forte	☐ Progynova 1mg
☐ Cycloprogynova 1mg	☐ Progynova 2mg
☐ Cycloprogynova 2mg	☐ Estraderm 25mcg
☐ Estrapak	☐ Estraderm 50mcg
☐ Estracombi	☐ Estraderm 100mcg
☐ Climaval 1mg	☐ Zumenon 1mg
☐ Climaval 2mg	☐ Zumenon 2mg
☐ Premique Cycle	☐ Ethinyloestradiol
☐ Premique	☐ Micronor
☐ Nuvelle	☐ Provera
☐ Kliofem	☐ Duphaston
☐ Livial	

☐ Do not know ☐ Implants ☐ Oestrogel

Other *(please write here)*

38. For how many years in total did you use the most *recent* type of HRT? ☐☐ years

(Please write "0" if you used this recent HRT for less than a year in total)

QUESTIONS ABOUT YOUR PERIODS

39. About how old were you when your periods started? ☐☐ years

40. Have your periods NOW stopped?

*Cross "**Yes**"-if you are not having periods now, either because of your menopause, after a hysterectomy or after stopping HRT.*
*Cross "**No**"- if you are still having regular periods now, even if they are because you are taking HRT.*
*Cross "**Irregular**"-if your periods have been irregular and you think it might be because of the menopause.*

☐ **Yes**- If **Yes**, how old were you when they **stopped**? ☐☐ years

☐ **No**

☐ **Irregular**

FINAL SECTION

41. So that we can find out about your health in the future we may need to contact you again or look at your screening or medical records. We would be grateful if you gave us permission to contact you again or to use information from those records. **We guarantee that all information obtained will be treated with absolute confidentiality and used for medical research only.** Of course, you do not have to give permission. Your response to this request will not affect your screening or the treatment you receive in any way.

If you give permission, please sign here and print your name, address and other details in the section below. Please print in BLOCK CAPITALS as clearly as possible.

Signature: ☐ today's date: ☐☐/☐☐/☐☐

Surname: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Given name(s): ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

House number and street: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

District: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Town: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

County: ☐☐☐☐☐☐☐☐☐☐ Postcode: ☐☐☐☐☐☐☐☐

Surname at birth: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Town of birth: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

NHS (National Health Service)Number: ☐☐☐☐☐☐☐☐☐☐
(The number on your medical card)

Breast Screening Number: ☐☐☐☐☐☐☐☐☐☐
*(This is in the top left hand corner of your **screening invitation letter** and starts with the letters LGL)*

Please bring this questionnaire to your breast screening appointment

If you would like to post this questionnaire back to us, please send it to:
THE MILLION WOMEN STUDY CO-ORDINATING CENTRE
ICRF-CEU, GIBSON BUILDING,
RADCLIFFE INFIRMARY,
OXFORD OX2 6HE

FREEPHONE: 0800 262 872

Breast Screening Unit
Linton House
Thirlestaine Road
Cheltenham
GL53 7AS

270 LGL ☐

THANK YOU VERY MUCH FOR YOUR HELP

D
Statistical analysis

D.1 Health Survey for England

The Health Survey for England (HSE) is an annual survey designed to collect information on the health and health-related behaviour of people living in private households in England [1]. The HSE collects both self-reported and measured height and weight on participants. This Thesis uses data from the 2012 and 2013 surveys for three main purposes: 1) to assess the impact of measurement error in BMI derived from self-reported height and weight on estimates of the association between BMI and admission rates and annual costs; 2) for plotting estimates of annual costs against categories of BMI, correcting for random and systematic reporting errors; and 3) to project cost estimates to the all women aged 55 to 79 years in England.

The 2012 and 2013 surveys contained information on 21,313 individuals (10,333 from 2012 and 10,980 from 2013). For the first two purposes it is necessary to restrict to women aged 50 to 64 years (the age of participants at the time at which height and weight were reported in the Million Women Study), leaving a combined sample of 2,087 women. Measured height and/or weight was missing for 315 participants (15%). Mean measured BMIs were estimated for each category of self-reported BMI.

For extrapolation, the HSE data was restricted to women aged 55 to 79 with self-reported BMI (N = 3,159). The distribution of women by BMI categories used in analysis was estimated and multiplied by the estimated number of women aged 55 to 79 years in England in 2013 from the ONS mid-year population estimate (N = 6,623,923) [2].

For both estimates, the above estimates were derived separately within each survey using the survey weights provided, and estimates were then combined across HES years using an unweighted average (see **Table D.1**).

D.2 Statistical modelling of cost data

Overview

Healthcare cost data often has characteristics that render statistical analysis complex [3]. In particular costs are often multimodal, usually with a non-trivial fraction

Table D.1: Distribution of women aged 55 to 79 in England in 2013 by BMI category and mean measured BMI within categories of self-reported BMI

BMI (kg/m^2)	Percentage of women	Number of women	Mean measured BMI (kg/m^2)
<18.5	1.70%	114,257	18.9
18.5 to <20	4.10%	273,554	20.2
20 to <22.5	14.20%	940,219	22.5
22.5 to <25	22.60%	1,497,925	25.1
25 to <27.5	20.30%	1,346,245	27.6
27.5 to <30	14.10%	930,615	30.1
30 to <35	16.00%	1,061,099	33.8
35 to <40	4.60%	302,367	39.1
$\geq$ 40	2.40%	157,641	45.1

BMI=body mass index

of zero-cost observations (reflecting non-users of healthcare), and the non-zero realisations of cost tend to be severely right-skewed with heavy tails. Furthermore, the variance is often a variable function of the mean and the response of costs to covariates not always linear [4]. To further complicate matters, rational economic decision-making requires estimation of mean costs on their natural scale [5], and so common methods for dealing with skewed data, such as median regression, are not appropriate [3].

A large number of statistical models for the estimation of cost data have been used or proposed for use [6]. In this section I briefly describe some of the more common methods used in applied costing research, namely, two-part models, linear regression, and generalized linear models. These are the models which were considered for the analyses undertaken in this Thesis. It is important to consider a variety of statistical models because, as methodological papers comparing models in different scenarios have consistently demonstrated, there is no model which is universally appropriate and the best model varies from application to application, depending on the particular characteristics of the data [7].

Two-part models

Cost datasets often contain a large proportion of zero cost observations; this is particularly common for inpatient data, where the majority of the population are not admitted to hospital in a given time period and hence incur no costs. In such situations it is recommended that a two-part or hurdle model is used [8]. In this, the first part is usually either a logistic or probit regression, modelling whether costs were incurred – analogous in this Thesis with the use of healthcare services in an annual period – and the second part models the level of annual costs conditional on some costs being incurred. This allows for separate processes to inform the probability of using healthcare services and the level of costs conditional on some use of healthcare services. Furthermore, a two-part specification can allow the application of more complex models for the second part which would not be able to account appropriately for zero cost observations or which would suffer from severe computation problems in such circumstances. Expected costs are calculated as the product of the expectation of each part.

Most studies in the methodological costing literature recommend using two-part models when confronted by a non-negligible proportion of zero-cost observations [8, 9]. However, only one study has directly compared single-equation and two-part models, and they found little difference in model fit between one-part and two-part models selected using common specification tests based on a data set with 8% zero-costs [10]. Other, currently unpublished work, has shown data indicated one-part and two-part models to show similar model fit in hospital cost data with 83% zero-costs [11].

Ordinary least squares regression

A common model applied to cost data is multivariate ordinary least squares (OLS) regression. Covariates are assumed to act additively and directly on the scale of interest, and consequently have a simple interpretation. OLS gives consistent and unbiased estimates of parameter coefficients even in the presence of non-normality and heteroskedasticity. However in the presence of such complicating features OLS

is inefficient. OLS gives equal weight to all observations and as such is susceptible to being dominated by extreme observations with high influence, potentially leading to poor out-of-sample performance [12]. Finally, the assumption that covariates act additively on costs may not be appropriate. Despite these manifold problems, many studies find the OLS to perform consistently well across a range of criteria and comparably, and often better, than more complex alternatives [7, 9], though such conclusions are not reached in all studies [13, 14]. Such models can be applied to all costs including zero observations or to only positive realisations of costs within a two-part model structure.

In response to the problems posed by the severe skewness, kurtosis and heteroskedasticity that characterise cost data, early research focused on transforming costs to promote normality and stabilise the variance prior to the application of standard linear regression techniques [15, 16]. The most popular transformation in applied work is the log transformation, though the square root has also been used. Both are special cases of the larger Box-Cox class of transformations [17]. Log transformation tends to be favoured because it offers an intuitive interpretation of coefficients, namely as having multiplicative or proportional effects on costs, and pulls in the right hand tail of the distribution to a greater extent than competing transformations such as the square root. However, following log transformation, estimation is on the log cost scale, with the expectation giving the geometric mean. However, as established above, health care decision-making is concerned with arithmetic mean costs, and so retransformation back to the original scale is required. However, this back transformation is non-trivial and can introduce considerable bias, particularly in the context of a heteroskedastic variance, which we often observe in healthcare costs [7, 9, 10, 18]. Consequently, the log-transformation has lost popularity in recent years, and, instead, researchers often use generalized linear models.

Generalized linear models

While generalized linear models (GLMs) have been used in numerous statistical applications for many decades, they have only recently gained popularity in health economics but are now one of the more common statistical responses to the complexities of cost data [4, 12, 19]. They overcome the retransformation problem by modelling mean and variance functions on the scale of interest. The mean (or link) function, $g(.)$, defines how the mean of the data (μ) relates to the linear specification of covariates. The mean is calculated from the linear predictor using the inverse link function $g^{-1}(.)$. Common link functions are the identity link, the log link, and square root link.

The variance function allows flexibility in modelling heteroskedasticity, where the variance is a power function of the mean: $v(C) = \theta_1(g^{-1}(x'\beta))^{\theta_2}$. Specific values of θ_2 correspond to standard variance-mean relationships: θ_2=0 corresponds to a normal error variance, θ_2=1 to a Poisson-like variance, θ_2=2 a gamma-like variance, and θ_2=3 an inverse-gaussian variance. The standard linear regression model can be replicated using an identity link and Gaussian variance, and perhaps the most commonly used GLM model in the applied costing literature is specified using a log link and a gamma-like variance. A further proposed advantage of quasi-likelihood methods is that zero cost observations should not cause problems for model estimation as they do for some distributions (e.g. gamma) under full distributional assumptions [4]. Hence, they can, in principle, be applied to conditional costs within a two-part model specification or to all costs including zero cost observations.

Misspecification of the variance function leads to inefficient estimates, while misspecification of the mean function can lead to bias [20, 21]. Where the mean function is misspecified, the variance function affects both efficiency and fit, and the choice of variance function could reflect a compromise between the two [10]. Manning and Mullahy [16] identify a bias-efficiency trade-off between GLMs and log normal models, with the GLM, though consistent in the presence of severe skewness and non-normality given appropriate specification of the mean, being highly inefficient. Hill and Miller [7] demonstrate the importance of carefully

choosing a GLM, showing that when the log link is not appropriate the GLM gamma model can perform poorly compared to competing models.

D.3 Selection of statistical models

D.3.1 Methods

Overview

For modelling annual rates of hospital admissions, primary care consultations, prescription items issued, and monitoring and diagnostic tests, GLMs with a log-link and Poisson-like variance are used. There are four main cost outcomes that are modelled: annual inpatient care costs, annual primary care consultation costs, annual prescription medication costs, and annual monitoring and diagnostic test costs. These are each modelled as a function of categories of body mass index and per unit higher BMI above some BMI. In this subsection, I describe the general framework for selecting a statistical model which is applied separately to each of these outcomes. All models were fitted with covariates as detailed in the respective chapters.

Candidate statistical models

For each outcome I considered three standard models – single-equation log-Poisson GLM, two-part OLS, and two-part log-gamma GLM – and two models selected based on the data – a two-part GLM model and a single-equation GLM model. The GLMs are selected from the data using common specification tests [16]. These specification tests are applied to annual costs including zero costs and only positive costs (i.e. for the second-part of a two-part model). All GLMs are estimated using quasi-likelihoods.

Appropriate variance functions were identified using a modified version of the Park test for heterogeneity [16]. In this, the square of the raw-scale (i.e. cost level) residuals from a given regression are regressed against log transformed predicted costs using log-gamma GLMs. The slope coefficient is an estimate of the power of the variance function, where the variance is a simple power function of the mean.

Values of 0, 1, 2, and 3 correspond to the gaussian, poisson, gamma and inverse-gaussian variance functions, respectively. Because the results may be sensitive to the initial model specification, the test was carried out for each standard link function – identity, Poisson, and gamma.

The link function is assessed using the Hosmer-Lemeshow and Pregibon link tests. The Hosmer-Lemeshow test regresses raw-scale prediction errors against deciles of the predicted cost distribution without a constant, and performs a joint F-test of significance on the decile indicators, with the null hypothesis that there is no pattern in the raw-scale residuals over the distribution of predicted cost [22]. The Pregibon link test aims to determine the linearity of response on the scale of estimation and is performed by regressing costs on the linear predictor and the square of the linear predictor using the same model as for the original estimation [23]. Significance of the squared term is used as evidence against linearity and hence indicates incorrect functional form or model misspecification (i.e. wrong link). These tests are conducted for three GLM models, with an identity, log and square root link – the standard link functions in applied work – and the link function specific variance function as indicated by the Modified Park's test.

Comparing statistical models

Having identified up to five models (fewer if the specification tests indicate a pre-selected model), these are then compared using common metrics of fit: 1) mean error (ME), which gives a measure of group-level bias; 2) mean absolute error (MAE), which indicates individual level predictive accuracy; and 3) root mean squared error (RMSE), which provides a measure of goodness of fit. These metrics are calculated overall and by deciles of predicted costs from an OLS regression applied to the full dataset. Assessing these metrics of fit on the same sample as used for estimation can lead to overfitting of data [24]. To test the out-of-sample performance of candidate models, the data set is split by women 2:1 into estimation and validation samples. All models are fitted on the estimation sample, and metrics of fit calculated in both estimation and validation samples.

D.3.2 Results

For all outcomes, a single-equation log-Poisson GLM was selected for the main analysis. At the aggregate level, all candidate models, with the exception of the single-equation log-gamma model in some scenarios, performed similarly according to all metrics of fit. Across deciles of the linear predictor (based on OLS models) and across categories of self-reported BMI the single-equation log-Poisson and two-part log-gamma models consistently performed as well as, or better than, other candidate models, and similar to each other, in both internal and external validation samples, particularly for ME but also, in some scenarios, for MAE. Moreover, these two models produced very similar estimates of annual costs by BMI category, and similar estimates of mean percentage differences in annual costs between BMI categories; the exceptions were for medication and test costs, where the two-part gamma model produced estimates 2-3% higher for grades 2 and 3 obesity. The single-equation log-Poisson model has the additional advantages that it is simpler and directly provides estimates of relative annual costs by BMI category.

D.4 Extrapolation

Estimates of annual costs at the women-year level were extrapolated to all women aged 55 to 79 years in England in 2013. I have already described the estimation of the number of women in the population within each category of self-reported BMI (**Table D.1**).

Projection of annual costs and contributions of overweight and obesity

The projection of costs to all women aged 55 to 79 years in England in 2013 is performed by combining the standardised estimates of annual costs per women per year with the estimated population distribution by BMI categories. Total annual costs are calculated as the sum of the products of the annual costs and number of women in the population by BMI category. To estimate total annual hospital costs attributed to overweight and obesity I do the following. First, I calculate marginal (or attributed) costs for all BMI categories for BMI $\geq$ 25 kg/m^2 relative

to a BMI of 20 to < 25 kg/m^2 using the standardised estimates of annual costs. The mean cost in the healthy weight BMI group is calculated as a weighted average of costs for BMI 20 to <22.5 kg/m^2 and 22.5 to <25 kg/m^2, where the weights are the estimated numbers in the total population in these BMI categories. Estimated marginal (or attributed) costs per person by BMI category (for BMI ≥ 25 kg/m^2) are then combined with corresponding estimates of the total number of women in each category to calculate total population attributable costs by BMI category. These are added together to calculate overall overweight and obesity attributable costs. Dividing this number by the total annual hospital costs provides an estimate of the proportion of total annual costs attributable to overweight and obesity.

Projection of contributions of overweight and obesity by health conditions

The process desrcibed above is repeated separately for each category of health conditions (for inpatient and day-case costs) or therapeutic use category (for prescriptions). The estimated overweight and obesity attributable costs for each condition are divided by the total overweight and obesity attributed costs to calculate the proportion explained by each category.

Uncertainty in projected estimates

Confidence intervals for total population attributable costs by BMI category overall and by category of health conditions or therpaeutic use category were calculated as follows. First, 1,000 simulated costs by BMI category were drawn based on the mean and standard errors of the standardised mean cost estimates, and the process of projecting costs described above was repeated for each simulation. Confidence intervals were calculated taking the 0.5th and 99.5th percentiles as the confidence limits. These confidence intervals incorporate the uncertainty in the parameter estimates but not the uncertainty in the population, which is held fixed.

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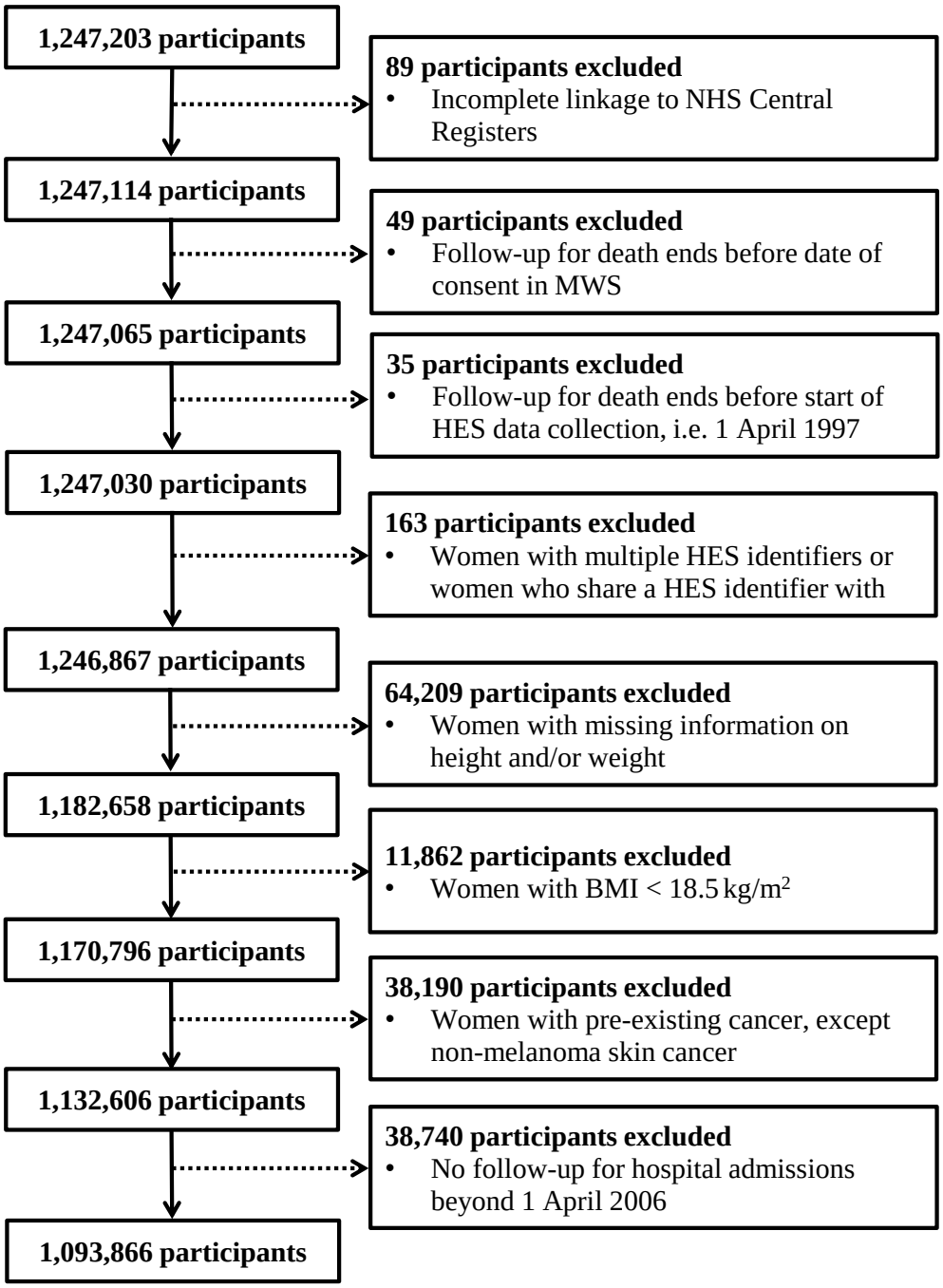
E

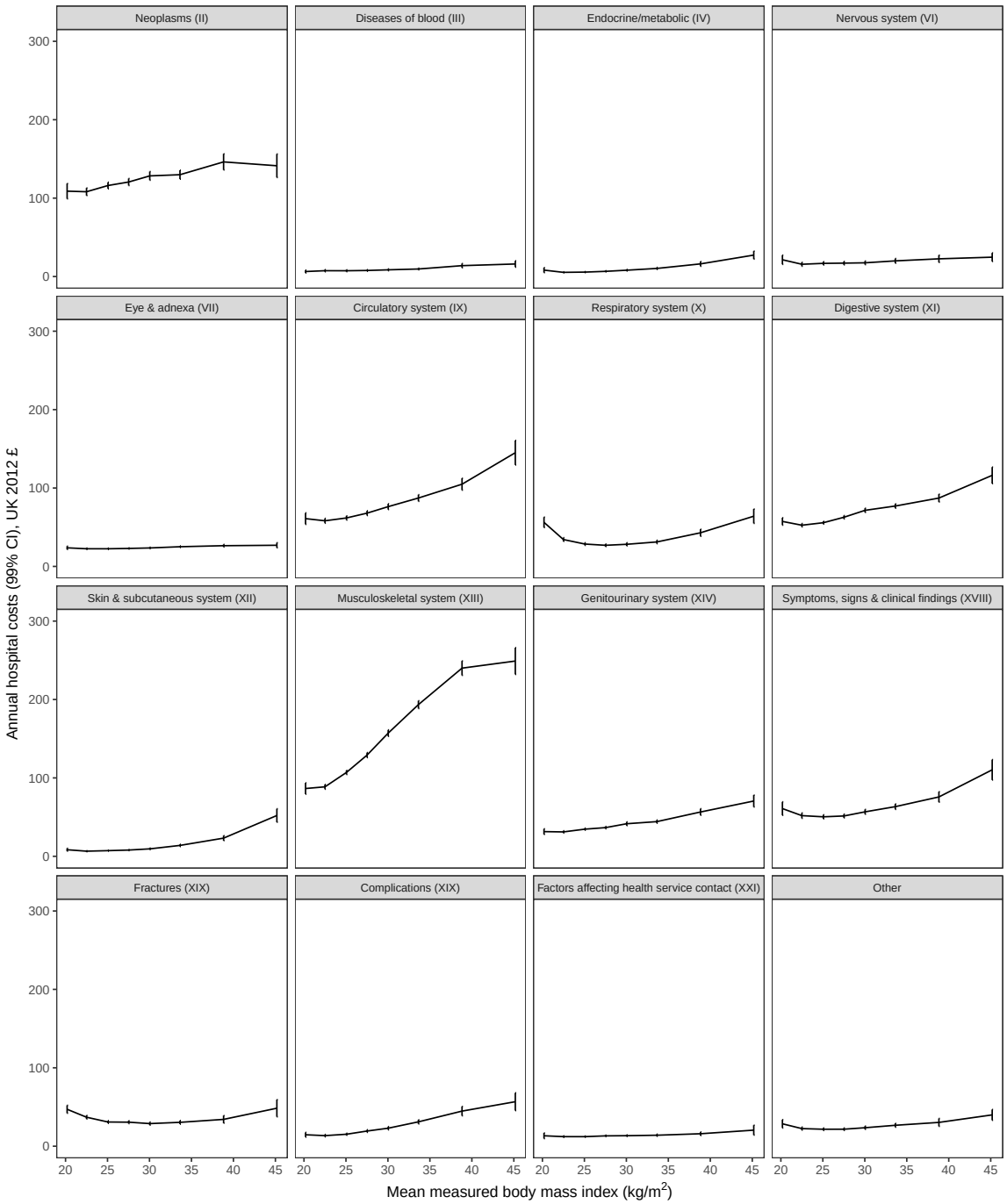
Admitted patient care costs

Figure E.1: Exclusion of participants from the main analysis



Restricted to participants in England only.
BMI=Body mass index; HES=Hospital Episode Statistics

Figure E.2: Annual hospital costs per woman by category of body mass index within diagnostic categories



Standardised estimates of mean annual costs are plotted against mean measured BMI within categories of self-reported BMI from the Health Surveys for England. The error bars show 99% confidence intervals.

Table E.1: Regression results for annual inpatient care costs

Variable	Mean (95% CI)
Body mass index in kg/m^2 (ref: 20-22.4)	
18.5-19.9	1.12 (1.09-1.16)
22.5-24.9	1.05 (1.03-1.06)
25-27.4	1.13 (1.11-1.15)
27.5-29.9	1.26 (1.24-1.28)
30-34.9	1.43 (1.40-1.45)
35-39.9	1.73 (1.69-1.77)
40+	2.15 (2.08-2.23)
Age in years (ref: <60 years)	
60-64	1.20 (1.18-1.22)
65-69	1.58 (1.55-1.61)
70-74	2.03 (2.00-2.07)
75+	2.86 (2.80-2.93)
Deprivation quintile (ref: least deprived)	
2	1.04 (1.02-1.05)
3	1.07 (1.05-1.08)
4	1.10 (1.08-1.12)
Most deprived	1.20 (1.18-1.22)
Missing	1.11 (1.05-1.17)
Region of recruitment (ref: Oxford)	
East Anglia	1.00 (0.97-1.03)
South West	1.09 (1.06-1.11)
Thames	0.99 (0.97-1.01)
West Midlands	1.04 (1.01-1.06)
North Yorkshire	1.10 (1.08-1.13)
Trent	1.06 (1.03-1.08)
North West (Mersey)	1.06 (1.04-1.09)
North West (Manc/Lancs)	1.15 (1.12-1.17)
Parity (ref: none)	
1	1.01 (0.98-1.05)
2	0.96 (0.93-1.00)
3+	1.00 (0.97-1.04)
Missing	1.18 (1.03-1.34)
Age at birth of first child (ref: <25 years)	
25-29	0.93 (0.92-0.94)
30+	0.95 (0.93-0.97)
Not applicable or missing	1.03 (0.99-1.06)
Smoking status (ref: ever smoker)	
Former	1.19 (1.18-1.20)
Current	1.45 (1.43-1.47)
Missing	1.09 (1.07-1.12)
Current alcohol use in units per week (ref: 0)	
<7 units / week	0.86 (0.85-0.87)

Table E.1 continued: Regression results for annual inpatient care costs

Variable	Mean (95% CI)
7+	0.82 (0.81-0.83)
Missing	1.02 (0.97-1.07)
Highest qualification (ref: none)	
Technical qualification	0.96 (0.95-0.97)
Secondary	0.92 (0.91-0.93)
Tertiary	0.90 (0.89-0.92)
Missing	1.05 (1.02-1.08)
Financial year (ref: 2006-07)	
2007-08	1.06 (1.05-1.07)
2008-09	1.11 (1.09-1.12)
2009-10	1.13 (1.11-1.14)
2010-11	1.13 (1.11-1.14)

Values are mean relative costs (95% confidence intervals) compared to the defined reference group for each variable.

Table E.2: Annual costs attributable to overweight and obesity among women aged 55 to 79 years in England by diagnostic category

Body mass index (kg/m^2)	Total annual costs (£million)	Costs attributable to excess weight	
		Absolute annual costs (£ million), 99% CI	Proportion costs attributable (%), 99% CI
Neoplasms (II)	804	57 (51-62)	7 (7-7)
Diseases of the blood (III)	56	7 (7-7)	13 (12-15)
Endocrine, metabolic, and nutritional disorders (IV)	53	16 (13-18)	29 (29-30)
Nervous system (VI)	119	9 (7-11)	8 (7-8)
Eye and adnexa (VII)	156	6 (5-7)	4 (4-4)
Circulatory system (IX)	481	80 (74-85)	17 (16-17)
Respiratory system (X)	215	2 (0-3)	1 (0-2)
Digestive system (XI)	433	70 (66-74)	16 (16-17)
Skin and subcutaneous system (XII)	70	23 (20-26)	33 (32-34)
Musculoskeletal system (XIII)	914	258 (249-265)	28 (28-28)
Genitourinary system (XIV)	256	37 (33-40)	14 (14-15)
Symptoms, signs, and clinical findings (XVIII)	377	36 (33-38)	10 (9-10)
Fractures (XIX)	218	0 (0-0)	0 (0-0)
Complications (XIX)	144	47 (42-52)	33 (33-33)
Factors affecting health service contact (XXI)	88	7 (5-9)	8 (6-9)
Other	159	12 (9-14)	7 (6-8)

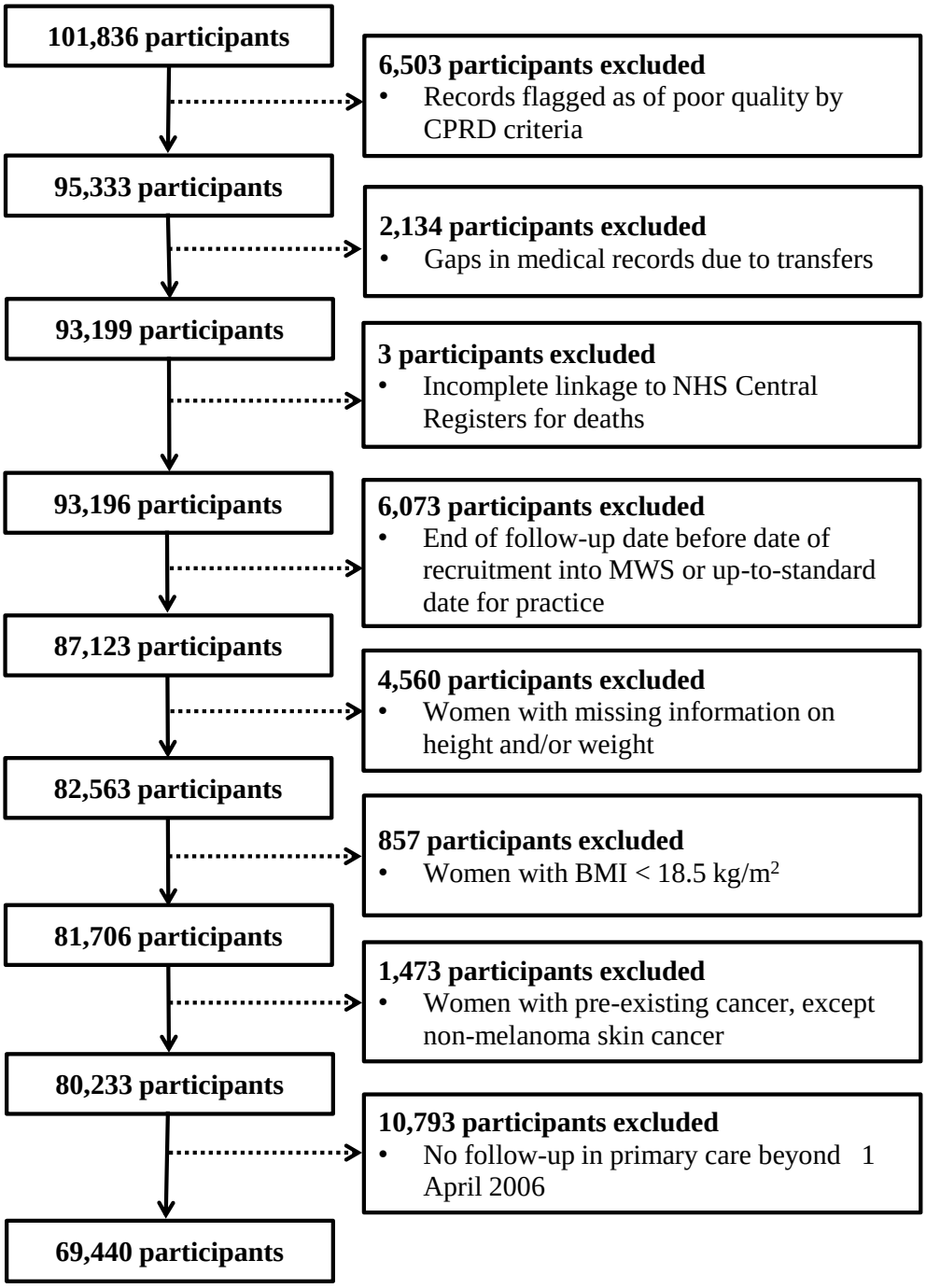
Table E.3: Annual costs attributable to overweight and obesity among women aged 55 to 79 years in England by musculoskeletal disease sub-category

Body mass index (kg/m^2)	Total annual costs (£million)	Costs attributable to excess weight	
		Absolute annual costs (£ million), 99% CI	Proportion (%), 99% CI
All musculoskeletal (XIII: M00-M99)	914	258 (249-265)	28 (28-28)
Arthropathies (M00-M25)			
Knee replacement with arthrosis (M17; OPCS: see NJR)	200	119 (113-125)	60 (59-60)
Hip replacement with arthrosis (M16; OPCS: see NJR)	184	41 (37-43)	22 (22-22)
Other arthrosis (M15-M19; not above)	113	42 (39-45)	37 (37-37)
Rheumatoid arthritis (M05-M06)	45	0 (0-0)	0 (0-0)
Other arthropathies	135	22 (20-24)	16 (16-17)
Dorsopathies (M40-M54)	120	23 (21-26)	19 (19-20)
Soft tissue disorders (M60-M79)	78	13 (11-14)	16 (15-17)
Connnective tissue & other musculoskeletal (M30-M36 & M80-M99)	39	0 (0-1)	1 (0-2)

F

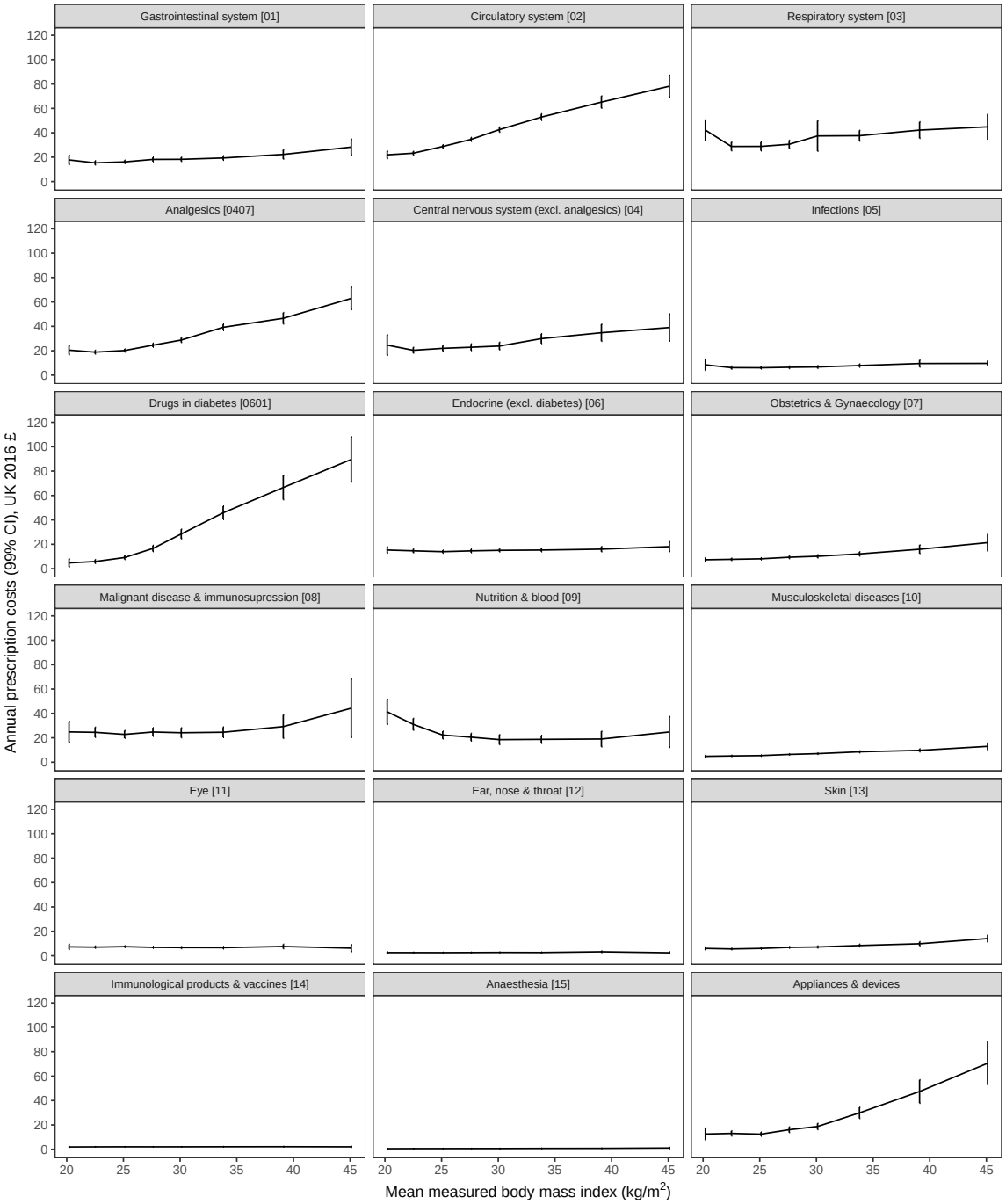
Primary care costs

Figure F.1: Exclusion of participants from the main analysis



CPRD=Clinical Practice Research Datalink; BMI=Body mass index

Figure F.2: Annual prescription costs per person by body mass index and category of therapeutic use



Standardised estimates of mean annual costs are plotted against mean measured BMI within categories of self-reported BMI from the Health Surveys for England. The error bars show 99% confidence intervals.

Table F.1: Categorisation of consultations by staff role and consultation type

	Category (frequency per 1,000 person-years)
Staff role	
General practitioner	Senior Partner (3663); Sole Practitioner (2194); Commercial Deputising service (320); Locum (238); Partner (55); GP Retainer (52); Assistant (19); GP Registrar (1); Consultant (14); Community Medical Officer (2); Non-commercial local rota of less than 10 GPs (3)
Nurse or allied healthcare or social care professional	Pharmacist (53); Carer (351); Non-qualified Dispenser (47); Stomatherapist (53); Health Visitor (139); Dispenser (9); Social Worker (36); Speech Therapist (62); Other Additional Clinical Services (20); Chiropractor (17); Community Psychiatric Nurse (4); Physiotherapist (17); Dietician (6); Osteopath (1); School Nurse (12); Dentist (5); Practice Nurse (3); Other Health Care Professional (4); Other Healthcare Scientists (2); Clinical Practitioner Access Role (3); Midwife (1); Other Medical & Dental (1); Phlebotomist (1)
Type of consultation	
Surgery or clinic	Surgery consultation (5663); Third Party Consultation (171); Clinic (717); Medicine Management (104); Triage (96); Acute visit (29); Emergency Consultation (24); Casualty Attendance (3); Follow-up/routine visit (15)
Home visit or out-of-hours	Out of hours, Non Practice (31); Home Visit (70); Nursing Home Visit (4); Residential Home Visit (3)
Telephone	Telephone call from a patient (191); Telephone call to a patient (286); Co-op Telephone advice (1)

Frequencies calculated for women included in the main analysis from 1 April 2006. Categories of staff role and consultation type not observed in the data used here are not reported.

Table F.2: Mean costs (in UK 2016 prices) per consultation, by staff role and consultation type

Staff roles[a]	Consultation type	Unit cost	Description
Senior Partner, Sole Practitioner, Commercial Deputising service, Locum; Partner, GP Retainer, Assistant, GP Registrar, Consultant, Community Medical Officer, Non-commercial local rota of less than 10 GPs	Surgery	£42.1	Cost per minute GP time: PSSRU 2016 (Table 10.3b). Average consultation length of 11.7 minutes: 2006-7 GP workload survey
	Clinic	£61.9	Cost per minute GP time: PSSRU 2016 (Table 10.3b). Average consultation length of 17.2 minutes: 2006-7 GP workload survey
	Home visit	£84.2	Cost per minute GP time: PSSRU 2016 (Table 10.3b). Average consultation length of 11.4 minutes: 2006-07 GP workload survey; assume average 12 minutes travel time for home visits: PSSRU 2009
	Out-of-hours	£41.0	Cost per minute GP time: PSSRU 2016 (Table 10.3b). Average consultation length of 11.4 minutes: 2006-7 GP workload survey
	Telephone	£25.6	Cost per minute GP time: PSSRU 2016 (Table 10.3b). Average consultation length of 7.1 minutes: 2006-7 GP workload survey
Practice Nurse, Pharmacist, Dispenser, Non-qualified Dispenser, Other Health Care Professional, School Nurse, Stomatherapist, Phlebotomist, Other Healthcare Scientists, Other Additional Clinical Services, Clinical Practitioner Access Role	Surgery, telephone	£14.7	PSSRU 2015, Table 10.6 (practice nurse). Mean hourly cost is £57 for face-to-face contact. Average consultation is 15.5 minutes: 2006-7 GP workload survey
	Home visit	£19.4	As above, but including 12 minutes travel time
Dentist, Other Medical & Dental	Surgery	£130	PSSRU 2016, Tables 10.5 (NHS performer only dentist) & 10.6 (providing-performer dentist). Weighted average of costs for hour long appointment by dentist type
Health visitor, Midwife	All categories	£54.7	PSSRU 2015, Table 10.3 (health visitor)
Community psychiatric nurse	All categories	£135	NHS Reference Costs 2013/14, inflated to 2015/16 using HCHS pay and prices index. Also reported in PSSRU 2016 (Table 12.1). Given as mean average weighted cost per face-to-face contact for all community health teams for older people with mental health problems; 43% of these staff were community nurses
Carer	All categories	£12	PSSRU 2016, Table 11.6 (home care worker). Mean hourly cost of all home care is £24. Mean duration is assumed to be 30 minutes
Social worker	All categories	£79	PSSRU 2016, Table 11.2 (social worker [adult services]). Cost per consultation not given; have assumed 1 hour
Dietician	All categories	£81	NHS Reference Costs 2015-16, currency code: A03
Speech and language therapist	All categories	£88.5	NHS Reference Costs 2015-16. Weighted average of group and one-on-one attendances (currency codes: A13A1 & A13AG)
Physiotherapist, Osteopath, chiropractor	All categories	£48.9	NHS Reference Costs 2015-16. Weighted average of group and one-on-one attendances (currency codes: A08A1 & A08AG)

[a] As defined in CPRD. Costs include qualification costs but do not include direct care staff costs.

Table F.3: Unit costs per test in UK 2016 prices (and frequency per 1,000 person-years)

Test (frequency per 1,000 person-years[a])	**Unit cost (UK 2016 prices)**	**Source in NHS Reference Costs**
Laboratory test		
Biochemistry (4830)	1.18	Directly accessed pathology services
Haematology (3426)	7.63	
Microbiology (273)	3.13	
Serology & Immunology (127)	6.42	
Other Pathology Tests (68)	3.10	
Diagnostic imaging		
Barium enema (1)	144.96	Diagnostic imaging, direct access; weighted average cost of currency code RD3
X-rays: Abdominal xray (1); Ankle x-ray (2); Chest x-ray (21); Foot x-ray (4); Hand x-ray (2); Hip x-ray (4); Knee x-ray (7); Mammogram (86); Neck x-ray (2); Pelvis x-ray (7); Shoulder x-ray (3); Spine x-ray (6); Upper leg x-ray (3); Wrist x-ray (2)	30.26	Directly accessed diagnostic services, direct access plain film (currency code DAPF)
Ultrasound: Abdominal ultra sound (5); General ultra sound scan (7); Pelvic ultra sound (2)	52.82	Diagnostic imaging, direct access; weighted average cost of currency code RD4
CAT scan (8)	107.52	Diagnostic imaging, direct access; weighted average cost of currency code RD2
MRI scan (6)	147.25	Diagnostic imaging, direct access; weighted average cost of currency code RD0
Other diagnostic imaging (20)	70.64	Diagnostic imaging, direct access; weighted average cost of all codes
Bone density studies (5)	68.29	Diagnostic imaging, direct access; currency code RD50Z
Other diagnostic tests		
Electrocardiogram (31)	88.00	Directly accessed diagnostic services, currency code AA33C
Colonoscopy (6)	421.32	Outpatient, FZ51Z
Sigmoidoscopy (3)	205.85	Outpatient, FZ54Z
Bronchoscopy	458.52	Outpatient, DZ69A
Endoscopy (8)	495.97	Outpatient, FZ42A
Echocardiogram (6)	88.83	Directly accessed diagnostic services, currency code EY50Z
ECG ambulatory (1); ECG exercise (1)	40.35	Directly accessed diagnostic services, currency code EY51Z
Doppler ultrasound peripheral pulse (2)	75.85	Diagnostic imaging, direct access; currency code RD47Z

[a]Frequencies calculated for women included in the main analysis from 1 April 2006.

Table F.4: Mean costs per prescription issued (in UK 2016 prices) by BNF chapter, section, and paragraph

BNF chapter	BNF section	BNF paragraph
Gastrointestinal system (£4.8)	Dyspep&Gastro-Oesophageal Reflux Disease (£6.1)	Antacids and simeticone (£17.1); Compound alginates and proprietary indigestion preparations (£5.6)
	Antispasmod.&Other Drgs Alt.Gut Motility (£13.7)	No paragraphs
	Antisecretory Drugs+Mucosal Protectants (£1.9)	H2-receptor antagonists (£2.1); Selective antimuscarinics (£99.0); Chelates and complexes (£97.2); Prostaglandin analogues (£11.4); Proton pump inhibitors (£1.9)
	Acute Diarrhoea (£4.3)	Adsorbents and bulk-forming drugs (£1.3); Antimotility drugs (£4.3); Enkephalinase inhibitors (£12.4)
	Chronic Bowel Disorders (£44.0)	Aminosalicylates (£42.0); Corticosteroids (£80.5); Drugs affecting the immune response (£NA); Food allergy (£70.7)
	Laxatives (£5.0)	Bulk-forming laxatives (£4.7); Stimulant laxatives (£3.4); Faecal softeners[a] (£12.0); Osmotic laxatives (£5.6); Bowel cleansing preparations (£13.8); Peripheral opioid-receptor antagonists[a] (£194.5); Other drugs used in constipation (£55.5)
	Local Prepn for Anal & Rectal Disorders (£7.7)	Soothing haemorrhoidal preparations (£9.3); Compound haemorrhoidal preparations with corticosteroids (£5.1); Rectal sclerosants (£6.3); Management of anal fissures (£40.6)
	Stoma Care (£5.5)	No paragraphs
	Drugs Affecting Intestinal Secretions (£50.5)	Drugs affecting biliary composition and flow (£45.7); Bile acid sequestrants (£NA); Aprotinin (£NA); Pancreatin (£53.1)
Cardiovascular System (£3.4)	Positive Inotropic Drugs (£3.0)	Cardiac glycosides (£3.0); Phosphodiesterase type-3 inhibitors (£240.2)
	Diuretics (£1.6)	Thiazides and related diuretics (£1.5); Loop diuretics (£1.2); Potassium-sparing diuretics and aldosterone antagonists (£3.7); Potassium-sparing diuretics with other diuretics (£3.7); Osmotic diuretics (£11.7); Mercurial diuretics (£NA); Carbonic anhydrase inhibitors (£NA); Diuretics with potassium (£3.8)
	Anti-Arrhythmic Drugs (£9.3)	Management of arrhythmias (£NA); Drugs for arrhythmias (£9.3)
	Beta-Adrenoceptor Blocking Drugs (£1.8)	No paragraphs
	Hypertension and Heart Failure (£2.1)	Vasodilator antihypertensive drugs (£17.3); Centrally acting antihypertensive drugs (£5.8); Adrenergic neurone blocking drugs (£NA); Alpha-adrenoceptor blocking drugs (£2.6); Drugs affecting the renin-angiotensin system (£2.0)
	Nit,Calc Block & Other Antianginal Drugs (£4.0)	Nitrates (£4.8); Calcium-channel blockers (£3.3); Other antianginal drugs (£11.7); Peripheral vasodilators and related drugs (£9.8)
	Sympathomimetics (£56.1)	Inotropic sympathomimetics (£1222.9); Vasoconstrictor sympathomimetics (£56.2); Cardiopulmonary resuscitation (£26.1)
	Anticoagulants And Protamine (£18.3)	Parenteral anticoagulants (£110.3); Oral anticoagulants (£15.7); Protamine sulfate (£NA)
	Antiplatelet Drugs (£2.0)	No paragraphs
	Stable Angina, Acute/Crnry Synd&Fibrin (£1800.0)	Management of stable angina and acute coronary syndromes (£NA); Fibrinolytic drugs[a] (£6.3)
	Antifibrinolytic Drugs & Haemostatics (£6.0)	No paragraphs
	Lipid-Regulating Drugs (£3.1)	No paragraphs
	Local Sclerosants (£9.6)	No paragraphs
Respiratory System (£15.6)	Bronchodilators (£10.6)	Adrenoceptor agonists (£4.2); Antimuscarinic bronchodilators (£34.5); Theophylline (£3.4); Compound bronchodilator preparations (£33.7); Peak flow meters, inhaler devices and nebulisers (£NA)
	Corticosteroids (Respiratory) (£33.7)	No paragraphs

Table F.4 continued: Mean costs per prescription issued (in UK 2016 prices) by BNF chapter, section, and paragraph

BNF chapter	BNF section	BNF paragraph
	Cromoglycate,Rel,Leukotriene Antagonists (£2.9)	Cromoglicate and related therapy (£39.0); Leukotriene receptor antagonists (£2.7); Phosphodiesterase type-4 inhibitors (£35.7)
	Antihist, Hyposensit & Allergic Emergen (£4.1)	Antihistamines (£2.9); Allergen immunotherapy (£121.7); Allergic emergencies (£52.5)
	Mucolytics (£15.4)	No paragraphs
	Aromatic Inhalations (£1.9)	No paragraphs
	Cough Preparations (£1.5)	Cough suppressants (£1.9); Demulcent and expectorant cough preparations[a] (£3.2)
	Systemic Nasal Decongestants (£3.0)	No paragraphs
	Antifibrotics (£1022.8)	No paragraphs
Central Nervous System (£8.9)	Hypnotics And Anxiolytics (£4.3)	Hypnotics (£5.8); Anxiolytics (£2.2); Barbiturates (£100.4)
	Drugs Used In Psychoses & Rel.Disorders (£8.3)	Antipsychotic drugs (£7.4); Antipsychotic depot injections (£64.5); Drugs used for mania and hypomania (£6.9)
	Antidepressant Drugs (£4.1)	Tricyclic and related antidepressant drugs (£7.5); Monoamine-oxidase inhibitors (£138.6); Selective serotonin re-uptake inhibitors (£1.6); Other antidepressant drugs (£6.0)
	CNS Stimulants and drugs used for ADHD (£43.2)	No paragraphs
	Drugs used in the Treatment of Obesity (£22.1)	Anti-obesity drugs acting on the gastro-intestinal tract (£22.1); Centrally acting appetite suppressants (£2.0)
	Obesity (£22.1)	Anti-obesity drugs acting on the gastro-intestinal tract (£22.1); Centrally acting appetite suppressants (£2.0)
	Drugs Used In Nausea And Vertigo (£5.5)	No paragraphs
	Analgesics (£7.8)	Non-opioid analgesics and compound analgesic preparations (£4.9); Opioid analgesics (£12.3); Neuropathic pain[a] (£17.3); Antimigraine drugs (£11.5)
	Antiepileptics (£22.4)	Control of the epilepsies (£22.1); Drugs used in status epilepticus (£123.9); Febrile convulsions (£NA)
	Antiepileptic Drugs (£22.4)	Control of the epilepsies (£22.1); Drugs used in status epilepticus (£123.9); Febrile convulsions (£NA)
	Drugs Used In Park'ism/Related Disorders (£25.2)	Dopaminergic drugs used in Parkinson's disease (£27.4); Antimuscarinic drugs used in parkinsonism (£16.3); Drugs used in essential tremor, chorea, tics, and related disorders (£41.5)
	Drugs Used In Substance Dependence (£13.9)	Alcohol dependence (£25.9); Nicotine dependence (£28.9); Opioid dependence (£8.4)
	Drugs for Dementia (£8.2)	No paragraphs
	Dementia (£8.2)	No paragraphs
Infections (£5.0)	Antibacterial Drugs (£5.0)	Penicillins (£3.3); Cephalosporins, carbapenems, and other beta-lactams (£3.2); Tetracyclines (£5.3); Aminoglycosides (£298.5); Macrolides (£4.8); Clindamycin (£37.0); Some other antibacterials (£182.4); Sulfonamides and trimethoprim (£2.1); Antituberculosis drugs (£36.2); Antileprotic drugs (£72.8); Metronidazole and tinidazole (£3.8); Quinolones (£5.5); Urinary-tract infections (£13.4)
	Antifungal Drugs (£5.3)	Triazole antifungals (£8.4); Imidazole antifungals (£369.7); Polyene antifungals (£2.3); Echinocandin antifungals (£196.1); Other antifungals (£5.2)
	Antiviral Drugs (£11.8)	HIV infection[a] (£94.9); Herpesvirus infections (£9.0); Viral hepatitis[a] (£23.1); Influenza (£15.2); Respiratory syncytial virus[a] (£16.0)

Table F.4 continued: Mean costs per prescription issued (in UK 2016 prices) by BNF chapter, section, and paragraph

BNF chapter	BNF section	BNF paragraph
	Antiprotozoal Drugs (£2.3)	Antimalarials (£2.1); Amoebicides (£85.7); Trichomonacides (£NA); Antigiardial drugs (£184.6); Leishmaniacides (£236.4); Trypanocides (£NA); Drugs for toxoplasmosis (£NA); Drugs for pneumocystis pneumonia (£604.5)
	Anthelmintics (£2.9)	Drugs for threadworms (£1.4); Ascaricides[a] (£1.4); Drugs for tapeworm infections (£196.8); Drugs for hookworms (£NA); Schistosomicides (£290.4); Filaricides (£221.0); Drugs for cutaneous larva migrans (£NA); Drugs for strongyloidiasis (£NA)
Endocrine system (£13.2)	Drugs Used In Diabetes (£19.0)	Insulins (£49.5); Antidiabetic drugs (£11.9); Diabetic ketoacidosis (£NA); Treatment of hypoglycaemia (£13.2); Treatment of diabetic nephropathy and neuropathy (£NA); Diagnostic and monitoring devices for diabetes mellitus (£26.0)
	Thyroid And Antithyroid Drugs (£5.2)	Thyroid hormones (£4.2); Antithyroid drugs (£60.1)
	Corticosteroids (Endocrine) (£14.7)	Replacement therapy (£28.5); Glucocorticoid therapy (£14.0)
	Sex Hormones (£10.4)	Female sex hormones and their modulators (£13.7); Male sex hormones[a] and antagonists (£42.3); Anabolic steroids[a] (£49.8)
	Hypothalamic & Pituitary Hormones & Antioest (£127.4)	Hypothalamic and anterior pituitary hormones and anti-oestrogens (£468.9); Posterior pituitary hormones and antagonists (£41.1)
	Drugs Affecting Bone Metabolism (£3.0)	Calcitonin and parathyroid hormone[a] (£154.5); Bisphosphonates and other drugs affecting bone metabolism (£2.9)
	Other Endocrine Drugs (£63.9)	Bromocriptine and other dopaminergic drugs (£59.0); Drugs affecting gonadotrophins (£39.2); Cushing's Syndrome (£409.4); Somatomedins[a] (£20.4)
Obstetrics, gynaecology, and urinary-tract disorders (£11.9)	Drugs Used In Obstetrics (£132.6)	Prostaglandins and oxytocics (£132.6); Mifepristone (£NA); Myometrial relaxants (£NA)
	Treatment Of Vaginal & Vulval Conditions (£11.8)	Preparations for vaginal and vulval changes (£17.0); Vaginal and vulval infections (£6.0)
	Contraceptives (£9.3)	Combined hormonal contraceptives (£7.7); Progestogen-only contraceptives (£10.9); Spermicidal contraceptives (£12.9); Contraceptive devices (£NA); Emergency contraception (£7.1)
	Drugs For Genito-Urinary Disorders (£13.2)	Drugs for urinary retention (£5.9); Drugs for urinary frequency, enuresis, and incontinence (£20.7); Drugs used in urological pain (£10.2); Bladder instillations and urological surgery (£46.2); Drugs for erectile dysfunction (£13.2); Drugs for premature ejaculation (£36.3)
Malignant disease and immunosupression (£50.7)	Cytotoxic Drugs (£91.7)	Alkylating drugs (£76.1); Anthracyclines and other cytotoxic antibiotics (£210.2); Antimetabolites (£94.0); Vinca alkaloids and etoposide (£NA); Other antineoplastic drugs (£87.6)
	Drugs Affecting The Immune Response (£46.1)	Antiproliferative immunosuppressants (£12.9); Corticosteroids and other immunosuppressants[a] (£40.5); Anti-lymphocyte monoclonal antibodies (£436.6); Other immunomodulating drugs (£1442.8)
	Sex Hormones & Antag In Malig Disease (£50.5)	Oestrogens (£136.5); Progestogens (£38.6); Androgens (£NA); Hormone antagonists (£50.1)
Nutrition and blood (£11.1)	Anaemias + Other Blood Disorders (£3.2)	Iron-deficiency anaemias (£3.8); Drugs used in megaloblastic anaemias (£2.1); Drugs used in hypoplastic, haemolytic, and renal anaemias (£312.1); Drugs used in platelet disorders (£520.1); G6PD deficiency (£NA); Drugs used in neutropenia (£464.8); Drugs used to mobilise stem cells (£NA)
	Fluids And Electrolytes (£7.5)	Oral preparations for fluid and electrolyte imbalance (£7.3); Parenteral preparations for fluid and electrolyte imbalance (£8.2)
	Intravenous Nutrition (£39.7)	No paragraphs
	Oral Nutrition (£49.1)	Foods for special diets (£44.3); Enteral nutrition (£51.9)

Table F.4 continued: Mean costs per prescription issued (in UK 2016 prices) by BNF chapter, section, and paragraph

BNF chapter	BNF section	BNF paragraph
	Minerals (£22.6)	Calcium and magnesium (£28.7); Calcium and magnesium (£28.7); Phosphorus (£54.4); Fluoride (£16.0); Zinc (£14.5); Selenium (£71.7)
	Vitamins (£4.8)	Vitamin A (£5.3); Vitamin B group (£4.5); Vitamin C (£25.1); Vitamin D (£4.6); Vitamin E (£34.0); Vitamin K (£48.3); Multivitamin preparations (£3.4)
	Bitters And Tonics (£463.0)	No paragraphs
	Metabolic Disorders (£896.6)	Drugs used in metabolic disorders (£896.6); Acute porphyrias (£NA)
	Foods (£70.4)	No paragraphs
	Compound Vit/Mineral Formulations (£7.5)	No paragraphs
	Health Supplements (£35.0)	No paragraphs
	Other Health Supplements (£10.7)	No paragraphs
Musculoskeletal and joint diseases (£6.1)	Drugs Used In Rheumatic Diseases & Gout (£5.9)	Non-steroidal anti-inflammatory drugs (£4.5); Corticosteroids (£4.7); Drugs that suppress the rheumatic disease process (£18.1); Gout and cytotoxic-induced hyperuricaemia (£2.5); Other drugs for rheumatic diseases (£20.2)
	Drugs Used In Neuromuscular Disorders (£11.8)	Drugs that enhance neuromuscular transmission (£53.8); Skeletal muscle relaxants (£9.9)
	Soft-Tissue Disorders & Topical Pain Rel (£5.5)	Enzymes (£6.9); Rubefacients, topical NSAIDs, capsaicin, and poultices (£5.5)
Eye (£7.5)	Anti-Infective Eye Preparations (£5.6)	Antibacterials (£5.4); Antifungals (£321.8); Antivirals (£18.2)
	Corti'roids & Other Anti-Inflamm.Preps. (£4.4)	Corticosteroids (£5.9); Other anti-inflammatory preparations (£3.6)
	Mydriatics And Cycloplegics (£28.8)	No paragraphs
	Treatment Of Glaucoma (£10.4)	No paragraphs
	Local Anaesthetics (£3.9)	No paragraphs
	Miscellaneous Ophthalmic Preparations (£4.7)	Tear deficiency, ocular lubricants, and astringents (£4.5); Ocular diagnostic and peri-operative preparations and photodynamic treatment (£17.9)
Ear, nose, and oropharynx (£6.1)	Drugs Acting On The Ear (£5.8)	Otitis externa (£6.0); Otitis media (£6.8); Removal of earwax (£2.4)
	Drugs Acting On The Nose (£6.3)	Drugs used in nasal allergy (£5.5); Topical nasal decongestants (£29.4); Nasal preparations for infection (£2.8)
	Drugs Acting On The Oropharynx (£5.6)	Drugs for oral ulceration and inflammation (£5.9); Oropharyngeal anti-infective drugs (£4.0); Lozenges and sprays (£3.0); Mouthwashes, gargles, and dentifrices (£4.0); Treatment of dry mouth[a] (£9.7)
Skin (£7.9)	Vehicles & Emulsifying Agents (£4.3)	Vehicles (£4.3); Suitable quantities for prescribing (£NA); Excipients and sensitisation (£NA)
	Management of Skin Conditions (£4.3)	Vehicles (£4.3); Suitable quantities for prescribing (£NA); Excipients and sensitisation (£NA)
	Emollient & Barrier Preparations (£6.7)	Emollients (£6.9); Barrier preparations (£3.2)
	Top Local Anaesthetics & Antipruritics (£6.2)	No paragraphs
	Topical Corticosteroids (£4.9)	No paragraphs
	Preparations For Eczema And Psoriasis (£41.9)	Preparations for eczema (£78.7); Preparations for psoriasis (£42.3); Drugs affecting the immune response (£35.3)
	Acne and Rosacea (£14.7)	Topical preparations for acne (£14.4); Oral preparations for acne (£16.5); Topical preparations for rosacea (£36.0)
	Preparations For Warts And Calluses (£10.2)	No paragraphs
	Sunscreens And Camouflagers (£31.4)	Sunscreen preparations (£32.9); Camouflagers (£18.1)

Table F.4 continued: Mean costs per prescription issued (in UK 2016 prices) by BNF chapter, section, and paragraph

BNF chapter	BNF section	BNF paragraph
	Shampoo & Other Preps For Scalp & Hair Cond (£5.8)	No paragraphs
	Anti-Infective Skin Preparations (£4.7)	Antibacterial preparations (£5.1); Antifungal preparations (£3.5); Antiviral preparations (£3.5); Parasiticidal preparations (£12.8); Preparations for minor cuts and abrasions (£4.7)
	Skin Cleansers,Antiseptics & Desloughing (£8.6)	Alcohols and saline (£5.9); Chlorhexidine salts (£7.0); Cationic surfactants and soaps (£9.0); Iodine (£8.3); Phenolics (£7.1); Oxidisers and dyes (£14.2); Desloughing agents (£249.5)
	Antiperspirants (£6.3)	No paragraphs
	Wound Management Products (£29.8)	No paragraphs
	Topical Circulatory Preparations (£4.9)	No paragraphs
	Miscellaneous Topical Preparations (£137.3)	No paragraphs
Immunlogical products and vaccines (£9.1)	Vaccines And Antisera (£9.1)	No paragraphs
	Immunoglobulins (£342.2)	Normal immunoglobulin (£441.5); Disease-specific immunoglobulins (£212.4); Anti-D (Rh0) immunoglobulin (£79.0)
Anaesthesia (£12.6)	General Anaesthesia (£12.6)	Intravenous anaesthetics (£79.3); Inhalational anaesthetics (£36.6); Antimuscarinic drugs (£21.7); Sedative and analgesic peri-operative drugs (£7.7); Neuromuscular blocking drugs (£NA); Drugs for reversal of neuromuscular blockade (£NA); Antagonists for central and respiratory depression (£42.6); Drugs for malignant hyperthermia (£NA)
	Local Anaesthesia (£12.6)	No paragraphs
Other (£20.9)	Preparations used in diagnosis (£118.2)	No paragraphs
	Other drugs and preparations (£28.0)	No paragraphs
	Dressings (£21.0)	No paragraphs
	Appliances (£13.4)	No paragraphs
	Incontinence appliances (£25.7)	No paragraphs
	Stoma appliances (£50.8)	No paragraphs

[a]In these paragraphs the case mix of drugs types observed in CPRD differed substantially from that in the PCA. For these paragraphs, costs were based on the case mix of drugs observed in CPRD and unit costs of these drugs in PCA.

Table F.5: Code lists used to identify diabetes

Diagnosis in Hospital Episode Statistics	Appearance of any of the following ICD-10 codes in any diagnostic position in an admission: E10, E11, E13, and E14
Diagnosis in Clinical Practice Research Datalink	Appearance of any of the following READ version 2 codes in CPRD data: C100112, C10F.00, C10FJ00, 66A4.00, C109.00, C109.11, 66A3.00, C109700, C10FC00, C10F500, C100111, C109600, C109.12, C109G11, C109012, C109.13, C109J12, C109J00, C10FM00, C10FB00, C10F600, C10F000, C10N.00, C10F.11, C109711, C109G00, C109C12, ZC2CA00, C10FQ00, C10F700, C10FL00, 66AV.00, C109900, C10FN00, C107200, C10A100, C10F200, C10FK00, C109400, C104100, C10FH00, C109K00, C10D.00, C109J11, C10FF00, C106100, C10F811, C109500, C109H00, C105100, C109612, C102100, C10F311, C10C.00, C109D00, C109E12, C10FE00, C109B00, C109712, C109212, C109512, C10C.11, C10FD00, C10F711, C10F100, C109B11, C109H11, C10F900, C109E11, C10F400, C10F611, C109G12, C109011, C109100, C10FB11, L180600, C109A11, C10G.00, C10FP00, C109000, C10F911, C109F00, C10F800, C101100, C109F11, C109411, 66AO.00, C109200, C109D11, C107400, C10F011, C109611, C10FG00, C103y00, C109C00, C109111, C10D.11, C109F12, C10FL11, C109D12, C109511, C109300, C10FA00, C107100, C10FR00, C10z100, C109C11, C10FJ11, C10F300, C109412, C109H12, C109211, C109E00, C109112, C109A00, 66Ao.00, C10FM11, C10F411, C10N100, C10FE11, C10FA11, C10FS00, C10ER00, C10F211, C10FD11, C10F111, 66At100, C10FC11, 66At111, C10FG11, C10F511, C10FF11, C109912, C10FP11, C10FN11, and C10FK11
Receipt of diabetes prescription	Record of any diabetes drug (British National Formulary section 0601) being issued
Diagnostic tests indicative of diabetes	HbA1c tests (entity code: 275) with result $\geq$ 6.5% or $\geq$ 48 mmol/mol; fasting glucose (entity code: 274) with a result $\geq$ 7.0%; glucose test of unknown type (entity code: 213) with result $\geq$ 11.0%. An individual was considered to have diabetes if they had more than one test result (of either type) indicative of diabetes.

Table F.6: Regression results for annual costs of primary care services

	Mean (95% confidence interval)		
Variable	**Consultations**	**Therapies**	**Tests**
Body mass index in kg/m^2 (ref: 20-22.4)			
18.5-19.9	1.01 (0.97-1.05)	1.13 (1.04-1.22)	1.07 (0.96-1.19)
22.5-24.9	1.03 (1.01-1.05)	1.03 (0.99-1.07)	0.98 (0.93-1.03)
25-27.4	1.09 (1.07-1.11)	1.16 (1.12-1.21)	1.00 (0.95-1.06)
27.5-29.9	1.17 (1.15-1.20)	1.33 (1.27-1.40)	0.98 (0.92-1.04)
30-34.9	1.31 (1.28-1.34)	1.63 (1.56-1.70)	0.97 (0.91-1.04)
35-39.9	1.49 (1.44-1.54)	2.03 (1.91-2.15)	0.98 (0.88-1.08)
40+	1.65 (1.56-1.74)	2.59 (2.38-2.81)	1.14 (0.96-1.36)
Age in years (ref: <60 years)			
60-64	1.11 (1.08-1.13)	1.17 (1.06-1.29)	1.03 (0.98-1.09)
65-69	1.28 (1.25-1.31)	1.45 (1.30-1.62)	1.16 (1.09-1.23)
70-74	1.50 (1.46-1.54)	1.78 (1.60-1.99)	1.24 (1.16-1.33)
75+	1.78 (1.73-1.83)	2.16 (1.93-2.42)	1.37 (1.26-1.48)
Deprivation quintile (ref: least deprived)			
2	0.98 (0.96-0.99)	1.03 (0.99-1.07)	1.02 (0.97-1.07)
3	0.99 (0.98-1.01)	1.06 (1.02-1.10)	1.02 (0.97-1.07)
4	1.04 (1.02-1.06)	1.13 (1.08-1.17)	1.01 (0.95-1.06)
Most deprived	1.07 (1.05-1.09)	1.23 (1.19-1.28)	1.00 (0.95-1.06)
Missing	1.06 (0.99-1.13)	1.07 (0.94-1.22)	0.55 (0.43-0.70)
Region of recruitment (ref: Oxford)			
East Anglia	0.92 (0.89-0.95)	1.09 (1.03-1.16)	1.29 (1.20-1.40)
South West	1.03 (1.01-1.05)	1.08 (1.03-1.12)	0.78 (0.73-0.82)
Thames	0.88 (0.86-0.90)	0.98 (0.94-1.03)	0.98 (0.92-1.04)
West Midlands	0.95 (0.93-0.97)	1.03 (0.98-1.08)	0.38 (0.35-0.42)
North Yorkshire	0.86 (0.84-0.89)	1.19 (1.12-1.26)	1.22 (1.13-1.33)
Trent	0.93 (0.90-0.95)	1.20 (1.11-1.30)	0.76 (0.70-0.82)
North West (Mersey)	0.87 (0.85-0.90)	1.18 (1.12-1.25)	1.04 (0.96-1.13)
North West (Manc/Lancs)	0.87 (0.85-0.89)	1.23 (1.18-1.30)	0.98 (0.92-1.05)
Parity (ref: none)			
1	1.11 (1.06-1.17)	1.11 (1.02-1.21)	0.87 (0.77-0.98)
2	1.07 (1.02-1.13)	1.03 (0.94-1.13)	0.86 (0.75-0.98)
3+	1.10 (1.04-1.16)	1.09 (1.00-1.20)	0.86 (0.75-0.98)
Missing	1.08 (0.94-1.24)	1.27 (0.84-1.93)	0.81 (0.49-1.32)
Age at birth of first child (ref: <25 years)			
25-29	0.95 (0.94-0.97)	0.89 (0.87-0.92)	0.96 (0.92-1.00)
30+	0.95 (0.93-0.98)	0.90 (0.86-0.95)	0.97 (0.91-1.04)
Not applicable or missing	1.05 (1.00-1.11)	1.05 (0.97-1.14)	0.87 (0.77-0.98)
Smoking status (ref: ever smoker)			
Former	1.10 (1.08-1.11)	1.18 (1.15-1.21)	1.05 (1.01-1.10)
Current	1.16 (1.14-1.18)	1.43 (1.38-1.48)	1.03 (0.98-1.08)
Missing	1.06 (1.03-1.09)	1.07 (1.02-1.13)	1.04 (0.96-1.12)
Current alcohol drinker (ref: no)			

Table F.6 continued: Regression results for annual costs of primary care services

Variable	Consultations	Therapies	Tests
Yes	0.91 (0.85-0.87)	0.75 (0.85-0.87)	0.95 (0.85-0.87)
Missing	0.98 (0.97-1.07)	0.93 (0.97-1.07)	0.99 (0.97-1.07)
Highest qualification (ref: none)			
Technical qualification	0.97 (0.95-0.97)	0.92 (0.95-0.97)	0.96 (0.95-0.97)
Secondary	0.94 (0.91-0.93)	0.88 (0.91-0.93)	0.99 (0.91-0.93)
Tertiary	0.95 (0.89-0.92)	0.89 (0.89-0.92)	1.04 (0.89-0.92)
Missing	1.06 (1.02-1.08)	1.01 (1.02-1.08)	0.82 (1.02-1.08)
Financial year (ref: 2006-07)			
2007-08	1.00 (1.05-1.07)	1.04 (1.05-1.07)	1.04 (1.05-1.07)
2008-09	1.01 (1.09-1.12)	1.09 (1.09-1.12)	1.13 (1.09-1.12)
2009-10	1.02 (1.11-1.14)	1.13 (1.11-1.14)	1.21 (1.11-1.14)
2010-11	1.03 (1.11-1.14)	1.16 (1.11-1.14)	1.21 (1.11-1.14)
2011-12	1.05 (1.15-1.18)	1.19 (1.15-1.18)	1.27 (1.15-1.18)
2012-13	1.06 (1.17-1.20)	1.23 (1.17-1.20)	1.33 (1.17-1.20)
2013-14	1.14 (1.20-1.23)	1.38 (1.20-1.23)	1.23 (1.20-1.23)

Values are mean relative costs (95% confidence intervals) compared to the defined reference group for each variable.

Table F.7: Estimates of annual consultation costs in relation to body mass index under various sensitivity analyses

	Body mass index category (kg/m^2)								
	18.5-19.9	20-22.4	22.5-24.9	25-27.4	27.5-29.9	30-34.9	35-39.9	≥ 40	Trend[a]
Base case analysis	0.9 (-3.8, 5.8)	0.0 (-2.0, 2.1)	2.7 (1.2, 4.3)	9.1 (7.3, 10.9)	17.5 (15.1, 19.8)	30.7 (27.8, 33.5)	48.9 (42.9, 55.3)	64.5 (53.5, 76.3)	5.2 (4.8, 5.6)
Including pre-existing cancer	0.8 (-3.8, 5.6)	0.0 (-2.0, 2.1)	2.6 (1.1, 4.2)	9.2 (7.4, 11.0)	17.4 (15.1, 19.7)	30.9 (28.1, 33.8)	48.9 (42.9, 55.1)	64.1 (53.2, 75.7)	5.2 (4.8, 5.6)
Using data from all years	2.9 (-1.3, 7.4)	0.0 (-1.8, 1.8)	2.9 (1.5, 4.3)	9.5 (7.9, 11.1)	18.1 (16.0, 20.2)	30.7 (28.2, 33.3)	49.6 (44.3, 55.1)	60.8 (51.9, 70.4)	5.1 (4.8, 5.5)
Excluding BMI > 50 kg/m^2	0.9 (-3.8, 5.8)	0.0 (-2.0, 2.1)	2.7 (1.2, 4.3)	9.1 (7.3, 10.9)	17.5 (15.1, 19.8)	30.6 (27.8, 33.5)	48.9 (42.9, 55.3)	62.1 (51.2, 73.9)	5.2 (4.8, 5.6)
Never smokers only	-0.9 (-7.4, 6.2)	0.0 (-2.7, 2.8)	4.7 (2.6, 6.9)	10.0 (7.5, 12.5)	18.6 (15.1, 22.2)	30.7 (26.7, 34.7)	54.6 (45.5, 64.4)	66.8 (49.6, 85.9)	5.3 (4.7, 5.9)
Excluding pre-existing heart disease & stroke	0.0 (-4.7, 4.9)	0.0 (-2.1, 2.1)	2.9 (1.4, 4.5)	9.2 (7.4, 11.0)	17.4 (15.0, 19.8)	30.8 (27.9, 33.8)	47.6 (41.1, 54.3)	61.7 (50.2, 74.0)	5.1 (4.7, 5.5)
Exclude year fatal events and 2 preceding years	0.8 (-3.9, 5.8)	0.0 (-2.0, 2.1)	3.0 (1.4, 4.6)	9.4 (7.6, 11.3)	18.1 (15.8, 20.5)	31.3 (28.5, 34.3)	49.5 (43.4, 55.8)	66.6 (55.2, 78.8)	5.3 (4.9, 5.7)
Imputing unknown staff roles	0.3 (-4.2, 4.9)	0.0 (-2.0, 2.0)	2.7 (1.2, 4.3)	9.1 (7.4, 10.9)	17.1 (14.9, 19.4)	30.8 (28.0, 33.5)	48.3 (42.5, 54.5)	63.6 (52.9, 75.1)	5.2 (4.8, 5.6)
Mean measured BMI									5.1 (4.7, 5.5)

[a]Percentage difference in annual costs per 2 kg/m^2 higher BMI above 20 kg/m^2.

Table F.8: Estimates of annual prescription costs in relation to body mass index under various sensitivity analyses

	Body mass index category (kg/m^2)								
	18.5-19.9	20-22.4	22.5-24.9	25-27.4	27.5-29.9	30-34.9	35-39.9	≥ 40	Trend[a]
Base case analysis	12.9 (2.5, 24.3)	0.0 (-4.0, 4.2)	2.6 (-0.6, 5.8)	16.4 (12.7, 20.2)	33.1 (26.8, 39.7)	62.8 (56.7, 69.1)	103.0 (90.1, 116.9)	158.7 (134.1, 185.9)	9.9 (9.2, 10.6)
Including pre-existing cancer	12.8 (2.6, 24.0)	0.0 (-4.0, 4.2)	2.1 (-1.0, 5.3)	16.6 (12.6, 20.7)	33.1 (27.0, 39.6)	63.7 (57.2, 70.5)	102.3 (89.5, 115.9)	156.4 (132.3, 183.1)	9.9 (9.2, 10.6)
Using data from all years	16.5 (6.1, 27.9)	0.0 (-3.9, 4.1)	1.1 (-1.9, 4.1)	12.8 (9.4, 16.4)	30.2 (24.5, 36.1)	57.3 (51.7, 63.1)	96.5 (84.7, 109.1)	142.8 (120.7, 167.1)	9.4 (8.7, 10.0)
Excluding BMI > 50 kg/m^2	12.9 (2.5, 24.3)	0.0 (-4.0, 4.2)	2.6 (-0.6, 5.8)	16.3 (12.7, 20.1)	33.1 (26.8, 39.7)	62.8 (56.7, 69.1)	103.1 (90.1, 116.9)	153.8 (129.1, 181.3)	10.0 (9.3, 10.7)
Never smokers only	-2.1 (-13.8, 11.2)	0.0 (-6.2, 6.7)	4.1 (-0.5, 8.8)	17.9 (12.3, 23.7)	37.4 (29.8, 45.5)	63.1 (54.1, 72.5)	120.1 (99.4, 142.9)	177.9 (137.2, 225.5)	10.5 (9.5, 11.6)
Excluding pre-existing heart disease & stroke	12.2 (1.5, 24.0)	0.0 (-4.2, 4.4)	3.0 (-0.3, 6.3)	15.8 (12.0, 19.7)	31.9 (25.2, 39.0)	60.8 (54.5, 67.3)	95.4 (82.2, 109.5)	148.8 (124.2, 176.1)	9.5 (8.8, 10.2)
Exclude year fatal events and 2 preceding years	12.8 (2.0, 24.7)	0.0 (-4.1, 4.3)	2.5 (-0.7, 5.8)	16.5 (12.8, 20.4)	34.2 (27.7, 41.1)	63.8 (57.6, 70.3)	105.2 (91.8, 119.5)	162.7 (136.7, 191.5)	10.1 (9.4, 10.8)
Mean measured BMI									9.6 (8.9, 10.3)

[a]Percentage difference in annual costs per 2 kg/m^2 higher BMI above 20 kg/m^2.

Table F.9: Estimates of annual monitoring and diagnostic test costs in relation to body mass index under various sensitivity analyses

	Body mass index category (kg/m^2)								
	18.5-19.9	20-22.4	22.5-24.9	25-27.4	27.5-29.9	30-34.9	35-39.9	$\geq$ 40	Trend[a]
Base case analysis	6.7	0.0	-2.0	0.4	-1.8	-2.6	-2.4	14.4	0.0
	(-6.0, 21.1)	(-5.4, 5.8)	(-6.0, 2.1)	(-4.2, 5.2)	(-7.4, 4.1)	(-8.6, 3.9)	(-13.1, 9.6)	(-8.0, 42.1)	(-1.0, 1.1)
Including pre-existing cancer	5.6	0.0	-2.2	0.2	-1.6	-2.9	-3.1	13.6	0.0
	(-6.8, 19.7)	(-5.4, 5.7)	(-6.1, 1.8)	(-4.3, 5.0)	(-7.2, 4.2)	(-8.9, 3.5)	(-13.7, 8.7)	(-8.4, 40.9)	(-1.1, 1.1)
Using data from all years	6.3	0.0	-1.4	1.4	-1.2	-2.0	-2.4	11.3	0.0
	(-5.4, 19.5)	(-4.8, 5.1)	(-5.0, 2.4)	(-2.9, 5.9)	(-6.3, 4.2)	(-7.6, 3.9)	(-12.2, 8.4)	(-9.4, 36.9)	(-1.0, 1.0)
Excluding BMI $>$ 50 kg/m^2	6.7	0.0	-2.0	0.4	-1.8	-2.6	-2.4	12.6	-0.1
	(-6.0, 21.2)	(-5.4, 5.8)	(-6.0, 2.0)	(-4.2, 5.2)	(-7.4, 4.0)	(-8.6, 3.9)	(-13.1, 9.6)	(-10.1, 40.9)	(-1.1, 1.1)
Never smokers only	2.5	0.0	-1.4	0.4	-0.3	-1.2	0.2	17.6	0.3
	(-14.7, 23.2)	(-7.0, 7.6)	(-6.8, 4.4)	(-5.9, 7.1)	(-8.6, 8.8)	(-9.8, 8.1)	(-14.8, 17.8)	(-17.7, 68.1)	(-1.2, 1.9)
Excluding pre-existing heart disease & stroke	8.0	0.0	-1.4	1.0	-0.5	-3.0	-6.3	10.9	-0.2
	(-5.1, 22.8)	(-5.5, 5.8)	(-5.5, 2.7)	(-3.7, 6.0)	(-6.3, 5.6)	(-9.2, 3.6)	(-16.9, 5.7)	(-11.8, 39.4)	(-1.3, 0.9)
Exclude year fatal events and 2 preceding years	8.4	0.0	-2.3	0.1	-1.7	-1.8	-1.8	16.1	0.2
	(-4.8, 23.3)	(-5.5, 5.8)	(-6.2, 1.9)	(-4.6, 4.9)	(-7.3, 4.2)	(-8.0, 4.8)	(-12.7, 10.5)	(-6.9, 44.9)	(-0.9, 1.3)
Mean measured BMI									0.0
									(-1.1, 1.0)

[a]Percentage difference in annual costs per 2 kg/m^2 higher BMI above 20 kg/m^2.

Table F.10: Annual prescription costs attributed to overweight and obesity among women aged 55 to 79 years in England, by therapeutic use

Body mass index (kg/m^2)	Total annual costs (£million)	Costs attributable to excess weight	
		Absolute annual costs (£ million), 99% CI	Proportion costs attributable (%), 99% CI
Gastrointestinal system [01]	119	13 (11, 15)	11 (10, 12)
Circulatory system [02]	248	73 (69, 77)	30 (29, 30)
Diuretics [0202]	16	6 (5, 6)	37 (37, 37)
Beta-adrenoceptor blocking drugs [0204]	16	4 (3, 4)	24 (23, 24)
Hypertension and heart failure [0205]	38	14 (13, 14)	36 (36, 36)
Nitrates, calcium-channel blockers, and other & antianginal drugs [0206]	43	12 (10, 13)	28 (27, 28)
Anticoagulants and protamine [0208]	54	17 (13, 19)	31 (31, 31)
Antiplatelet drugs [0209]	16	4 (4, 4)	26 (25, 26)
Lipid-regulating drugs [0212]	58	15 (14, 16)	26 (25, 26)
Other cardiovascular system	7	2 (1, 3)	28 (27, 33)
Respiratory system [03]	222	26 (14, 36)	12 (8, 14)
Analgesics [0407]	181	51 (46, 54)	28 (28, 28)
Central nervous system (excl. analgesics) [04]	163	20 (15, 25)	12 (11, 14)
Infections [05]	46	5 (3, 6)	10 (10, 10)
Drugs in Diabetes [0601]	153	102 (88, 113)	67 (65, 69)
Endocrine system (excluding diabetes) [06]	98	4 (3, 4)	4 (3, 4)
Obstetrics, gynaecology, and urinary-tract disorders [07]	65	13 (9, 16)	20 (17, 22)
Malignant disease and immunosuppression [08]	164	9 (2, 14)	5 (2, 7)
Nutrition and blood [09]	153	0 (0, 0)	0 (0, 0)
Musculoskeletal and joint diseases [10]	44	9 (8, 10)	20 (20, 21)
Eye [11]	46	0 (0, 0)	0 (0, 0)
Ear, nose, and oropharynx [12]	18	0 (0, 1)	3 (1, 4)
Skin [13]	47	8 (6, 9)	17 (15, 18)
Immunological products and vaccines [14]	13	0 (0, 0)	1 (0, 1)
Anaesthesia [15]	4	0 (0, 1)	9 (7, 10)
Dressings and appliances	132	48 (38, 56)	36 (35, 37)