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Imperial College of Medical Sciences

Outcomes of the Metabolically Healthy Obese

Osama M. Moussa
BM BCh, BSc, MRCS

Supervised by

Mr Paul Ziprin (MD, FRCS)

Mr Omar Khan (PhD, FRCS)

Mr Sanjay Purkayastha (MD, FRCS)

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Declaration of Authorship

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

Copyright Declaration

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Signed:

Osama M Moussa

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Outcomes of the Metabolically Healthy Obese

Abstract

Introduction: Obesity is a worldwide epidemic, Metabolic Healthy Obesity (MHO) is a vital sub cohort of obesity that needs to be further investigated and epidemiologically defined. This has not received the clinical and public health attention it deserves and would help in targeting lifestyle and interventions (surgery) to those best suited.

Methods: This thesis utilised long term primary care follow up using the Clinical Practice Research Datalink (CPRD) to quantify prevalence, investigate transition, investigate all-cause mortality in the sub-cohort and study intervention outcomes in the United Kingdom.

Results: Total number of 414,522 patients were extracted, of which 231,399 (55.8%) had a body mass index (BMI) recorded. This thesis utilised 180,560 patients after exclusions. The prevalence of MHO in the UK population was 128,191/180,560 (71.0%), of which 71,485/128,191 (55.8%) remained healthy (p=<0.01) with a mean follow-up of 68.2 months. There was a 3.7% mortality rate in the MHO vs the metabolically unhealthy cohort 7.1% with an increased risk of mortality associated with a high BMI, late age at diagnosis and male gender. Frequency of bariatric surgery was generally was performed more in the metabolically healthy than unhealthy, 2.2% vs 1.9%. On Cox regression analysis, bariatric surgery remained a nonsignificant independent factor of survival within both the metabolically healthy and unhealthy obese.

Conclusion: The implication of this study is that a diagnosis of obesity as an independent factor for immediate determination of impending complications. It is imperative that the body mass index of an obese patient is laid side by side with their metabolic rate indices. On the grounds of conclusions from this thesis, further studies into the pathophysiology of metabolically unhealthy obesity are necessary, with a close reference to the presence or absence of comorbidity.

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List of abbreviations

BMI – Body mass index
B – Unstandardised regression coefficient
CI – Confidence interval
CRP – C-reactive protein
CT – Computerised tomography
CVD – Cardiovascular disease
CPRD - Clinical Practice Research Database
DM - Diabetes Mellitus
GPRD - General Practice Research Database
HbA1c – Glycated haemoglobin
HDL – High density lipoprotein
HES - Hospital Episodes Statistics
HOMA – Homeostatic model assessment
HR – Hazard ratio
ICD - International Classification of Diseases
IDF – International Diabetes Federation
IFG - Impaired Fasting Glucose
IR - Insulin Resistance
IL-6 – Interleukin-6
MET – Metabolic equivalent
MH - Metabolically Healthy Obese
MOOSE – Meta-analysis of Observational Studies in Epidemiology
MRI – Magnetic resonance imaging
N – Sample size
NBSR - National Bariatric Surgical Registry
NCEP ATP III – National Cholesterol Education Program Adult Treatment Panel III
NHS - National Health Service
NHANES – National Health and Nutrition Examination Survey
PR – Prevalence ratio
QOL - Quality of Life
ONS - Office of National Statistics
OPCS - Office of Population and Census Surveys
OR – Odds ratio
RR – Relative risk
READ - Coding for primary care databases
WHO - World Health Organisation
kg/m² - Kilogram per metre-squared
mmHg – Millimetres of mercury
mmol/l – Millimoles per litre
µg/min – Micrograms per minute
mg/min – Milligrams per minute
km/h – Kilometres per hour
β – Standardised regression coefficient

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3. O.Moussa & M.Ardissino, S.Muttoni et al. Long-term effect of bariatric surgery on the incidence and outcomes of obesity-related peripheral vascular disease. Some Vasc surgery/Obesity journal?
4. Bariatrics surgery outcomes in the Metabolically healthy obese

5. Validity of CPRD – ONS
6. GP consultations before and after Bariatric surgery in the community

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(WITH PUBLISHED ABSTRACTS)

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Chapter 1

Introduction

1 – 1. Definition of Obesity

'Obesity affects not just appearance, but disease processes as well' —Malorye Allison

The Obesity Medicine Association's definition: "a chronic, relapsing, multifactorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences."

Obesity is defined in terms of being excessively overwieght in relation to one's height. It has also been defined as a condition characterised by the accumulation of excess adipose tissue and visceral fat that impairs physical and mental health. (1) There are various ways in which an individual's health relative to their weight can be categorised, but the commonly used approach is Body Mass Index (BMI), which is an instrument used to assess the association between weight and stature in people of all ages. BMI is calculated by dividing an individual's body weight by the square of his or her height [BMI = Weight (kg)/ Height $(m)^2$].

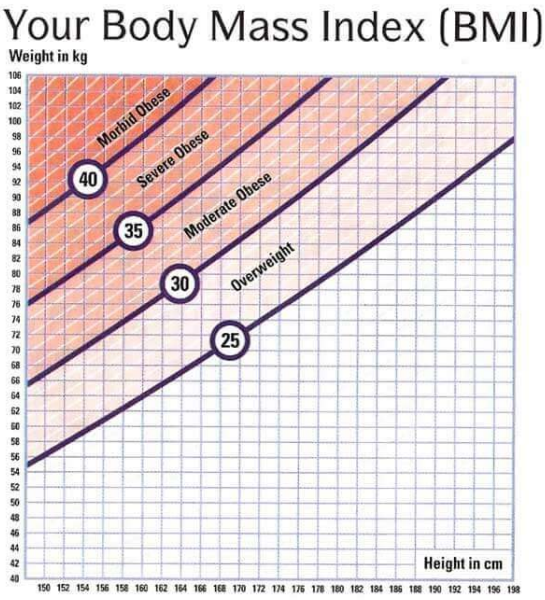
The most commonly used definition was established by the World Health Organisation (WHO) in 1997.(2) This is defined by the BMI and can be further evaluated in terms of fat distribution via the waist–hip ratio and total cardiovascular risk factors. The BMI is closely related to both percentage body fat and total body fat. In adults, specific BMI ranges are used to classify people as underweight (BMI < $18.5Kg/m^2$), normal weight ($18.5Kg/m^2 \leq$ BMI < $25.0Kg/m^2$), overweight ($25.0Kg/m^2 \leq$ BMI < $30.0Kg/m^2$) or obese (BMI ≥ $30.0Kg/m^2$). Children's weight however is classified according to how far their BMI deviates from the median BMI for their age and gender (Overweight > +1 standardard deviation; Obese > +2 standard deviations).(3)

The use of BMI in determining obesity however has limitations. For instance, it is only a surrogate measure of adiposity as it measures body weight rather than excess fat. It also does not take into account factors which may affect the relationship between BMI and body fat, such as age, ethnic backgrounds, muscle mass, and sex. There are several examples which illustrate the inappropriate use of body mass index in certain individuals, such as people with high muscle mass. Lastly, it does not reflect people's distribution of body fat. It has been shown that patients can have high levels of pericardial and visceral abdominal adipose tissue independent of subcutaneous fat.(4) These patients therefore may be in the normal BMI range, but still have associated metabolic abnormalites, such as diabetes and cardiovascular diease.(5) Despite these limitations, the use of BMI measurements in the evaluation of underweight, overweight and obesity in adults is used ubiquitously as it is cheap, easy to measure and demonstrate trends over time. More expensive methodologies to measure adiposity have been developed but they hae yet to make their way into clinical practice.(6) There is very good correlation between BMI and the percentage of body fat in large populations.

1 – 2. Classification of Obesity

The WHO classification of obesity is further categorised into three grades:

- Grade 1 obesity has a BMI of between 30 and 35 kg/m^2;
- Grade 2 has a BMI of between 35.1 and 40 kg/m^2, while
- Grade 3 has a BMI of greater than 40 kg/m^2. Grade 3 obesity is also described as "extreme" or "severe" obesity.



Patients with more severe grades of obesity have been demonstrated to be at increased risk of all-cause mortality. BMI association with mortality follows a J-shaped curve with a BMI between 20.0 Kg/m^2 and 25.0 Kg/m^2 having the lowest risk.(7) In addition to mortality those patients with higher BMIs typically suffer from a higher number of complications from obesity. Some of the causes of obesity include excessive food intake, sedentary lifestyle, genetic factors, or a combination of these elements.

1 – 3. Aetiology of obesity

Obesity is considered a chronic disease process that is prevalent in all age categories. It is currently a worldwide epidemic. Whilst obesity is typically viewed through the eyes of the layperson as a simple causation model of energy imbalance; when intake of calories exceeds expenditure of calories, with the surplus energy is stored as body weight. However, through extensive research an extensive model of the underlying factors that affect a person's risk of

becoming obese has been developed.(8) Obesity is thought to be a result of the interaction of environmental factors as well as genetic predisposition. This has been shown by large-scale epidemiological studies conducted in different populations.(9–11) Obesity has a heterogeneous phenotypic expression and the molecular mechanisms involved in its development are diverse. Three major factors modulate body weight: metabolic factors, diet, and physical exercise, each predisposed by genetic traits.

There is gradual emerging evidence that environmental and nutritional differences in certain periods of development can have effects on the predisposition to obesity and the development of metabolic diseases associated with this.(12) Some studies have demonstrated that a mother's weight during pregnancy can reflect and affect the later body composition of the infant in later life.(13) Maternal nutrition during gestation is also an important determinant of metabolic profiling and programming, which will have a subsequent impact on a child's weight. Certain other factors have been associated with higher risk of childhood obesity such as birth to diabetic mothers (14) and birth to mothers who smoke during pregnancy.(15)

It is thought that a large component of adolescent obesity is established before five years of age and studies disclose that childhood obesity typically persists into adulthood specifically when parents are obese.(16) As such, obesity in adolescence may be associated with increased risk of severe obesity in adulthood.(17)

Monogenic mouse models and human genetic syndromes have helped to elucidate specific genes associated with increased risk of obesity. However, the genetic predisposition to obesity in most people is a result of the interaction between the expressions of a number of different genes as identified by genome-wide association studies.(18) These genes may also be switched on or off according to environmental pressures, termed epigenetics., Specific genes produce a

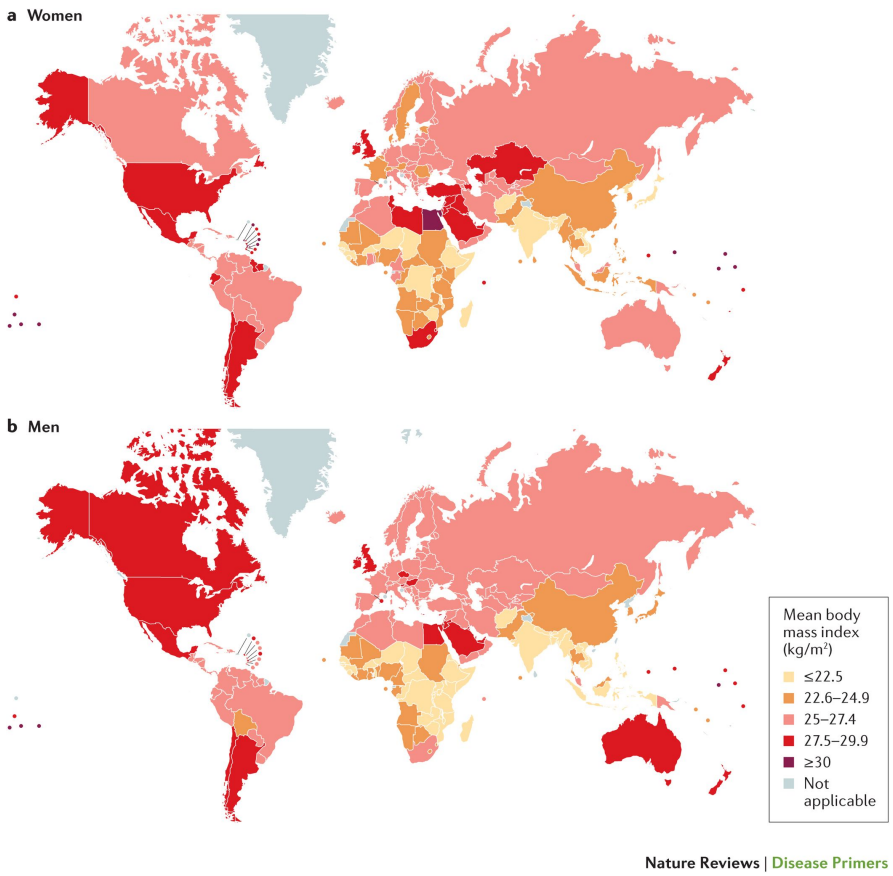
susceptibility risk for development of obesity by accounting for variations in energy requirements, fuel utilisation, muscle metabolic characteristics, and taste preferences.

This constellation of genetic factors takes place amongst the backdrop of increasingly obesogenic societal factors. Declining levels of physical labour as populations move from rural to urban settings and abandon walking in favour of driving, labour-saving devices in the home, and the replacement of active sport by television and computer games all contribute to an increasingly sedentary lifestyle. Consumers are now provided easy access to calorie-dense and nutrient-poor food at increasingly low prices in comparison to nourishing food, which is typically more expensive and difficult to access. This is coupled with technological advances that enable a more sedentary lifestyle both at work and home. Social, economic, educational and cultural factors are important underlying causes of obesity, although how they interrelate to promote or protect against the development of obesity is complex and varies by country, region and household.

1 – 4. Worldwide impact of obesity

Obesity is a major global public health problem, with 67% of the US, 63% of the UK, and 64% of Australia's populations being classified as overweight or obese, in 2014.(19) A meta-analysis concluded that elevated BMI is associated with increased cancer incidence for several common adult cancer types. In England alone, apart from the 24.9% of purely obese patients, another significant percentage number of 61.7% are overweight conducted by the World Cancer Research Fund (WCRF) (20). The prevalence of obesity has gradually amplified over the last decades and has increased threefold.(21,22)

Regional distribution around the world varies; prevalence ranges from less than 6% in Korea and Japan to more than 30% in Hungary, New Zealand, Mexico and the United States. More than one in four adults are obese in Australia, Canada, Chile, South Africa and the United Kingdom.(23) Overweight and obesity rates have grown rapidly in England, Mexico and the United States since the 1990s, while the increase has been slower elsewhere.(24) Over the past decade, the prevalence rate of overweight and obesity has increased in Canada, France, Mexico, Switzerland and the United States, while it has stabilised in England, Italy, Korea and Spain. There is, however, no clear sign of reduction in prevalence in any country.(25)



Worldwide distribution of obesity.(26)

There is a high social importance and impact worldwide around the problem of obesity and surrounding associated comorbidities and relevant management due to the substantial amount of economic losses associated with this worldwide problem.

Obesity is a complex state, with grave social and psychological effects, that permeates all age and socioeconomic groups in both developed and developing countries. In 1995, it was estimated there were 200 million obese adults worldwide. As of 2000, the number of obese adults had increased to over 300 million. This has placed a burden on both individuals and health systems as over 115 million people currently suffer from obesity-related problems.(2)

Obesity is an important threat to national and global public health in terms of prevalence, incidence and economic burden. In 2014, more than 2.1 billion people, nearly 30% of the global population, were overweight or obese and 5% of the deaths worldwide were attributable to obesity. If the incidence continues at this rate, almost half of the world's adult population will be overweight or obese by 2030.(27)

Such a high prevalence of obesity has an associated economic impact in terms of both direct and indirect costs. Direct costs include all medical and non-medical costs for diagnosis, treatment and transportation; whilst indirect costs are the lost productivity and foregone economic growth as a result of lost work days, lower productivity at work, morbidity and early mortality. (28) Studies of the macroeconomic effects of obesity have demonstrated.(29–32)

Obesity is viewed as one of the most serious public health problems of the 21st century.(33) It is a one of the leading avoidable causes of morbidity and mortality worldwide. (2) In 2015, 600 million adults (12%) and 100 million children were obese.(34) Obesity is more common in women than men.(35) In 2014, more than 1.9 billion people were reported to be overweight

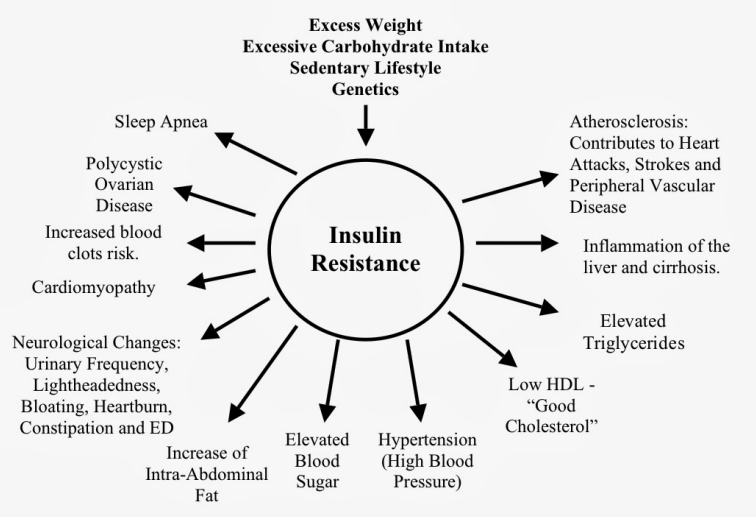
by the World Health Organisation. Additionally, it was also reported that 13% of the global population were obese. (36)

Worldwide statistics show that overweight and obesity are the fifth leading cause of death, with deaths associated with this condition increasing in both children and adults. Overweight and obesity are associated with more deaths globally compared to underweight. Obesity continues to receive stigmatisation in most parts of the modern world.

Even though obesity is a common condition, it has not received the clinical and public health attention it deserves in most countries around the world. This condition has been found to lead to various comorbidities. In the past two decades, obesity has risen globally and is the highest in the United States. In the July 6, 2017 issue of the *New England Journal of Medicine*, members from the Global Burden of Disease 2015 Obesity Collaborators presented compelling data about the global prevalence of overweight and obesity in youth and adults and the impact of obesity on health outcomes.(34) The collaborators estimated that obesity contributed globally to nearly 4 million deaths annually and almost 5% of the disability-adjusted life years from any cause. Most of the obesity-related deaths and disability-adjusted life years were from cardiovascular diseases. Diabetes was identified as the second obesity-related cause for deaths and disability-adjusted life years. The global prevalence of overweight and obesity is a public health problem as it affects the health, function, and well-being of a large number of people, and it has as its major impact, the reduction of the health of individuals or society rather than purely a social, aesthetic, economic or other non-health impact.

1 – 5. Metabolic syndrome

Metabolic syndrome originated as a concept rather than a diagnosis.(37) The metabolic syndrome wasfirst described in 1920 when Kylin, a Swedish physician, demonstrated the association of high blood pressure (hypertension), high blood glucose (hyperglycemia), and gout.(37) Later in 1947, Vague described that the visceral obesity was commonly associated with the metabolic abnormalities found in cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM).(38) Following this, in 1965, an abstract was presented at the European Association for the Study of Diabetes annual meeting by Avogaro and Crepaldi which again described a syndrome which comprised hypertension, hyperglycemia, and obesity.(39) Metabolic syndrome entered into the common consciousness of the medical field following a seminal Banting Lecture given by GM Reaven in 1988.(40) In his talk he described “a cluster of risk factors for diabetes and cardiovascular disease”, naming it “Syndrome X”. He is regarded as the one of the first to describe the acquisition of insulin resistance in patients. However, obesity or visceral obesity was admitted from his definition. In 1989, Kaplan coined the name “The Deadly Quartet” to describe upper body obesity, glucose intolerance, hypertriglyceridemia, and hypertension; however, in 1992, it was again renamed, this time as “The Insulin Resistance Syndrome”.(41)



Several groups have attempted to develop diagnostic criteria for the diagnosis of the metabolic syndrome. (42) In the late 1990s and early 2000s a spate of criteria were provided by professional groups including: the WHO diabetes group [1998], European Group for the study of Insulin Resistance (EGIR) [1999], National Cholesterol Education Program Adult Treatment Panel (NCEP/ATP) [2001], American Association of Clinical Endocrinologists (AACE) [2003] and the International Diabetes Federation (IDF) [2005].

Metabolic syndrome, still sometimes known by other names, is now defined as a clustering of at least three of the five following medical conditions: abdominal obesity, high blood pressure, high blood sugar, high serum triglycerides and low high-density lipoprotein (HDL) levels.(43) The syndrome is believed to be caused by an underlying disorder of energy utilisation and storage. The cause of the syndrome is an area of ongoing medical research. Other associated conditions include hyperuricemia, fatty liver progressing to nonalcoholic fatty liver disease, polycystic ovarian syndrome (in women), erectile dysfunction (in men), and acanthosis nigricans.

The metabolic syndrome is a major and escalating public-health and clinical challenge worldwide in the wake of urbanization, surplus energy intake, increasing obesity, and sedentary life habits. It presents a 5-fold increase in the risk of type 2 diabetes mellitus (T2DM) and a 2-fold increase in the risk of developing cardiovascular disease (CVD) over the next 5 to 10 years.(44)

The pathophysiology of metabolic syndrome is still undergoing intense medical research. Several disease models currently exist. The model of primary insulin resistance proposes that genetic and environmental influences result in insulin resistance which causes the development of metabolic syndrome traits. Another model suggests that in patients with metabolic syndrome they have saturated their levels of adipose tissue resulting in ectopic fat deposition around abdominal viscera causing insulin resistance and metabolic syndrome tests. A supplementary model suggets that altered adipose cell chemokines (adipokines) leads to impaired regulation of adipose tissues resulting in loss of homeostasis and secondary insulin resistance and impaired lipid management.(45)

Although there is general agreement in the medical community that obesity and its medical complications, including the metabolic syndrome, deserve greater attention, there has been considerable disagreement over the terminology and diagnostic criteria related to the metabolic syndrome. Because of this disagreement, although there appears to be a consensus in the medical field that the term metabolic syndrome is acceptable for the condition of the presence of multiple metabolic risk factors some confusion remains on the part of clinicians regarding how to identify patients with the syndrome. Several definitions mentioned above for MHO were formulated based on metabolic-body mass index (BMI) phenotypes. To reiterate the various definitions of metabolic syndrome studied in the literature implied on different populations to define the metabolically healthy obese were:

1. National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III)
2. Homeostatic model assessment of insulin resistance (HOMA-IR) value
3. The WHO first developed its definition in 1998 (Alberti and Zimmet, 1998).(46)
4. In 1999, the European Group for the Study of Insulin Resistance (EGIR) proposed a modification to the WHO definition (Balkau and Charles, 1999)(47)
5. In 2005, the International Diabetes Foundation (IDF) published new criteria for metabolic syndrome (Zimmet et al., 2005)(48)
6. Inflammatory indicators or C-Reactive Protein (Hinnouho et al., 2013)(49)

1 – 6. Metabolically Healthy Obese

Within the obese population, a subgroup which does not show the common metabolic impairments associated with obesity has been identified. This group of individuals is thought to be at a lower risk of developing obesity-related complications, and are referred to as the Metabolically Healthy Obese (MHO).(50) Based on the characteristics stated above, there has been a surge in interest in a unique group of obese people having normal metabolic features despite their elevated adiposity. MHO has throughout time been defined in diverse ways. MHO was formerly described as a subgroup of obese people lacking type 2 diabetes and hypertension.(4) Apart from body fat content and resistance to insulin, there are other metabolic risk factors that are important in the description of metabolically healthy obesity given their well-established link to the risk. They include lipid profiles, physical fitness, inflammation, and blood pressure.

No universally accepted criteria exist to define the already accredited MHO;(51) definitions generally require the patient to be obese and to lack metabolic abnormalities such as dyslipidaemia, impaired glucose tolerance, or metabolic syndrome.(52) However, currently, existing definitions agree that the patient must be obese and lack metabolic impairments (10) or metabolic syndromes.(53,54) Some researchers are of the view that MHO is manifested by

obesity devoid of individual metabolic diseases, such as type 2 diabetes, dyslipidaemia, and high blood pressure.(38) Others highlight normal blood glucose, lower inflammatory markers, normal or near-normal lipid profile, and normal blood pressure. Controversial research debates that MHO is a condition characterised by preserved insulin sensitivity.(55) MHO individuals also show lower amounts of visceral adipose tissue, small adipose cells, and decreased inflammatory profile compared to metabolically-impaired obese individuals.(11,56)

1 – 7 – 1 Prevalence of MHO and literature review

A possible explanation for the observed differences in MHO prevalence is the variety of ways in which MHO has been conceptualised and operationalised by different researchers. Findings from various studies displayed that MHO prevalence varies across the spectrum depending on the possible criteria associated with it, and varying populations and demographics. A literature review was undertaken to validate and study the definitions and relevant prevalences in the literature and identify a baseline in the United Kingdom.

Obesity has been outlined using different criteria. One of the most common definitions is based on BMI.(50,51,57–62) Other definitions of obesity include the presence of metabolic syndrome factors such as high-density lipoproteins, elevated triglycerides, high glucose levels, increased waist circumference, and high blood pressure. Obesity has been associated with elevated mortality risk. However, individuals with obesity have been found to have diverse mortality risks.(62) This suggests that there may be additional factors, probably metabolic, which may have an impact on the risk of death in different BMI categories. Individuals in the same BMI category have been found to have many different metabolic features, including blood pressure, fasting plasma glucose, insulin resistance and inflammatory mediators associated with increasing waist circumference.(50)

As evidenct in clinical practice and obesity research, there is a group of individuals who are obese but uniquely have normal metabolic features despite being obese, as defined by BMI. This group has been described as the 'metabolically healthy obese'.(50) MHO has been defined in diverse means. No universally accepted criteria exist to define the already accredited MHO,(51) definitions generally require the patient to have obesity and to lack metabolic abnormalities such as dyslipidaemia, impaired glucose tolerance, or metabolic syndrome. (52) Centred on BMI, individuals with metabolically healthy obesity have been described as having BMI>30 kg/m^2 with usually less than two or three metabolic syndromes or metabolic risk factors. An individual can also be placed in the group that is metabolically healthy if he or she meets the conditions for obesity but has no history or prior diagnosis of certain morbidities such as cardiovascular diseases, diabetes, dyslipidaemia or hypertension. A scrutiny of the available literature on MHO shows that the prevalence of this condition varies depending on the definition used when conducting the studies.

1 – 7 – 2 Methods of literature review

This literature review utilised all studies published before December 2016 in Medline, Web of Science and Excerpta Medica (EMBASE). As there were no medical subject headings (MeSH) terms found which defined MHO, the following terms were used: 'metabolically healthy obesity' OR 'metabolically healthy obese' OR 'metabolically unhealthy obese' OR 'healthy obesity' OR 'healthy obese' OR 'metabolic benign obesity' OR 'metabolic benign obese' OR 'obese phenotype' OR 'uncomplicated obesity' OR 'metabolically normal obesity' OR 'metabolically abnormal obesity'. As such, these terms were merged with 'prevalence'. These expressions aimed to identify all original studies of epidemiology that described subgroups of subjects with obesity based on their metabolic features. In addition, a manual search of the reference lists of the selected articles was implemented.

Only full-text studies published in English were selected. Editorials, reviews, case reports, academic theses and abstracts/posters from congresses were not included in this study. Only studies scrutinising and reporting MHO prevalence findings (according to various definitions) were included in the review. There was no unanimous definition of MHO which guided the choice of the studies.

1 – 7 – 3 Metabolically healthy obesity definition

Studies presented several clear definitions for MHO based on metabolic-body mass index (BMI) phenotypes. Various definitions of metabolic syndrome were studied in the literature implied on different populations, these are given in Section 1-6 above

First screening was carried out based on the title and abstract of eligible publications. Subsequently, full articles were retrieved and reviewed. Characteristics of the 'Metabolically Healthy Obese' have been defined in the literature, and Rey-Lopez et al.(63) similarly examined prospective and cross-sectional studies.

1 – 7 – 4. Results of literature review

There were 374 abstracts identified, 268 without duplicates. Eventually, after examining all abstracts, 40 studies were integrated from the electronic searches, all published in English. Most of these studies were cross-sectional studies. The full text of the identified studies were reviewed and scrutinised by two authors. The studies chosen differed in the number recruited to participate in the study. The smallest study (n= 503) participants was conducted in Russia. (57) On the other hand, the largest sample size (n= 163,517) was undertaken in the Netherlands. (64) Most of the studies had been carried out on participants who were adult and aged 35 years

and above. Very few studies examined MHO prevalence in children. Only a few studies investigated gender distribution in MHO prevalence.

Definition of MHO and Related Prevalence

The differences in prevalence reflected different MHO definitions. One of the studies described individuals who are metabolically healthy as those having less than one of the comorbidities that comprise the components of metabolic syndrome, based on the Joint Interim Statement (JIS) definition, and displayed a prevalence of 12.8%. Another study defined MHO as BMI greater than 30kg/m^2 and the presence of less than two of the following markers: high-density lipoproteins of less than 1.30 in females and 1.04 mmol/l in males; elevated triglycerides >1.7 mmol/l; high glucose levels; waist circumference >88cm for women, >102cm for men; and blood pressure greater than 130/85 mmHg or on therapy. (63) Accordingly, the authors reported a prevalence of 41.5% in participants aged 25-65 years. In a study which utilised a BMI> 30kg/m^2 and healthy levels of glucose, lipids, and blood pressure to define MHO, a prevalence of 19% was obtained.(65)

In a study aimed at evaluating the prevalence of MHO phenotypes and a relevant association with cardiorespiratory fitness and inducible myocardial ischemia, individuals who were considered metabolically healthy were defined as those without dyslipidemia, high blood pressure, or diabetes. When more than one of these conditions were present, an individual was categorised as metabolically unhealthy.(52) Accordingly, the authors reported MHO prevalence of 23.5% in patients with obesity.

In a Chinese study, the researchers defined MHO as the absence of the metabolic syndrome. In this study, MHO prevalence was 23.1%.(66) Other studies described MHO using more than

one criteria. For instance, a Canadian cross-sectional study conducted to determine the differences in prevalence and predictors of MHO in adolescents defined MHO as the possession of less than one metabolic syndrome and the absence of high blood pressure, type 2 diabetes, and dyslipidemia. The authors also defined MHO as the lack of metabolic syndrome criteria, insulin resistance, and inflammation.(67) Based on the former definition, the prevalence of MHO was found to be 42% in males and 74% in females while the latter yielded a prevalence of 7% in males and 12% in females.(67) Moreover, other studies utilised the International Diabetes Federation metabolic syndrome criteria, and quoted a prevalence of 17.4%.(68,69)

In a study from South Korean, metabolic syndrome was defined based on 2005 American Heart Association/National Heart, Lung, and Blood Institute criteria and the National Cholesterol Education Program/Adult Treatment Panel III. This was defined as having a BMI >25 kg/m^2. (58) Moreover, MHO was defined in another study as the absence of cardiometabolic risk factors.(58) The use of this definition resulted in MHO prevalence of 9.1%.(58) Using BMI and ATP-III criterion to define MHO, researchers found MHO prevalence of 4.2% in a study from China.(51) A study from the Netherlands described MHO as obesity (BMI>30 kg/m^2), lacking the metabolic syndrome components, and no prior diagnosis of cardiovascular disease.(64) MHO prevalence in males ranged from 7-28% in women and 2-19% of femlaes in this study.(64) Furthermore, another study classified obesity and metabolic status using BMI and the number of abnormalities in metabolic syndrome. This criterion resulted in MHO prevalence of 27.9%.(60)

In another manuscript from Brazil that investigated the association of different subgroups of obesity with inflammatory-cardiometabolic abnormalities, individuals who were MHO were defined as those who had less than two metabolic risk factors. Based on this criteria, researchers found that 40% of individuals with obesity were of the metabolic health phenotype.(70) In a

cross-sectional analysis that examined differences in physical activities between MHO and metabolically unhealthy groups with obesity, individuals who were metabolically healthy were those who had less than 2 of the following factors: high blood pressure, elevated blood glucose, elevated triacylglycerol, low high-density lipoproteins cholesterol, and insulin resistance. (71)

Gender and MHO

A few studies investigated the prevalence of MHO in men or women. In a cross-sectional study with participants who were male carried out to compare the food intake of MHO men to MHO men of other weight status, the researchers found MHO in 44% of men with a Caucasian background, and in 58% of patients with an Afro-Carribean background. When HOMA-IR was used to identify MHO, MHO prevalence was 20% in individuals with obesity and white and 21% with obesity and Afro-Carribean.(72) In a cross-sectional study with participants who were exclusively female, the purpose of which was to investigate the relationship between knee osteoarthritis and four body size characteristics based on the presence or absence of metabolic disorder and obesity, the researchers reported a 4.3% prevalence of MHO.(73)

In another report, which compared the prevalence, dietary factors and lifestyle behaviours of MHO and metabolically unhealthy patients with obesity and participants who do not have obesity using different criteria, the study recognised that the prevalence of MHO varied between 6.8% to 36.6% among individuals with obesity.(74) In a cross-sectional study from China, the researchers examined the prevalence and predictors of MHO in a rural population of China with obesity. Research findings indicated that MHO prevalence was 23.1%, and showed a decrease with an increase in age in the group of female gender. However, there was no significant changes in prevalence with increasing age in the male gender group. In conclusion, the study established that age <55 years, current non-smoking state, pre-menopause, and non-hyperuricemia were independent predictors of MHO. (60)

In a Canadian study that explored the variances in the prevalence and predictors of MHO in adolescents, prevalence was found to be 42% in males and 74% in females, while 7% in males and 12% in females using two different criteria. This also disclosed that waist circumference and lower insulin resistance were good predictors of MHO.(67)

Age Group and MHO

In a South Korean study involving only participants who are children, the authors quoted a lower mean BMI (23.02 kg/m^2) in individuals who were MHO than in those who were metabolically unhealthy (24.83 kg/m^2), and the prevalence was 20.7% compared to 59.4% prevalence in the group that was metabolically unhealthy.(59) In a cross-sectional register-based study from Finland the general clinical presentation in children and with occurrence of cardiometabolic risk factors, the prevalence was only 3% of participants who were metabolically healthy.(75) In a study targeting obesity in children aged 2 to 10 years, researchers aimed to identify MHO phenotype in this age group. In this study, MHO was defined as the absence of risk from glucose, HDL-cholesterol data, and triglyceride. Based on this definition, the prevalence of MHO phenotype was found to be 4%. (76)

A Brazilian cross-sectional study investigated an aging population and its association with subclinical cardiovascular disease. Findings from this study indicated that the prevalence of MHO was 13.5%.(64) On the other hand, in studies whose participants were aged 18 to 80, the prevalence of MHO was found to range from 3% to 44%.(51–53,56,57,61,64,71,74,75,77–82) Similarly, a study to investigate the prevalence of MHO in a population from Italy with obesity disclosed a higher prevalence among the subjects who were young and with obesity,(83) quoted as 27.5%. Moreover, in Icaria, Spanish, and Estonian studies, individuals who were metabolically healthy were also reported to be younger, commonly female, and physically active.(84–86) The prevalence rates were 87.1%, 2.2% and 6.5% respectively.

In conclusion, the reviewed studies on age and MHO do not clearly indicate whether age is a factor in MHO. Also, the findings of the various studies reviewed do not clearly show whether MHO decreases or increases with an increase in age. However, one study reported that individuals who are young with lower BMI, lower waist circumference, and undertake high physical activity were more likely to have the MHO phenotype.(50)

MHO and Race

Few studies investigated the prevalence of MHO across different races. In a cross-sectional study conducted to examine the differences in food intake between men who are metabolically healthy to men who are metabolically healthy but of other weight categories, the researchers reported MHO prevalence of 20% of men who were Caucasian and 21% in men who were of Afro-Carribean origin and have obesity when HOMA-IR was used to define MHO.(72) This shows that the differences in the prevalence of MHO in the two races are small. A cross-sectional study that determined the obesity phenotypes in Cameroonians of African race established that 10.1% of participants were of the MHO phenotype.(87)

In a study conducted to determine whether hyperinsulinemia and hyperleptinemia are BMI-independent factors of morbid obesity in a population who were Qatari (predominantly Arab) versus a population who were Caucasian, the participants were categorised into a group who were MHO and another group who were pathological with obesity using the HOMA index. The findings of the study showed that the prevalence of MHO in subjects who were Qatari (Arab) was 13% while that of the Caucasians was 28%.(61) In a study investigating the prevalence of elevated adiponectin or hypoadiponectinemia among individuals who have obesity as well as an African American background, researchers found that 28% of the subjects met the criteria of the MHO phenotype.(88) There were several studies involving subjects of Asian descent. A study that investigated the prevalence of MHO in **a** rural population in Chnia

with obesity, prevalence of MHO was 23.1%.(67) Other studies involving individuals of Asian origin reported prevalence rates in the range of 4.2% to 2.9%.(51,58–60,89,90)

MHO by Region

Among studies appraised, three were Brazilian, one was from Cameroon, one from Canada, four were from China, one was from the Czech Republic, one was from Finland, one was from France, two came from Germany, one was from Iran, one originated from the Netherlands, three were from Russia, five from South Korea, one from the UK, and one from the USA. In Brazilian studies, the prevalence of MHO ranged from 13.5% to 40% of the obese.(52,79,81) In studies from China, prevalence ranged from 4.2% to 27.9%.(51,60,89) The Canadians reported a prevalence of 42% in men and 74% in women(67) while in a Cameroonian study it was 10.1%.(87) Findings from these studies suggest that prevalence of MHO by region seems to be the lowest in Africa. For instance, Cameroon has a 10.1% prevalence. A population prevalence rate from China appears to be reported relatively low (4.2% to 27.9%.) compared to a similar population from Brazil (13.5% to 40%) and Canada (42% in men and 74% in women).

MHO, Metabolically unhealthy phenotype and Mortality

There have also been research efforts to establish the relationship between obesity and mortality. For instance, a Korean prospective cohort study investigated the association between BMI and metabolic syndrome mortality in elderly (over 60 years of age) individuals of Korean descent. Moreover, the researchers compared mortality in participants who were metabolically normal-weight and MHO. Findings from this study showed that among subjects with metabolic syndrome, all-cause, and cardiovascular mortality were more prevalent in individuals having normal weight than those individuals who were overweight or obese, after controlling for

confounding variables. More specifically, normal-weight subjects who were metabolically unhealthy displayed the highest risk of death while the individuals who were overweight lacking metabolic syndrome showed the lowest risk of mortality.(62) It is worth noting that all-cause mortality was significantly higher in individuals who were obese and were metabolically unhealthy compared to individuals who were MHO. This shows that the MHO phenotype is associated with longevity.

Summary of main characteristics and MHO prevalence of the included studies in literature review

Study	Type of study[b]	*n*[c]	Obese (*n*)	Sex	Age	Ethnicity	Prevalence of MHO (MHO subjects/obese population)
ASIA							
China							
Ding et al. (91)	Prospective	1183		Men/Women		Chinese	Overall: 36.7%
Chang et al.(92)	Cross sectional	14828	3254	Men/Women			
Hwang et al.(93)	Prospective	3,629	668	Men/Women	18–59	Asian	Overall: 29% (24% men, 35% women)
India							
Geetha et al.(94)	Cross-sectional	2,350	660	Men/Women	≥20	Asian	Overall: 47% (42% men, 51% women)
South Korea							
Lee	Cross-sectional	5,267	1,685	Men/Women	>20	Asian	Overall: 48 (44% men, 51% women)
							20–39 years: 58% men, 79% women
							40–59 years: 39% men, 55% women
							>60 years: 35% men, 28% women
Choi et al.(95)	Prospective	2,317	1,038	Men/Women	≥60	Asian	Overall: 58%
Lee et al.(96)	Prospective	2,352	745	Men/Women	40–69	Asian	Overall: 18%
Hong et al.(97)	Cross-sectional	16,190	5,096	Men/Women	>18	Asian	Overall: 48%
Chang et al.(98)	Cross-sectional	14828	3254	Men/Women		Asian	Overall: 21.9%
Yoo et al.(99)	Cross-sectional		186	Men/Women	NR	Asian	Overall: (Men 24.2%, Women70.4%)
EUROPE							
Belgium							
Bervoets et al.	Prospective cohort	156	29	Men/Women	NR	Caucasian	Overall: (Men 6.4% men, Women 19.2%)
Estonia							
Eglit et al.(100)	Cross-sectional	495	158	Men/Women	20–74	NR	Overall: 12% (11% men, 13% women)
Finland							
Pajunen et al.(101)	Cross-sectional		2849	Men/Women	45-74	NR	Overall: Men 9.2%, Women 16.1%
Ireland							
Phillips et al. (102)	Cross-sectional	2,047	NR	Men/Women	45–74	Caucasian Irish	Overall: Aguilar-Salinas: 7%
							Overall: Karelis: 14%
							Overall: Meigs (A): 30%
							Overall: Meigs (B): 37%
							Overall: Wildman: 24%
Phillips et al.	Cross-	2,04	NR	Men/Wo	50-69	Caucasian	Overall: Aguilar-Salinas: 2.2%

(103)	sectional	7		men		Irish	
							Overall: Karelis: 4.7%
							Overall: Meigs (A): 9.9%
							Overall: Meigs (B): 11.9%
							Overall: Wildman: 7.7%
Italy							
Calori et al.	Prospective	2,011	380	Men/Women	20–79	Caucasian	Overall: 11%
Netherlands							
Van der A et al.(104)	Prospective	22,654	4,579	Men/Women	20–59	NR	Overall: 19% (13% men, 23% women)
De Rooij et al.(105)	Prospective		2449	Men/Women	40-75	Caucasian	Overall: 19.4%
Spain							
Martinez-Larrad et al.(106)	Cross sectional	3844	NR	Men/Women	35-74	Caucasian	Wildman: 9.65%
							Wildman Modified: 16.29%
							Consensus societies metabolic syndrome: 39.94%
Ferrer et al.	Case-control	-	32	Men/Women	21-61	Caucasian	NR
Soriguer et al.(107)	Prospective	715	217	Men/Women	18–65	NR	Overall: Criterion A 51%
							Overall: Criterion B 10%
							Overall: Criterion C 13%
							Overall: Criterion D 44%
Gomez-Huelgas et al.(108)	Cross-sectional	2,270	520	Men/Women	18–80	Caucasian	Overall: 10% (7% men, 12% women)
Lopez-Garcia et al.(86)	Cross-sectional	11,520	2,611	Men/Women	≥18	NR	Overall: 29%
Sweden							
Ärnlöv et al.(109)	Prospective	1,758	96	Men	All 50	Caucasian	Overall: 31%
Lind et al.(110)	Prospective	985	220	Men/Women	All 70	Caucasian	Overall: Without metabolic syndrome: 46%
Switzerland							
Marques-Vidal et al.(111)	Cross-sectional	962	881	Men/Women	35-75	Caucasian-Swiss	Wildman: 42.2%
							Karelis: 21.9%
							Meigs (A): 43.6%
							Meigs (B): 43.0%
							Lynch: 41.8%
							Aguilar-Salinas: 41.5%
Velho et al.(112)	Cross-sectional	5,360	894	Men/Women	Mean 54 (±10.8) Mean 53 (±10.8)	Caucasian	Men
							BMI
							Aguilar-Salinas: 25%
							Karelis: 3%
							Meigs (A): 30%
							Meigs (B): 32%
							Wildman: 16%
							Lynch: 10%
							Women
							BMI
							Aguilar-Salinas: 35%
							Karelis: 11%
							Meigs (A): 39%
							Meigs (B): 43%
							Wildman: 22%
							Lynch: 15%
United Kingdom							
Hinnouho et al.(113)	Prospective	5269	638	Men/Women	35-55	Caucasian UK	ATP-III: 4.5%

							Wildman: 2.8%
							Karelis: 2.3%
							Matsuda: 1.1%
							HOMA: 4.9%
Hamer and Stamatakis et al.(114)	Prospective	22,203	5,288	Men/Women	Mean 54 (±12.7)	NR	Overall: 22%
Hamer et al.(115)	Prospective	3,851	1,057	Men/Women	Mean 63 (±8.9)	Caucasian	Overall: 34%
Ul-Haq et al.	Cross-sectional	5,608	1,468	Men/Women	≥20	NR	Overall: 75%
NORTH AMERICA							
USA							
Wildman et al.(116)	Cross-sectional	5,440	1,665	Men/Women	Mean 45 (±0.4)	Multi-ethnic[d]	Overall: 32% (29% men, 35% women)
							20–34 years: 48% 35–49 years: 31%
							50–64 years: 20% 65–79 years: 14% ≥80 years: 22%
Prince et al.(117)	Cross-sectional	181	57	Boy/Girl	8-17	Caucasian American	Overall: Insulin resistance 31.50% Cardiometabolic risk factors: 21.50%
Manu et al.(118)	Prospective	6,485	1,513	Men/Women	20–79	Multi-ethnic[d]	Overall: 21%
Kuk and Ardern et al.(119)	Prospective	6011	NR	Men/Women	18–65	Multi-ethnic[d]	Overall: HOMA-IR and ATP-III: 6%
							Overall: HOMA-IR: 30%
							Overall: ATP-III: 38%
Hankinson et al.(120)	Cross-sectional	4,680	775	Men/Women	40–59	Multi-ethnic	Overall: 19% (20% men, 19% women)
Heinzle et al.(67)	Prospective	622	622	NHANES	12-19	NR	Overall: (Boys 7%, Women 12%)
Doumatey et al.(121)	Cross-sectional	822	343	Men/Women	Mean 43(±10)	African–American	Overall: 28% (29% men, 28% women)
Durward et al.(122)	Prospective	4,373	1,160	Men/Women	18–59	Multi-ethnic[d]	Overall: HOMA-IR: 20%
							Overall: ATP-III: 44%
							Overall: Combined 8%
Camhi et al.(123)	Cross-sectional	541	541	Men/Women	19–85	Multi-ethnic[d]	Overall: 40% 19–44 years: 54%
							45–85 years: 24%
OCEANIA							
Australia							
Appleton et al.(70)	Prospective	4,056	1,027	Men/Women	≥18	NR	Overall: 44%
AFRICA & Middle East							
Keihani et al.(124)	Prospective	3754	881	Men/Women	25-84	Persian	Men 12.4%, Women 23.5%
Egypt							
Abd EL Hafez et al.(125)	Case-control	75	80	Men/Women	NR	Egypt	NR

1 – 7 – 5. Discussion of literature review

This literature review sought to find out MHO prevalence. Its findings showed that MHO prevalence varies across the studies reviewed. A possible explanation for the observed differences in MHO prevalence is the variety of ways in which MHO has been conceptualised and applied by different researchers. When HOMA-IR was used to identify MHO, MHO prevalence was 20% in men who were Caucasian and 21% of men who were black with obesity.(72) This highlights the importance of considering how different criteria of measuring MHO may yield different MHO prevalences. It is, therefore, important for researchers in this field to develop a common approach of defining MHO to allow for accurate comparisions of prevalence across races, gender, and geographical areas.

Another potential explanation for the observed disparities in the prevalence of MHO may be the demographic characteristics of the contributors enrolled in the study. For instance, age was found to significantly affect MHO occurrences. Some studies reported a decreased prevalence of MHO with increased age hence indicating that the MHO phenotype is associated with young age. (50) Race affected the prevalence of MHO when adjusted for. Moreover, one study reported that MHO is more prevalent in races such as Arabian than in Caucasians.(61)

1 – 7 – 6. Conclusion of literature review

A review of the literature on MHO prevalence showed that no standard definition of MHO exists; with different studies utilising different defining terms. Moreover, there were no significant differences in prevalence across gender, race, and region. However, results of the various studies showed that the prevalence of MHO reduces with aging. (89) Lastly, a review of literature showed that the MHO phenotype is beneficial to individuals as it is associated with longevity and decreased risk of certain diseases, especially cardiovascular diseases. (62)

In another report which compared the prevalence, dietary factors and lifestyle behaviors of MHO and metabolically unhealthy obese and non-obese participants using different criteria, the study recognised that the prevalence of MHO varied between 6.8% to 36.6% among the obese individuals. In a 2-Cohort (Prospective) study that assessed the physical activity and sedentary behaviour among the obese, researchers sampled 2,449 men and women between the ages of 40 and 75 years. The subjects were classified as either metabolically healthy or unhealthy obese and metabolically healthy or unhealthy non-obese based on obesity and metabolic syndrome. Their daily physical activities were monitored. The results of the study showed that 19.4% of the study population were MHO. The MHO individuals had less sedentary lifestyles and so were engaged in more physical activities than their metabolically unhealthy counterparts.(25)

This highlights the importance of considering how different criteria of measuring MHO may yield different estimates for MHO prevalences. It is, therefore, important for researchers in this field to develop a common approach of defining MHO to allow for accurate comparisions of prevalence across races, gender, and geographical areas.

An updated review of the literature reported the included studies published after 2004, most were conducted in the United States or Europe. In total, 4,822,205 participants were included, with a median prevalence of MHO of 6.6% (range, 1.2–31.0%). The median participant age was 49.9 (30.3–74.0) years; the median proportion of women was 52.0% (0–100%); and the median smoking rate was 20% (5.7–67.6%). The median follow-up duration was 10.6 (1.0–30.0) years. (126)Also, due to the absence of harmonized criteria, other studies reported MHO individuals to be 20-30% of obese individuals depending on the definition. (127,128)

Obesity was classified using BMI, the highest prevalence of MHO was obtained from HOMA criteria (13.6%, 95% CI 11.0–16.2), followed by CDS (11.4%, 95% CI 8.7–14.1), ATPIII (10.3%, 95% CI 7.6–13.0), and Wildman (5.2%, 95% CI 2.4–8.0), whilst the lowest prevalence of MHO was derived from the criteria of Karelis (4.2%, 95% CI 1.4–7.0). In contrast to MHO, the highest prevalence of MUO was derived from the criteria of Karelis (20.1%, 95% CI 17.6–22.6), which was 2-fold higher than the lowest prevalence from HOMA (10.6%, 95% CI 7.9–13.3). The MUO prevalence for Wildman, ATPIII, and CDS was 19.1% (95% CI 16.5–21.7), 14.0% (95% CI 11.4–16.6), and 12.9% (95% CI 10.2–15.6), respectively. (129)

Several studies proposed that MHO is a transient state, and it may turn into MUO in a later life stage. A follow-up study from England (115) showed that 44.5% of MHO individuals had transited into an unhealthy metabolic state within 8 years. In the present study, when using WC to define obesity, the age-specific prevalence of the 2 obesity phenotypes supported the hypothesis that MHO is the intermediate state of MUO. For example, after 65 years of age, the prevalence of HOMA-defined MHO increased, but MUO had an opposite trend. The prevalence of BMI-defined MHO decreased with age after 45 years, and the prevalence of MUO increased with age during 45–65 years, which supported that both MHO and MUO were in an unstable state. However, the prevalence of BMI-defined MHO and MUO both obviously decreased after age 65 years, which implied that a number of obese people transformed into a nonobese state. (129)

The prevalence of WC-defined obesity remained increased with aging, whilst the age-specific prevalence of BMI-defined obesity remained stable before age 65 years and then decreased gradually afterward, and this was similar to the findings of Xu et al. (130) in China.

1 – 8. Implications of obesity and the metabolically healthy obesity

Obesity is a global epidemic which is currently affecting over a third of the adult population and poses significant health problems to both individuals and society. Over the past 30 years, the dominance of obesity has gradually increased worldwide becoming a major public health concern (131) The increasing prevalence of the disease is a major threat to people's health and quality of life. Based on the latest projections by the WHO, at least one in every 3 adults in the world's population is overweight and one in every 10 adults is obese implying that the epidemic is affecting many people across the globe.(2) Over 40 million children aged five years and below are overweight as reported by the WHO.(80) In the current century, it poses one of the greatest challenges to the healthcare systems globally as it increases the risk of other chronic diseases. It is a preventable risk factor for cardiovascular-related mortality, cancer-related mortality and all-cause mortality. Physically active lifestyles are promoted as the first-line option towards preventing the obesity epidemic. Being obese or overweight has serious impacts on one's health as the excess fat causes severe health problems like cardiovascular diseases, cancer, and musculoskeletal disorders which result in substantial disability or premature death (133).

Obesity is associated with a higher risk of health complications or metabolic syndrome which entails high cardiovascular disease, high blood pressure, diabetes, and high cholesterol. These complications are not experienced by all the people with high BMI and not everyone exhibits all of them as some people have only one metabolic problem. Based on studies, approximately 35% of obese people may be metabolically healthy lacking any of the complications.(134) Due to its epidemic proportions and its role in increasing the risk of various chronic diseases, obesity has become a major public health problem globally. The reason as to why some individuals with obesity have metabolic problems while others do not is linked to their healthy lifestyle habits and their likelihood of causing weight loss.

The existence of metabolically healthy obesity (MHO) has been confirmed by several studies and shown to account for about 40% of the obese population.(135) Although MHO was initially regarded to be a static condition, as some individuals are able to maintain their health status, it has been recently evident that it is transient in nature as some individuals with obesity convert from being metabolically healthy to metabolically unhealthy and vice versa. The health status of people changes over time and the obese people who are currently metabolically healthy may develop health problems in the future. According to studies, 30% to 40% of MHO individuals converted after about 6 years of follow-up to metabolically unhealthy obesity (MUO) (49). The majority of women who are metabolically healthy are more likely to become metabolically unhealthy and develop obesity-related complications like cardiovascular diseases over time as compared to men.(136) Healthy lifestyles such as smoking cessation, healthy diet and high levels of physical activity helps to prevent the transition from being metabolically healthy and metabolically unhealthy.

Metabolically healthy obese individuals are at a lower risk of developing cardiovascular diseases as compared to those with metabolically unhealthy obesity. Researchers found in 2016 that although there was a strong link between high BMI and cardiovascular disease, the people with MHO were less likely to develop cardiovascular diseases.(137) However, physicians should not be reassured by the absence of metabolic abnormalities in patients regarding the risk of cardiovascular diseases but should direct their efforts towards reversing the condition to promote their health and well-being. The treatment goals for MHO should be focused on the reduction of weight and metabolic derangements. To facilitate direct and effective comparison of results, it is important to adhere to the uniform criteria for the definition of metabolic syndrome and the phenotypes associated with it (133). Every obese individual should be motivated to attain a normal weight in the long-term sufficient for the transition from being metabolically unhealthy to metabolically healthy, thus lowering the risk of adverse health

outcomes. Obesity is prevented by adopting healthy lifestyles to help attain an energy balance between the energy consumed and calories used.

A better understanding of specific obese individuals who are susceptible to complications is required for the treatment and prevention of health problems. Development of standard criteria for defining MHO and a better understanding of the biological mechanisms behind the condition could also help achieve an effective treatment. As argued by Philips (102), the unclear definitions of metabolic obesity and health in studies act as an obstacle to advancing the understanding of MHO. A clear definition of MHO is, therefore, required to enable a better knowledge of the link between obesity, metabolic health, and inflammation and help in the development of drugs for protecting illnesses to which many obese people are susceptible. By distinguishing individuals with MHO from those with obesity and metabolic disorders, more cost-effective and appropriate forms of treatment could be developed. People with obesity need proper treatment, whether diagnosed as metabolically healthy or not, to promote their health, well-being, and quality of life.

The people with obesity who make healthy food choices and are physically fit continue to derive similar benefits in life as those who are not obese. Based on studies, the same mortality risk to slimmer individuals was reported for obese or overweight people who had the four healthy habits regardless of their BMI which include moderate alcohol intake, being a non-smoker, eating 5 or more servings of fruits and vegetables daily, and doing 30 minutes of exercise daily. According to a 2015 study, people with MHO may have different clinical characteristics as compared to those with obesity and metabolic disorder (138). For instance, those with MHO and who are female and young less likely to drink heavily or smoke and more likely to exercise regularly. A study published in 2017 suggested that sleep quality was linked to cardio-metabolic health (139). Based on the study, women with MHO had sleep disturbances regularly but did not have a problem with the overall sleep quality and sleeping duration as

compared to those with metabolically abnormal obesity (MAO). Lifestyle intervention and modification of environmental factors that promote obesity are effective ways of preventing the global epidemic.

1 – 9. Impact of obesity and metabolically healthy obesity

According to the WHO, obesity is a major global public health problem affecting 67%, 63% and 64% of the population in the US, the UK, and Australia repectively.(135) The global prevalence of obesity and overweight affects the health, well-being, and function of many people and causes the reduction of the health of individuals and society, in general, leading to low quality of life. Based on the systematic review with a standardised meta-analysis performed by the World Cancer Research Fund (WCRF), it was concluded that an elevated or high BMI is associated with the increased incidence of cardiovascular diseases, sleep apnea, cancer, and type 2 diabetes worldwide.(31) Obesity highly contributes to the global incidence of these illnesses and morbidity. The MHO phenotype affects the risk factors for cardiovascular diseases especially those related to the metabolic syndromes like poor blood sugar control, abnormal blood fats and high blood pressure, thus doubling the risk of cardiovascular diseases like stroke and heart attack. Some individuals with obesity, and more in the industrialised countries than the non-industrialised ones, also experience disability as a result of obesity-related cardiovascular disease and type 2 diabetes which affect their functionality and quality of life. Obesity involves social and psychological dimensions which affect all socioeconomic and age groups and as a result act as a threat to both the developing and developed countries.

The epidemic causes an economic burden to countries due to the excessive health care expenditures associated with its treatment and prevention, including direct non-medical and medical costs for transportation, diagnosis, and treatment.(140) High direct medical costs are

incurred in the diagnosis and treatment of obesity and other obesity-related serious health conditions. Substantial indirect costs, especially productivity costs, are linked to obesity and related health complications especially due to absenteeism, disability and premature mortality because the condition affects the functionality and productivity of workers. The increased body weight of obese individuals increases the spending on fuel and larger vehicles are required to transport them. Indirect costs are also incurred due to the higher greenhouse emissions produced by the vehicles. The rising prevalence of obesity results in higher per capita spending in an attempt to address the epidemic. Obesity-related conditions cost more than 150 billion dollars annually and cause approximately 300,000 premature deaths in the United States.(133) Obesity also imposes costs in the form of forgone economic growth due to lower productivity at work, lost work days permanent disability and mortality.

According to the worldwide statistics, obesity is the fifth leading cause of death and with the increasingly growing rate in children and adults is viewed as one of the most serious public health problems in the 21st century.(31) In 2015, researchers found that obesity contributed to approximately 120 million disability-adjusted life years and 4 million deaths globally. The rate of obesity-related global mortality had increased by 28.3% while the rate of disability-adjusted life years had increased by about 35.8% since 1990.(141) The cardiovascular disease resulting from the condition highly contributes to the increased rate of morbidity and mortality worldwide. Many deaths occur as a result of obesity and other obesity-related health complications. The condition has been found to result in various comorbidities and in the past two decades it has increased globally, becoming the highest in the US. Based on the New England Journal of Medicine issued in July 2017, the Global Burden of Disease 2015 obesity collaborators estimated that obesity contributed to about 4 million deaths annually across the globe and approximately 5% of the disability-adjusted life years especially resulting from cardiovascular diseases.(142)

Most individuals suffering from obesity, especially adolescents and children, often experience psychological impairments and stigmatisation. These occur due to weight-related discrimination, bias, torment, low self-esteem, body dissatisfaction, and also depression in different areas of their lives causing their psychological well-being to be compromised. Obesity also affects academic performance and hinders the educational attainment of children and adolescents, which is also a potential economic impact due to the associated costs of human capital accumulation.

1 – 10. Future impact of metabolically healthy obese versus non metabolically healthy obese

Future projections based on the Behavioral Risk Factor Surveillance System of the Centre of Disease Control and Prevention (CDC) show that by 2030, approximately 42% of the US population will be obese and about 11% of Americans are likely to be severely obese. As per the results and findings of eight studies conducted among a total of 30,000 participants, both metabolically healthy and unhealthy obese people are linked to a high risk of symptoms of depression. However, the metabolically unhealthy obese individuals have about 23% higher odds for depression as compared to the metabolically healthy obese individuals.(143) The metabolically unhealthy obese individuals are also likely to experience economic burdens due to the increased medical costs incurred in diagnosis and treatment of obesity and other obesity-related health complications likely to arise. The quality of life of these individuals is also reduced, making it difficult to function properly and support their lives and, due to stress, they are more likely to suffer from depression in the future as compared to the metabolically healthy obese individuals who do not experience metabolic syndromes. The metabolically healthy people have the ability to lead their lives just like those with normal weight and improve their quality of life since they do not experience the obesity-related health complications which

undermine people's functionality. The findings showed that the high risk of depression linked to obesity increases with an increase in the number of co-occurring metabolic risk factors with obesity. In the future, depression will more likely be suffered by metabolically unhealthy obese individuals and not the metabolically healthy. Metabolically unhealthy obesity is also likely to increase the risk of developing other mental health problems among the affected individuals in the years to come.

Metabolically healthy obesity will continue to have a lower chance and risk of cardiovascular diseases and mortality than metabolically unhealthy obesity in the future. Based on a study performed by an international group of researchers, the prevalence of obesity has doubled in about 73 countries across the world since 1980 and has increased steadily in others and the health complications associated with being obese and overweight currently affect approximately 2 billion people.(113) The metabolically unhealthy and obese people are reported to have a higher risk of developing type 2 diabetes and cardiovascular diseases than the metabolically unhealthy obese individuals, which increases the risk of mortality.(113) In the future, a higher rate of mortality associated with obesity-related complications will be reported among the metabolically unhealthy obese individuals than the metabolically healthy obese individuals. However, since metabolically healthy obesity is a transient condition, some individuals with the particular obesity phenotype may convert to be metabolically unhealthy in the years to come, increasing their risk of developing obesity-related complications and even mortality.(144) These individuals have a chance of developing glucose intolerance, hypertension, and other elements of metabolic syndrome in the future which are likely to increase their risk for coronary heart disease and even death. The obesity condition, especially the metabolically unhealthy obesity phenotype, is closely linked to future heart disease and higher rates of heart-related deaths. Obese individuals, especially children, have a higher risk of developing eating disorders which lead to the accumulation of fat in the heart posing the risk

of heart-related health complications. Obesity-related disability is likely to increase, particularly in the low- and middle-income countries, in the future due to insufficient insulin supply. It is also projected that disabling nephropathy, retinopathy, arteriosclerosis, and neuropathy will increase in these countries.

The dependence on health care and health insurance will increase in future. It will be higher for individuals with metabolically unhealthy obesity than the metabolically healthy as they experience other obesity-related health complications thus placing more stress on the health care delivery system. Due to the increased spending associated with the obesity epidemic, especially the metabolically unhealthy obesity phenotype involving multiple health complications, individuals will not be able to pay for the costs incurred in treatment and will therefore require health insurance to cater for their medical bills. It will pose an increased burden to insurers and national governments in an attempt to address the epidemic. The increased number of individuals with obesity also implies that healthcare providers will be faced with increased workloads and the burden of providing services to the high number of obesity patients in the future. The metabolically unhealthy obese individuals are more likely to develop multiple health complications than the metabolically healthy, which need to be addressed independently.

Several epidemiological studies conducted suggest that metabolically healthy obese individuals have a lower risk of developing cardiovascular disease as compared to metabolically unhealthy obese individuals.(141) By maintaining healthy habits and lifestyles through eating a healthy diet, having regularly physical activity, and avoiding smoking, individuals with metabolically healthy obesity are likely to remain healthy, thus reducing the risk of developing other serious health problems. On the other hand, the metabolically unhealthy obese individuals are prone to health problems due to their low health status and are more likely to develop health complications in the future, reducing their ability to survive. A

study conducted on population samples from England and Scotland found that MHO individuals did not have any big risk of cardiovascular diseases. Metabolically healthy obese individuals have a lower risk of cardiovascular disease and all-cause mortality as compared to their metabolically unhealthy obese counterparts.

With the increasing obesity levels, healthcare expenses, including direct and indirect medical spending in the diagnosis and treatment of the phenotypes of obesity, are likely to rise further in the future. The healthcare costs are ballooning and getting higher and higher over time. According to Lightwood et al. (145), the costs associated with obesity and its related complications account for about 9% of the total medical costs in the United States annually. A higher economic burden or cost will be associated with metabolically unhealthy obesity as compared to metabolically healthy obesity as individuals can maintain their health status over time. In the future, the high rates of obesity in America and across the world will be a major cause of substantial direct healthcare, human capital, and transportation costs which are directly linked to the obesity epidemic. Due to the increased medical spending and the high costs incurred due to the epidemic, the economic growth of nations will be greatly undermined in future.(140) More costs are likely to be associated with metabolically healthy obesity than with non-metabolically healthy obesity. The reduced productivity resulting from the absence of workers due to obesity-related illnesses, early mortality, disability, and lower quality of life will affect the economy and businesses in the future. As the overweight children mature, businesses will be faced with an increased number of obese workers, leading to a significant decline in productivity.(146) Because of the rising rate of mortality due to obesity and other related health problems, the populations will decline leading to a reduction in the number of people required in the production sector to promote the economic growth of a nation. As a result, the economy of specific countries, and the world in general, will be greatly affected. Obesity, which has become a public health crisis due to its increased prevalence at an alarming

rate, causes the impairment of people's health and quality of life and a significant increment to the national healthcare budget of countries across the world. (146)

1 – 11. Aim of thesis

The aim of this research is to measure the impact of demographics and interventions on the outcome of metabolically 'healthy' obese patients in the United Kingdom with the aid of a large UK- based primary care database. This would allow future studies to examine and compare long-term outcomes of early and aggressive medical and surgical interventions when compared between the two groups, i.e. the metabolically healthy and unhealthy. This would determine which group would benefit more metabolically and therefore allow adjustments to appropriate funding into future weight loss surgeries.

1 – 12. Hypotheses

Model 1 – Are the characteristics associated with transition from the metabolically healthy obese to unhealthy predictable

Model 2 – Is metabolic 'healthiness' a surrogate of survival in the obese

Model 3 – Are bariatric surgery outcomes comparable within the metabolically healthy obese

1 – 13. Objectives of thesis

To elicit the outcomes of the metabolically healthy obese in the UK, this thesis utilises the aid of a large United Kingdom database that would easily determine short- and long-term outcomes of healthy individuals when compared to unhealthy obesity. I sought to define this through a national UK database that can accurately define obesity and isolate metabolic health as a

phenotype. This was based on BMI and the clinical diagnosis of comorbidities defined within the metabolic syndrome. The most appropriate database that would fulfil this was the Clinical Practice Research Datalink (CPRD).

This combination of long-term follow-up of obese patients as well as documentation of chronic diseases associated with obesity allows for interrogation of outcomes of both MHO and those with metabolic syndrome alike. Long-term community follow-up, specifically for metabolic outcomes and interventions, is sparse amongst the obese population worldwide. This thesis aimed at exploring this on a long-term basis using one of the largest community databases in the world (CPRD), and hence to reflect on several aspects of obesity, metabolic health and outcomes.

The CPRD contains important information on patients' healthcare such as comorbidities, smoking, BMI and death. BMI within the CPRD is recorded in 48-65% of patients.(147) The CPRD has been demonstrated to be an accurate representation of the population of England and Wales. However, it has been noted that a bias towards collection of BMI in diabetic patients.(148)

1 – 14. Project overview

Through the CPRD, the health records of more than 5 million individuals currently registered for primary care at more than 680 family practices in the UK are available. From the CPRD database I aimed to initially define and identify the prevalence of the metabolically healthy within the United Kingdom population. This allowed them to identify and statistically interrogate a cohort of 'metabolically healthy obese' individuals within the obese population without any existent comorbidities who were followed up for the duration of the database. This was to study and understand trends in transition to unhealthiness from baseline throughout

time. I also aimed to study those of the obese population who underwent obesity surgery using READ codes (which are a coded thesaurus of clinical terms) for obesity. This allowed me to look at any recorded peri-operative and long-term primary care documentation and outcome with this regard.

Obese healthy and surgical patients were studied longitudinally on a multifactorial level to analyse and predict factors of transition and poorer outcome. Multiple databases within the large datasets were accessed to measure the rate of obesity and the sub-group of the metabolically healthy obese. Then, the role of primary care in monitoring obesity surgery outcome was evaluated. CPRD was used to identify metabolic 'health' recorded in primary care. This was measured and correlated against risk factors including comorbidities, BMI, age, gender, smoking status, regional distribution, Index of Multiple Deprivation, and Charlson score. Then, the role of primary care in monitoring obesity surgery outcome was also evaluated by the number of visits after bariatric surgery compared to prior to the time of surgery.

The effect on all cause mortality was compared amongst the two healthy and unhealthy cohorts to elicit the impact of metabolic syndrome on health and survival. Bariatric or weight reduction surgery as a factor were also considered seperately and analysed to compare both groups of surgical and non-surgical patients for medium- to long-term outcomes. This allowed more depth on the operative cohort in order to associate perioperative outcomes from the primary care database in bariatric surgery and related specifics.

1 – 15. Study population:

The population included for the purpose of this thesis were

- patients over the age of 18
- diagnosis of obesity at any time since initial registration
- BMI of or greater than 35 kg/m^2

- patients who are metabolically healthy (i.e. 0 comorbidity)
- database interrogated for erroneous weight, height and BMI recordings

1 – 16. Study Type

The study consisted of primarily descriptive and longitudinal analytical research.

1 – 17. Study Design

This is a population-based retrospective cohort study. It identified through CPRD all 'metabolically well obese' from a cohort of obese patients with a READ diagnosis translated into individual medcodes. Medcodes are individualised alphanumeric codes unique to individual readcodes. This was cross-referenced with recorded BMI measurements. Records within the CPRD were filtered to exclude and interrogate those who have no comorbidities, but also to sub-define the population. The cohort was aggregated and analysed. Independent predictors of 'healthy obesity' were identified from primary care data from the current literature and examined. The initial recorded BMI readings were formulated to a BMI reading of greater or equal to 35 kg/m^2; erroneous readings of weight, height and BMI were eliminated. A BMI 35 kg/m^2 was the cutoff of obesity throughout this thesis for two main reasons. Firstly, the authors considered the National institute of Clinical Excellence (NICE) guidelines for consideration of surgery as BMI of 35 kg/m^2 and above associated with 1 or more comorbidity. Secondly, more importantly, to eliminate selection bias in this thesis for a true reflection of the metabolically healthy obese as the association of a lower BMI category would potentially mean a more healthy subcohort of obesity and hence a falsely condensed prevalence of metabolic health.

1 – 18. Sample Size

Our extract from the CPRD contained 414,000 patients of which 231,399 patients had both a medical diagnosis of obesity and a cross-referenced BMI reading of ≥ 35 kg/m^2. This was the cohort used for chapters 4 and 5. Therefore, a cohort study would allow comparison of pathways between the introduction of obesity surgery to the metabolically healthy obese population. Studies have shown that there are up to 3,882 obese patients from the community database who also underwent obesity surgery.(76)

The intention was to assess the safety and fate of metabolic health associated with morbid obesity. The pathway of this sample of the population was initially traced by identifying them through READ codes from the CPRD database. This also allowed post-operative evaluation of operative outcomes as well as mortality rates.

Chapter 2

Materials and Methods

The use of a large database

Clinical Practice Research Datalink (CPRD)

2 – 1. Background

The Clinical Practice Research Datalink is an observational data research service, jointly funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA), designed to maximise the use of NHS clinical data to enable many types of observational research and convey research outputs that are beneficial to the public. It is an administrative dataset of routinely collected data that collates information from UK primary care. The CPRD harnesses general practice data and produces a primary care dataset, which is one of the largest databases of longitudinal medical records from primary care in the world. Established in London in 1987, the small Value Added Medical Products (VAMP) dataset grew to become the General Practice Research Database (GPRD) in 1993 before expanding to become the CPRD in 2012.(150–152)

In November 1993, its parent company was acquired by Reuters Health Information, which donated the database to the Department of Health in 1994, at which time it became the General Practice Research Database (GPRD). This was operated by the Office for National Statistics until 1999, at which point the Medicines Control Agency (MCA) took over. This agency became the Medicines and Healthcare products Regulatory Agency (MHRA) on 1 April 2003 following a merger with the Medical Devices Agency (MDA). Since then, use of the database has expanded within the UK and overseas. The GPRD was run as a sub-division of the MHRA.

In March 2012 the database was renamed the Clinical Practice Research Datalink (CPRD). The research utility of CPRD has been dramatically enhanced by linkage to other datasets on an individual patient level. External datasets included the Hospital Episode Statistics, death certificates, the national cancer registry and MINAP (cardiovascular disease) registry.

Since 1987, when the CPRD was founded, over 600 general practices in the United Kingdom have registered with it. Primary care practitioners in these practices use the Vision Clinical System® software (In Practices Systems Ltd) or EMIS health (Intelligent conversation) to maintain electronic health records for patients and record information during consultations in real-time. From this system, anonymised patient information is automatically uploaded to the CPRD database, which is updated monthly and made available to subscribers through the online server (CPRD-GOLD). There is an opt-out clause for patients in consenting practices to withdraw from upload of their information.

The UK CPRD is a computerised database containing longitudinal medical records from primary care that have been anonymised. As of March 2011, there were over 12 million patient records that were translated to over 64 million years of prospectively collected data. With the transition from the GPRD to the CPRD, the volume of patient records has been estimated to have increased to 52 million.(151) The information available through the CPRD includes patient demographic data, symptoms, signs, referrals, immunisation history, behavioural factors, diagnostic tests, medical diagnosis, and prescription history, as well as health outcomes.(152) The CPRD is constantly assembling anonymised data from millions of individuals, currently approaching almost 10% of the UK population, with consistent research standard data. (153) Patients who are registered with a participating primary care practice are included, unless the patient has requested not to be part of the data-sharing.(150) The CPRD database is extensively utilised in observational studies such as research on clinical epidemiology, disease patterns, drug utilisation, and outcomes research, producing over 800 publications.(4) The major advantage of CPRD as a research tool is its large volume of records, attributes of patient visits as well as practice features (154), along with a past medical history

(however, it suffers from missing data of patients owing to the fact of voluntary input).(154) For this reason, the CPRD is useful as an apparatus for epidemiological research.

A dataset obtained from the CPRD typically contains data on a patient's gender, age, year of birth and details of registration. General practices that are participating in the database share the details of every episode of illness along with any new symptom, as well as every pertinent morbidity event, such as most clinical contact, most significant diagnoses and test results, and every outpatient clinic attendance and hospital they have been referred to and admitted in.(155) For the general practitioner (GP) the most suitable diagnosis is within a drop-down list of possible options, which corresponds to the Oxford Medical Information Systems (OXMIS) and READ codes. The therapeutic data obtained from CPRD includes prescriptions with the utilisation of codes from the Prescription Pricing Authority, complete with the date, dosage and method of administration of that medication. Other data in the database include vaccinations, body weight and blood pressure values, and results of laboratory analysis as well as information on lifestyle.

I set out to assess the quality and completeness of the obtained data to help appreciate the validity of research results derived from the CPRD. For example, it was the data obtained from the CPRD that provided insight into the diagnostic coding of autism.(156,157) The number and high validity of a recorded diagnosis of autism shown in such studies was a deciding factor that facilitated enforcing that the results of the study were accredited. The CPRD engages in several ongoing validation processes to ensure that the information is compatible with a minimal standard of completeness and quality; this is made up of patient data (e.g. age, sex, details of registration and dates the events occurred), extent of completeness, continuity and plausibility of electronic data recording in key areas at the practice level (for instance, making certain that a minimum specified percentage of deaths comes with the recorded cause of death, a minimum referral rate per 100 patients, and a minimum number of prescriptions per patient

per month).(153) Furthermore, prescription information in the CPRD is well documented, as the GP uses the system to produce electronic prescriptions that are automatically recorded in the database. This marks the therapy file as comprehensive,(158) with the exception of prescriptions that were issued in secondary care as well as drugs that were bought over the counter.(157) On the other hand, new diagnoses may be manually recorded on the system and even though it is required that every significant diagnosis must be included, sometimes they may not be complete. Also, certain conditions may be misdiagnosed or miscoded in GP records, and provisional diagnoses coded as if they are certain. To explore the veracity of this claim investigators have evaluated the validity of certain computerised diagnoses through validation studies.

Studies that have investigated the validity of diagnoses in the CPRD have postulated that there is a high validity, as well as reporting to have found strong measures of positive predictive value (PPV), sensitivity, and specificity.(159,160) However, there is also a systematic review of all validation studies of diagnoses that aims to evaluate if the evidence presented is accurate.(153)

The aim of the following review of the literature is to determine how accurately and completely the data regarding diagnosis is recorded in the CPRD. Furthermore, it seeks to evaluate the methodology used to validate diagnoses in the CPRD, summarise the findings of these studies, and evaluate the quality of reporting of validation methods and results.

Diagnostic algorithm

Description

The presence of codes for specific signs/symptoms, prescriptions, and/or confirmatory test results were used to validate a diagnosis.

Example

Eastwood et al. (161) validated diabetes by using medication, hyperglycaemia, diabetes medication, blood tests, diabetes complications, and cardiovascular disease risk factors.

Manual review of anonymised free text on computerised records.

Description

The entire computer records (including the anonymised free text) for persons with a diagnosis were evaluated to confirm evidence of disease status.

Example

Wang et al. (162) were able to validate ovarian cancer by reviewing the computerised records to search for clinical events to confirm the diagnosis

Sensitivity analysis

Description

An analytical study was used to identify the measurement of effectiveness using a broad set of disease/therapeutic codes and their counterpart validation method.

Example

Charlton et al. (163) analysed the risk of neurodevelopmental disorders (NDDs) following prenatal antiepileptic drug (AED) exposure in children born to women with epilepsy.

External

Questionnaire to GPs

Description

A questionnaire was sent to GPs to investigate several aspects of the computerised diagnosis.

Example

Rodriguez (164) used a questionnaire sent to GPs to validate prostate cancer by comparing answers with computerised diagnosis

Record request to GPs

Description

GPs were requested to provide anonymised hard copies of medical records, hospital discharge summaries or death certificates. The results obtained were used to examine and validate the diagnosis, by utilising more diagnostic criteria.

Example

Hall et al**.** (165) sought for medical records of lung cancer patients to verify the cancer diagnosis made in the computerised records

Comparison of rates

Description

Measures of disease incidence, prevalence or patterns (e.g. time trends) from CPRD data were compared with a non-CPRD, UK-based data source

Bhatnagar et al.(166) compared the mortality, morbidity and treatment of cardiovascular diseases in England with those of Ireland and Scotland.

A total of 1,720 non-duplicate abstracts were sourced from the PubMed, EMBASE and website searches, of which 927 were not CPRD studies, following review of the title and abstract.

Furthermore, reviewing articles and a thorough search of related journals and conference proceedings produced a further 310 studies. The factors that led to a study being excluded were: having no validation of the diagnosis being investigated (n = 652); if the data source used was not CPRD (n = 98); if the source included a repeat diagnosis validation (n = 85); or if a diagnosis was not investigated (n = 181), e.g. a study that did not include prescriptions or procedures. Fifty-eight of the 310 publications carried out a validation of a single diagnosis utilising a combination of methods. For example, Ruigomez (167) (2005) carried out three validations of atrial fibrillation: initially, a manual review of computerised records, followed by a questionnaire to the GP, and finally comparing incidence of the disease to an external source. Thirty-five papers validated more than one diagnosis, e.g. Hippisley-Cox et al. (168)(2014) validated cardiovascular disease, ischaemic stroke, type 2 diabetes, osteoporotic fracture and hip fracture, moderate and severe kidney failure, venous thromboembolism as well as intracranial bleed and upper gastrointestinal haemorrhage. There were 21 publications where validation was the major focus of the research. The majority of the validations (85%) were external, with use of a questionnaire to the GP being the most frequently used (56%) and studies that compared the rates of conditions being 33% of the 310 validations. With regards to internal methods, 52 studies utilised this method, with several of them (30) using a manual review.

Estimates of validity

Overall, a high number of cases were confirmed for all diseases, with a median of 86% and a range 24–100%. This means that 86 of 100 cases that had a computerised diagnosis were confirmed with further internal or external information. However, in every disease co-morbidity the frequency of cases confirmed varied, even though the median proportion was greater than 83% for the majority of the categories. The findings could not individually confirm the cases through rate comparisons and sensitivity analyses, but offered further evidence of a high validity of diagnoses in the CPRD. Although the number of such studies was small, the

rate of disease incidence and prevalence based on CPRD data were in line with other UK population-based datalinks. For example, Watson et al. (2003) (169) reported that based on data from the CPRD, the incidence rate of rheumatoid arthritis (RA) was 50% higher than previous studies, and this was because GPs participating in the CPRD were certain of an RA diagnosis compared with rheumatologists. On the other hand, Jordan et al. (170) reported that the prevalence of musculoskeletal diseases in the CPRD was lower and probably underestimated in comparison to other general practice databases. The majority of the sensitivity analyses did not show a variation in the measures of effect calculated with a wide range of codes and those with limited set of codes, showing that many of the cases that were part of the original definition were verified using firmer standards.

Discussion

With the extensive strategy that it utilised, this study intended to capture as much validation of the CPRD diagnostic data that was published within the period of interest. The most valid technique of validation is likely to be asking for further information from the GP, because this method utilises external data to clarify the status of the disease of individual cases. Many of these validations were limited to evaluating or reviewing the responses GPs provided to the questionnaires, thus providing an estimate of the positive predictive value (PPV) of that set of codes. Even though the PPV is a measure, it differs depending on disease prevalence; thus if the disease incidence has not altered over time, utilising historical validations may not be exclusively correct.

There may be a difficulty with the generalisation of the findings of validation studies, since there are certain CPRD practices that do not give consent to research studies. So, even though a high number of practices comply with researchers, the observed PPV will only be obtained from cases within a subgroup of practices only. By doing so, practices that do not take part in validation studies may end up providing data for solitary cases. For example, Thomas et al.

(171) found that certain practices refused to provide copies of very large case files, plausibly leading to selection bias among researchers.

A comparison of rates of validation provides a quick indication of the reliability of the CPRD. Such comparisons do not validate separate cases or offer a statistically significant estimate of validity. In studies comparing prevalence rates, the CPRD may show decreased lower prevalence since it is not necessary for GPs to code prevalent diseases after every consultation.(171) Even though the findings are essential for descriptive purposes, comparing the rates of disease conditions lacks the ability to identify data or cases that have been misclassified between varying diagnoses.(153) Thus relying on this technique to ascertain the validity of a diagnosis in the CPRD should be done carefully and it will not be useful in analytic studies that require individual validity. In the same manner, while sensitivity analysis indicates the quality of diagnosis, it is not a significant validation of the data. Nested case-control studies make up the majority of the research done with CPRD data. Thus, future researches using case-control studies need to engage similar inclusion and exclusion criteria. On the other hand, validation studies that are based only on cases may deliver more insightful criteria for cases than for controls.

Conclusion

The CPRD is a very useful and effective tool for researching morbidity as recorded in primary care, even though the quality of studies using the information is dependent on the validity of data input. It is therefore imperative for researchers to carry out certain forms of validation before using the data. Currently, robust validations seeking further clarification from GPs are limited in size due to the cost involved, thus compromising the generalisability of the findings owing to many practices declining to participate in studies. The database is also being updated

to expand the CPRD as a genuine tool for controlled randomised trials and as a sampling frame in order to get genetic data. Linking the CPRD with other healthcare databases, morbidity registers, and death certificates will enable researchers to synchronise diagnoses made in the hospital. On the other hand, the utilisation of such associations will bring up questions regarding how to solve the problem of unrelated or missing diagnoses in the linked databases. It is hoped that this study will provide greater discussion about how best to evaluate the quality of the database to further improve the validity and the effectiveness of the CPRD in future research studies.

2 – 2. Funding

The CPRD is owned by the UK Department of Health and operates within the MHRA. It has received funding for studies from the MHRA, Wellcome Trust, Medical Research Council, NIHR Health Technology Assessment programme, Innovative Medicines Initiative, UK Department of Health, Technology Strategy Board, Seventh Framework Programme EU and various universities, contract research organisations and pharmaceutical companies.(150)

2 – 3. Population:

The database, originally known as the GPRD, has recorded patient data since April 1987. Although this equates to almost a quarter of the UK population, patients who move practices are given a new unique patient identifier and may be double-counted. The number of patients with more than one identifier in the CPRD is not known. However, the CPRD quotes that the population coverage of their database to be roughly 8.9%. (150,172) This covers all four countries in the UK and the population coverage has been found to be geographically representative of the UK population through comparisons of demographic and mortality data from the Office of National Statistics (ONS).(173)

2 – 4. Cohort description:

The extract consisted of patients in the CPRD who had primary care records that met the CPRD acceptability criteria, were of male or female gender, and were registered at an up-to-standard, practice for at least one day during the study period of 1st January 1987 to 31st of August 2016.

The primary care database provided events in the community such as consultations before referral to hospital for comorbidities and complications managed by the primary care physician. The relevant READ codes were obtained from the NHS Information Authority Clinical Terminology Browser.

Outcomes varied of this cohort of metabolically healthy obese patients and determine what the specific outcomes are compared to the other unhealthy type of obese patients. Specifically, I was looking for primary outcomes of mortality and secondary outcomes of coronary heart disease, stroke, cerebrovascular accident, obstructive sleep apnea, and hyperlipidemia as well as depression on long-term follow-up of this cohort.

The main covariate was introduction of bariatric surgery to the initial cohort of metabolically healthy obese and identifying the effects of this covariate on the short- and long-term outcomes.

2 – 5. Data extraction

The CPRD extracts data onto a secure access gateway accessible by only certain keyholders who have subscribed to receive data access. Once the ISAC protocol is approved the data handlers are able to extract data with certain medical READ codes that resemble a clinical diagnosis or a measurable factor. Once the complete set of READ codes have been collated, the author has access to a look-up online data dictionary to establish a list of medical alphanumeric codes that can be extracted. This means that any time this alphanumeric code is

recorded within the whole CPRD duration database, the entire relevant patient details and every related non-identifiable data field ever entered for this patient are extracted.

2 – 6. Database structure

Each subscriber can extract records from the CPRD database via the CPRD GOLD online data access server. The data is received in text files. Due to the size of each database subsection, each subsection is divided into multiple text files that require merger to form a complete dataset. The entirety of the database is correlated to a specific separate aspect of care related to the patient and all linked by a nonidentifiable patient identification number. The individual database files within the CPRD constitute:

1. Clinical
2. Therapy
3. Patient and practice
4. Consultation
5. Additional
6. Test

Comorbidities can be extracted through medcodes from the relevant clinical dataset, for example:

Diabetes
Hypertension
Coronary artery disease
Congestive cardiac failure
Peptic ulcer disease
Diabetes and diabetic complications
Chronic liver disease and severe liver disease
Renal failure
Stroke/ CVA/Paraplegia
Cerebrovascular accident
Chronic pulmonary disease
Dyslipidaemia
Asthma
Obstructive sleep apnoea

Individual text files are then read using statistical software, namely the Statistical Package for Social Sciences (SPSS) [IBM Statistics version 24/25 SPSS Inc., (New York), USA], and these

numerous SPSS database files are merged into a large final dataset. This dataset is saved on a secure access gateway as the main extract combined dataset for ease of access for future analysis; relevant other datasets are then merged onto the main combined dataset accordingly as needed. The methodology and the use of these large datasets are much influenced by the required criteria and factors looked at on a particular study and the aim of the hypothesis.

2 – 7. Data/ Statistical analysis

All analyses were performed on SPSS (version 24.0 for Windows, SPSS Inc.). Descriptive analyses of the study population included the number of GP practices, years that the practices have participated in the GPRD/CPRD, deprivation, and geographical location of the practices. The precision of the obesity prevalence calculations was denoted by the reporting of 95% confidence intervals. The rate of metabolically healthy obesity was compared according to risk factors (age, sex, socioeconomic status, BMI, cancer stage, and Charlson score), mortality and process measures (number of consultations, re-referral to original team, and referral to other specialty). Univariate analysis was used (independent and paired t-tests, non-parametric Mann-Whitney and Wilcoxon sign rank tests), bivariate analysis (Chi-squared test for qualitative variables, simple linear regression, Pearson and Spearman correlation), and multivarite analysis (Multiple linear regression, binary logistic regression, Kaplan-Meier survival analysis and Cox regression).

The reliability of generated regression models was examined through sensitivity analyses. Once characteristics or risk factors had been identified then a multilevel regression and correlation were undertaken for the long-term outcomes after addressing confounders such as demographics, regional distribution and socioeconomic status. Subsequently, subanalysis of the subgroup with Bariatric surgery exposure within our cohort was conducted and cross-matched to compare various outcomes compared to unhealthy patients matched for age,

comorbidities and characteristics. Multivariate analysis, Cox regression, was performed for this as well as a Kaplan-Meier survival analysis.

2 – 8. Plan for addressing confounders

The robustness of the analysis and regression results were examined through sensitivity analyses. Multilevel hierarchical modelling clustered patients, practices and secondary care providers. Both cohorts were matched and adjusted for any confounders. Survival analysis was performed by Cox regression analysis from time of diagnosis to transition to unhealthy and from time of diagnosis to death.

2 – 9. Plan for addressing missing data

Patients with missing data were excluded as the author included a complete case analysis approach without any imputation of missing fields. This thesis assumed that most missing data would be so completely at random and that this percentage would be small. For BMI, previous studies have shown that data may be missing in up to 50% of non-diabetic individuals and therefore this data is missing at random and the missingness is dependent on whether the patient is diabetic.(147) In this circumstance, as the missing data rate is high, multiple imputation by chained equations were used to model the association between BMI and outcomes. Patients who had left a practice were identified using the 'transfer out date' code in the CPRD. Out of these patients, those who have died were identified using the transfer out reason code (toreason) and included in the analysis. Data linkage to the Office of National Statistics was undertaken to overview the accuracy of mortality recording, which is a means of external validation. This was considered when assessing overall mortality for comparison between both the metabolically healthy and unhealthy. Patients were also verified by date of death and date of transfer out and ensured there were no repetitive similar patient identifiers and year of births

deceased or transferred out on the same date. There was no apparent literature about the validity of transfer out deaths from the CRPD database.

2 – 10. Limitations

Limitations of the study design, data sources, and analytical methods include:

- This study relies on the detail recorded by the GP or other health care professional at the time of consultation, which may vary between general practitioners and between various practices across the UK.
- The timing of the start of diagnosis of obesity is not reliably available through GP READ codes as this usually depends on registration date and date of first weight recorded relatively. This thesis would consider both diagnosis of obesity date cross-referenced to the weight and height data entry date equating to the body mass index.
- The definition of obesity diagnosis could vary according to practice criteria.
- The CPRD contains data derived from an existing coding system that was not designed specifically to measure bariatric procedures or other procedural codes but was instead more specific to clinical and quantitative measurements codes as well as therapeutic codes for relevant prescription medications.
- Various codes are available for similar comorbidities seen in the search criteria.
- Patients often have operations privately or overseas and data on these only rely on the patient's knowledge of the type and timing of operation and hence are not precise documentations.
- Missing BMI recordings mostly, but compensated by the diagnosis of obesity in seldom cases although overall BMI recordings were more frequent and reliable.
- Patients moving or changing practice and hence lost to follow-up.
- Some variables are poorly documented, such as ethnicity.

2 – 11. Information Governance

In addition to anonymisation of the patient identifiers, the data collection software also encrypts practice numbers and the identity numbers of doctors and other practice staff who entered data

into the database. Strong identifiers, such as NHS number, postcode and name, are not collected. The owners of the CPRD have obtained ethics approval for all observational studies using their database. This means that users do not require ethical approval for each individual study undertaken. However, all studies resulting in publication need to be approved by the Regulatory Agency's Independent Scientific Advisory Committee (ISAC), who are consulted to ensure studies undertaken are of an appropriately high scientific standard. ISAC approval was obtained for this investigation on the 16th August 2016 (Appendix 1).

The College's institutional Data Protection Number is Z5940050. Data was accessed throughout the length of research in a secure locked room on a personal computer that is not connected to the internet. There was encrypting software, password protection log-in, Caldicott Guardian and Care Record Guarantee in place. To protect confidentiality, all person-identifiable data processed was compliant with the Data Protection Act 1998 and Department of Health guidelines. Annual reporting of information security was in line with BS7799 Information Security Management Code of Practice.

2 – 12. Ethics

Scientific approval was acquired from the Independent Scientific Advisory Committee (ISAC approval registration number 16_140R2), and ethical agreement was sought through the Health Research Authority (IRAS Project ID: 203143). A full proposal was submitted and accepted after vigorous data governance and compliance checks for continuous data access.

Chapter 3

Transition of the metabolically healthy obese

(A study from the Clinical Practice Research Datalink)

Transition of the metabolically healthy obese

3 – 1. Introduction

As discussed above, the term obesity can be defined as a state of being excessively overweight. Obesity is a global epidemic that affects more than 600 million adults. In 2014, more than 1.9 billion people were reported to be overweight by the WHO.(2) A phenotype of patients who do not present metabolic abnormalities among the obese population is referred to as the metabolically healthy obese (MHO).(103) This group of individuals is believed to be associated with a subordinate risk of developing obesity-related complications.(26) The natural course of the MHO condition is unidentified and no agreement exists on the precise MHO definition.(68)

Research on the clinical outcomes of the MHO has produced different results.(174) A few studies have shown that MHO individuals have a lower risk of cardiovascular disease than unhealthy counterparts but different research has reported no differences between MHO individuals and normal-weight ones in terms of these risks.(102,175) Further studies have reported that MHO can significantly increase the risk of developing diabetes (114). Clinical results in MHO may be influenced by differences in fitness, the percentage of fat, bone, water, and muscle in the human body, and inflammatory profiles. MHO individuals have been reported to have better fitness than metabolically at-risk obese individuals (176). They have also been found to have more favourable inflammatory profiles than individuals with metabolically abnormal individuals.(177) Several definitions have been put forward to explain the presence of Metabolic Syndrome in adults by five different sources (36,38,178,179).

To identify the magnitude of this cohort of patients in the UK, the author set out to use the UK CPRD, a computerised database established in 1987 containing anonymised longitudinal

primary care medical records. Of all the European databases, the CPRD in the UK is considered amongst the largest and has been the most widely used for pharamcoepidemiological research.(180) The ability to offer prospective follow-up data for research is driven by the fact that all residents in the United Kingdom are registered with a National Health Service general practitioner. The availability of long-term follow-up data since 1987 inspired this study to investigate what happens to metabolic healthy individuals within a large UK community database.

The CPRD is constantly assembling anonymised data from millions of individuals, currently denoting almost 10% of the UK population, with other consistent research standard data (181). Studies that have investigated the accuracy of diagnoses in the CPRD have postulated that a high accuracy exists within its recordings, as well as reporting to have found strong measures of positive predictive value (PPV), sensitivity, and specificity.(153,159) This was particularly demonstrated in cardiovascular disease,(181) dementia,(182) cancers (183,184) and other morbidity diagnostic codes generally.(159,160,173,185)

3 – 2. Aim

The CPRD is a large-scale clinical general practice care database tool for community clinical follow-up. The aim of this analysis was to assess the stability of, and evaluate the factors associated with a transition into an unhealthy outcome in, a metabolically healthy obese population in the UK. I sought to determine the prevalence of metabolic health within this obese population from long-term follow-up within the primary care setup.

3 – 3. Methods

3 – 3 – 1. Clinical Practice Research Datalink

Data for this study was extracted from CPRD records to the end of August 2016. Obesity diagnosis was made with a recorded BMI greater than or equal to 35 kg/m^2 on at least 2 occasions, (to eliminate bias from a smaller BMI cohort towards metabolic health), and the reference date was the first recorded BMI date. The medcodes (medical diagnostic codes entered by general practitioners on the CPRD) use a code list to extract a subset of the data, adding a row with a category for each record. Similarly, prodcodes (therapeutic medications codes) are numeric vectors representing relative therapies. I used READ terms to establish the relevant medcodes of comorbidities and other associated characteristics examined.

3 – 3 – 2. Metabolic Health definition

Various definitions of metabolic syndrome and health in obesity are available. Participants were further classified as metabolically healthy according to a strict modified definition to accommodate criteria accessible from the CPRD. I defined the metabolic healthy obesity as those patients with no comorbidity and not on any relevant therapy for the metabolic syndrome-associated morbidities of established diabetes, hypertension, Dyslipidaemia, cardiovascular disease, or cerebrovascular disease, liver or renal disease and obstructive sleep apnea. This definition was used to define metabolic health at baseline and follow-up to determine the prevalence of MHO. The database was compiled to include patient demographics, regional distribution and Index of Multiple Deprivation (IMD). IMD is a score of the socio-economic background of a neighbourhood considering: income, employment, health deprivation and disability, educational attainment, barriers to housing and services, crime, and living environment.(24)

3 – 3 – 3. Data restriction

The initial cohort extracted limited to a BMI ≥ 35Kg/m^2 was 231,399 patients; primarily this was restricted to between 18-60 years of age, excluding 48,141 patients of which 44,265 were aged 60 years and above. The cut-off age of 60 years was chosen to reduce age bias and assess follow-up for a period of at least 5 years. Similarly, a further 6,574 patients with erroneous extremes of weight and BMI measurements were excluded.

Data restrictions:

- BMI 231,399
- Age restricted (18-60 years) 187,134
- Weight restricted (60-220 Kg) 187,028
- Follow-up restricted (300 months) 180,560
- Deceased 8,534 (4.7%)

3 – 3 – 4. Timeline definitions

The first BMI≥35kg/m^2 reading was considered the baseline reference date. Comorbidities were considered at baseline, similar to previous studies,(173) and the definition of time to diagnosis within 3 years prior and up to 6 months after initial reference baseline diagnosis. As in earlier research, this was to avoid left censoring, accounting for patients already diagnosed and on therapy and not repeatedly coded longitudinally as a new onset diagnosis or therapy at baseline. End of follow-up was defined as the last episode entered for a diagnosis, therapy, relevant associated clinical episode or as transfer out of practice reasons (including death). Similarly, time to unhealthy outcome indicates the time to either acquire a comorbidity code or be started on a regular relevant therapy prodcodes.

Time to final outcome, unhealthy outcome, or final follow-up was limited to patients followed up after 1987 (i.e. the start of CPRD database collection nationwide).

3 – 3 – 5. Statistical Analysis

Data was prepared and analysed using the Statistical Package for Social Sciences (SPSS) [IBM Statistics version 24 SPSS Inc., (New York), USA]. Normally-distributed continuous outcomes were presented as means (standard deviations [SD]), while non-normal variables were presented with medians and interquartile ranges [IQR], and categorical outcomes were presented as relative frequencies (%). Significance of differences among BMIs with metabolically healthy or unhealthy phenotypes were tested. A Chi-squared test was used to compare categorical variables. Student's t-test and one-way analysis of variance (ANOVA) were applied to compare between 2 groups, or more than 2 groups in case of normally-distributed quantitative variables. To evaluate the factors associated with a metabolically healthy status, survival analysis was performed using unhealthiness due to metabolic comorbidities as the status and with independent variables such as gender, age categories, BMI categories, geographical region, smoking status, and bariatric surgery as well as index of multiple deprivation.

3 – 3 – 6. Associations and longitudinal analysis

Univariate and then multivariate analyses were undertaken to determine associations and predictors of transition into an unhealthy status. A Kaplan-Meier and Cox regression hazard analysis was implemented to assess factors associated with time to final outcomes allowing for censored cases lost to follow-up.

3 – 4. Results

3 – 4 – 1. Patients extraction

The Clinical Practice Research Datalink contained 123,760,872 records for 414,522 patients who had a clinical medcode diagnosis of obesity. There were 231,399/414,522 (55.8%) actual measured BMI ≥35 Kg/m^2 recorded, and therefore initially included in our study population.

After age, BMI, and weight restriction for erroneous values our cohort contained 180,560 patients. There were 155,113 patients with up to 10 years follow-up and prevalence of MHO was 64,732 (41.7%). This displays the strength of long-term follow-up on CPRD. Time to final outcome ranged between 1 and 1,088.7 months; erroneous date entry within the CPRD database is recognised and to eliminate time bias this was limited to 300 months (25 years). The final number of patients in this study included amounted to 180,560 patients.

3 – 4 – 2. Baseline patient characteristics:

The mean age in the study was 40.3 (SD 11.5) years and the majority of patients were in the age group 40-50 years (27.4%). There were 57,990 (32.1%) males in the cohort while 122,570 (67.9%) were females. Weight was recorded in 180,560 patients, with a mean of 108.6 (SD 17.2 kg). Recorded BMI was available for 180,560 patients with a mean of 38.8 (SD 4.5 kg/m^2). Most of the patients were in the BMI category 35-40 kg/m^2 (70.4%) and the BMI category with least patients was >60 kg/m^2 (0.4%).

3 – 4 – 3. MHO prevalence

Metabolic health was defined as a strict absence both of coded diagnosis of comorbidity and of therapeutic codes for relevant medication. Therefore, the prevalence of MHO within the obese population from the CPRD was 128,191/180,560 (71.0%).

3 – 4 – 4. Follow-up

All obese patients were followed up until a final outcome within database to a restricted range of up to 300 months (25 years). Data was also verified for comorbidities in the entirety of their database presence; this reflected that 80.8% of patients were never diagnosed or started on

treatment prior to the 3 years to first body mass index date. Overall, of those patients who were metabolically healthy at baseline, 71,485/128,191 (55.8%) remained healthy on follow-up, (Chi-square 16.0, p=<0.01) with a mean follow-up of 68.2 (SD 62.6) months. Meanwhile, of the 56,706 (44.2%) metabolically healthy at baseline recorded as comorbid on follow up: 23.8% (p<0.01) had one comorbidity, 11.7% (p<0.01) had 2 comorbidities and 20.2% (p<0.05) 3 comorbidities or more on Chi square cross-tabulation.

Mean follow up varied between metabolically healthy 68.15 (SD 61.61) months and and non healthy 23.46 (SD 38.38) months, p<0.001. Nevertheless, a life table was constrcuted for time to metabolic unhealthiness and found a decreasing annual rate, from an initial 26% in the first year to a gradual decrease over the years to 7% annual cumulative incidence of developing an unhealthy state over a 10-year follow-up period, and a nearly similar rate when performed over a 30-year period (Table 1). Median time to transition was calculated for different age (Figure 1) and BMI categories (Figure 2). Further characteristics of metabolically healthy obese versus those individuals who transition to unhealthy are displayed in Table 2.

BMI loss was also interrogated to eliminate bias secondary to the influence of weight loss on the prevalence and continuity of weight loss in the population. BMI loss was similar in both metabolically unhealthy and healthy with a mean of 4.72 (SD 4.76) Kg/m^2 versus 4.88 (SD 4.91) Kg/m^2 respectively. Furthermore, understandibly there was a significant difference in BMI loss from 4.71 (SD 4.72) Kg/m^2 to 10.59 (SD 7.29) Kg/m^2 p<0.002, between non bariatric surgery and Bariatrc surgery.

Table 1 Life table of annual prevalence of unhealthy outcome

Interval starting time	Number entering interval	Number withdrawing during interval	Number of terminal events	Proportion terminating (%)	Cumulative proportion surviving at end of interval
0	181754	8532	50003	28	72
12	123219	7479	10257	9	66

24	105483	6762	8064	8	60
36	90657	6023	6643	8	56
48	77991	5767	5680	8	52
60	66544	5240	4858	8	48
72	56446	5031	4070	8	44
84	47345	4309	3574	8	41
96	39462	4112	2961	8	37
108	32389	3659	2489	8	34
120	26241	15991	10250	56	15

Figure 1 Kaplan Meier Time to survival without comorbidity for age category

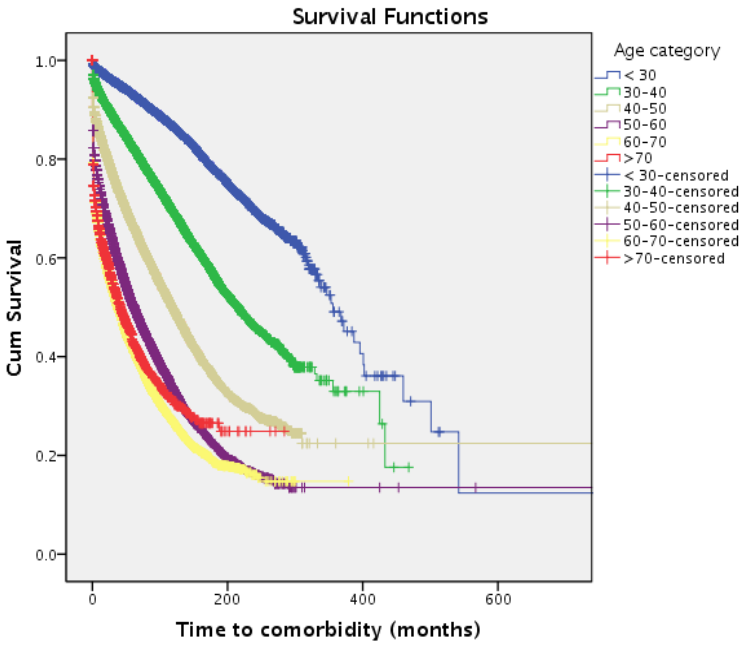


Figure 2 Kaplan Meier Time to survival without comorbidity for BMI category (Time to survival without comorbidity used throughout the manuscript indicates the time longitudinally to either acquire a comorbidity code or be started on a relevant therapy prodcodes).

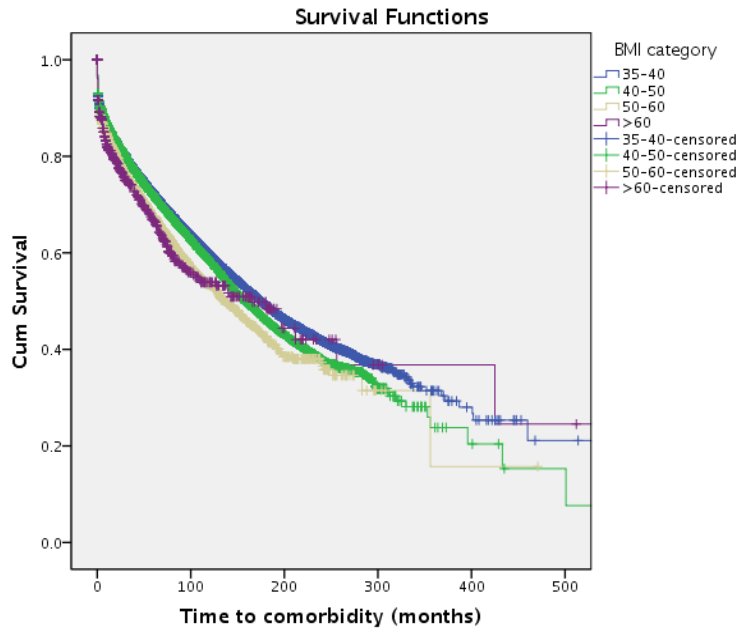


Table 2 Those patients who were healthy on baseline and went on to develop comorbidities on follow up in 72,352/159,961 patients.

		MHO		Non-MHO			
Variable		**n**	**%**	n	%	**Chi**	**Sig**
Gender	M	19792	27.4	28465	32.5	496.5	p = <0.01
	F	52560	72.6	59138	67.5		
Smoker	Y	42523	33.4	4803	3.8	273.5	p = <0.01
	N	73964	58.1	5963	4.7		
Region							
Highest	London	13414	10.5	Wales	1.3	516.3	p = <0.01
Lowest	North	2538	2	Yorkshire	0.2		
Age category							
Highest	40-50	28942	40.0	27261	31.1	16649.5	p = <0.01
Lowest	50-60	7324	10.1	14110	16.1		
BMI category							
Highest	35-40	51887	74.2	60838	72.0	96.8	p = <0.01
Lowest	>60	268	0.4	396	0.5		
Bariatric	Y	1290	1.8	2184	2.5	94.0	p = <0.01
	N	71062	98.2	85425	97.5		
Deceased	Y	1072	1.5	6044	6.9	2735.7	p = <0.01
	N	71280	98.5	81565	93.1		
Index of	Highest	10194	23.7	111962	24.0	13.3	

A univariate Kaplan-Meier analysis, as displayed in Table 3, was performed for BMI categories (Figure 2) to unhealthy transition and was longest in the 35-40 kg/m^2 BMI group (median 114.2 months, p=<0.01), while shortest in the BMI >60 kg/m^2 (median 96.3 months, p=<0.01). Difference in gender transition was significantly reduced in males (87.9 months) compared to females (123.1 months). Smoking was associated with a reduction in disease-free period (104.8 months compared to 116.3 months, p=<0.01) in non-smokers (Figure 7). Regional distribution was found to vary; the longest was demonstrated in Yorkshire and the Humber, averaging 86.2 months (p = <0.01), with the shortest being in the North West of England (59.6 months, p=<0.01). Regional metabolically healthy distribution was demonstrated (Figures 3,4).

Figure 3. Bar chart of regional distribution of Metabolically healthy vs non-healthy (0-Non-healthy, 1-Healthy)

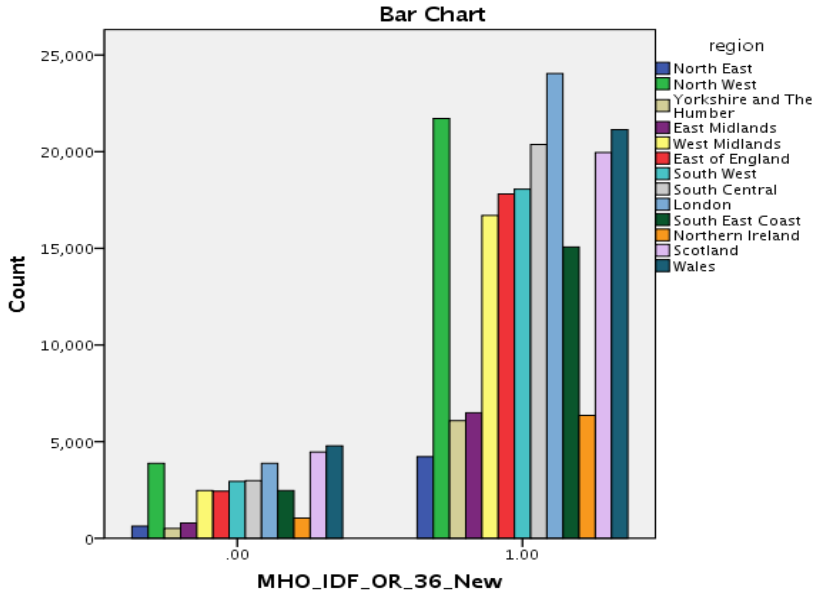


Figure 4. Map region distribution of prevalence of metabolically healthy obesity within UK

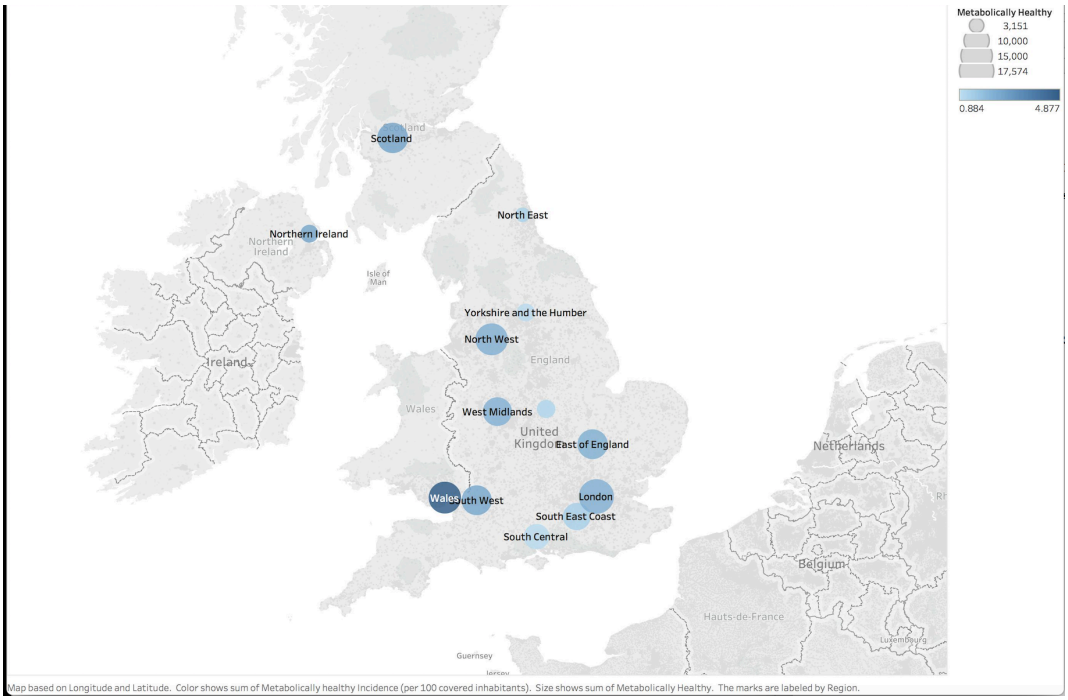


Table 3 Univariate analysis of independent variables associated with transition to unhealthy state

Variable (Total = 180560)		n	Median (95% CI) months	p
Gender	Male	57990	87.9 (86.8-89.0)	
	Female	122570	123.1 (122.2-123.9)	p=<0.01
Smoking	Absent	114082	116.3 (115.4-117.2)	
	Present	66478	104.8 (103.6-105.9)	p=<0.01
Age category	<30	37030	174.4 (172.8-176.0)	
	30-40	35917	127.6 (126.2-128.9)	p=<0.01
	40-50	32832	88.5 (87.3-89.7)	p=<0.01
	50-60	22412	60.6 (59.4-61.8)	p=<0.01
BMI category	35-40	90621	114.2 (113.4-115.1)	p=<0.01
	40-50	29536	107.9 (106.6-109.4)	p=<0.01
	50-60	3256	97.8 (93.6-102.1)	p=<0.01
	>60	475	96.3 (86.6-106.0)	p=<0.01
Index of Multiple Deprivation	1	16147	120.1 (117.7-122.5)	
	2	18570	115.3 (113.2-117.5)	p= 0.24
	3	21811	114.4 (112.4-116.4)	p=<0.01
	4	23622	111.4 (109.4-113.3)	p=<0.01
	5	24964	107.6 (105.7-109.5)	p=<0.01
Bariatric surgery	No	176738	111.8 (111.1-112.5)	
	Yes	3822	121.2 (111.4-112.8)	p=0.01
Lipase inhibitor	No	162885	110.9 (110.1-111.6)	
	yes	7525	119.8 (116.7-122.8)	P=<0.01
Region	North East	3804	72.5 (66.7-78.2)	p=<0.02
	North West	20243	59.6 (57.3-61.9)	p=<0.01
	Yorkshire	5165	86.2 (80.6-91.8)	p=<0.01
	East Midlands	5786	78.4 (73.3-83.3)	p=<0.05
	West Midlands	14931	71.1 (67.8-74.3)	p=<0.01
	East of England	15864	83.1 (79.6-86.1)	p=<0.02

	South West	16067	74.3 (70.9-77.4)	p=<0.01
	South Central	18358	82.8 (79.6-86.1)	p=<0.01
	London	22180	74.7 (72.1-77.4)	p=<0.01
	South East Coast	13790	79.1 (75,6-82.6)	p=<0.01
	Northern Ireland	5917	72.4 (67.4-77.5)	p=<0.02
	Scotland	18623	65.0(62.3-67.8)	p=<0.01
	Wales	19765	62.6 (60.2-65.1)	p=<0.01

There were various independent factors all found to affect progressing to comorbidity significantly on univariate Cox regression analysis, being: male gender (HR=1.43 CI 1.41-1.45, p = <0.01) (Figure 5); higher age group, mostly 50-60 years (HR=4.16 CI 4.07-4.24, p=<0.01); BMI of 50-60 kg/m^2 at baseline (HR=1.28 CI 1.13-1.36, p=<0.01); and a higher index of multiple deprivation (HR=1.14 CI 1.11-1.17, p = <0.01) (Figure 6), on univariate (Kaplan-Meier) analysis. Bariatric surgery (HR=0.92 CI 0.89-0.96, p = <0.01) was a significant independent protective factor from progression to unhealthy state. Being on a lipase inhibitor also had a protective factor (HR=0.89 CI 0.86-0.91, p = <0.01) against transition into an unhealthy state.

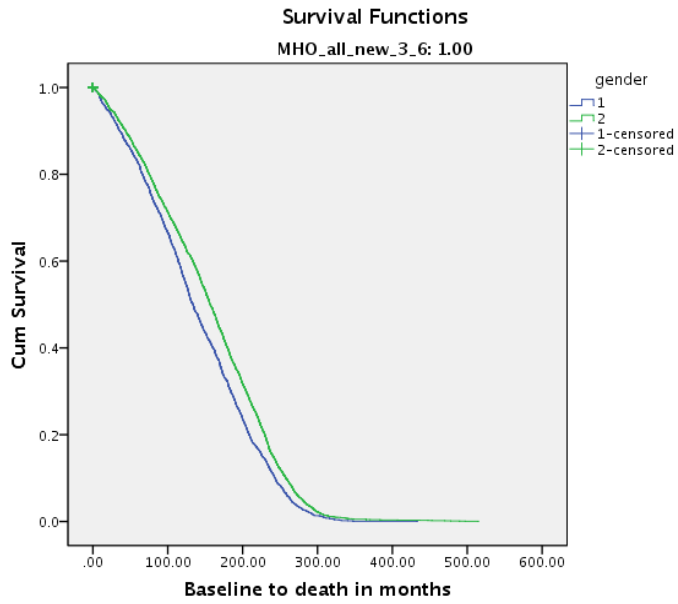


Figure 5: Kaplan Meir curves to transition curves for metabolically healthy within genders on baseline

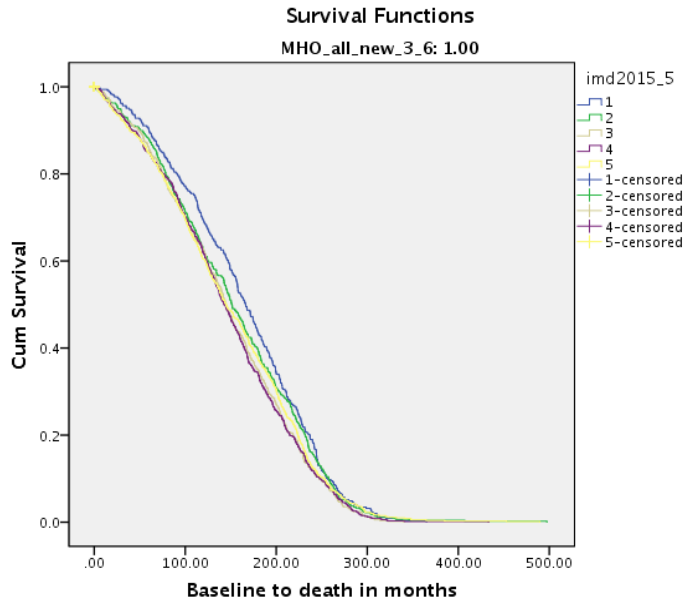


Figure 6: Kaplan Meir curves to transition curves for metabolically healthy within index of multiple deprivations on baseline

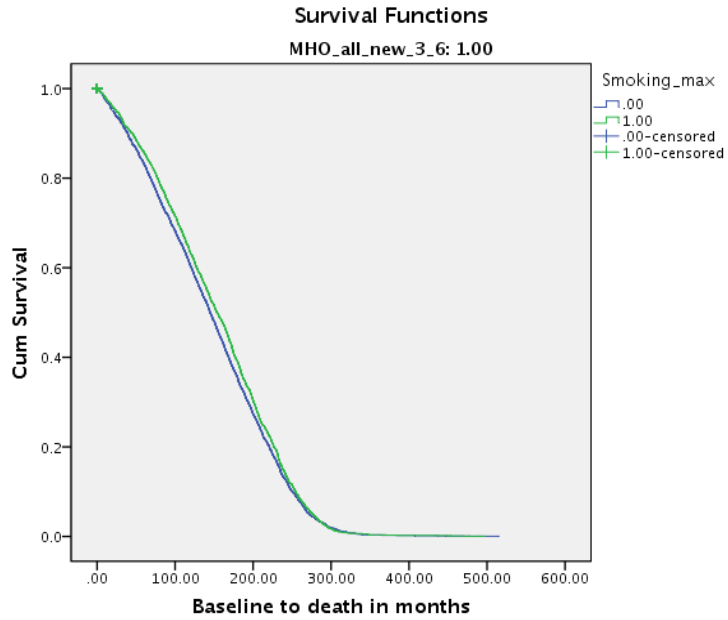


Figure 7: Kaplan Meir curves to transition for metabolically healthy within smokers on baseline

A multivariate analysis Cox hazard regression model was performed using the significant univariate factors which also confirmed significant variables affecting transition to unhealthy outcome on follow-up as demonstrated in Table 4.

Table 4 Multivariate analysis of independent variables associated with transition to unhealthy state

Variable		n	HR (CI 95%)	p
Gender	**M**	32113	1	
	F	69786	1.23(1.21-1.25)	p=<0.01
Smoking	**Absent**	64230	1	
	Present	37669	1.07(1.05-1.09)	p=<0.01
Age category	**18-30**	25387	1	
	30-40	26356	1.64(1.59-1.69)	p=<0.01
	40-50	27557	2.65(2.58-2.72)	p=<0.01
	50-60	22559	3.93(3.82-4.04)	p=<0.01
BMI category	**35-40**	74715	1	p=<0.01
	40-50	23891	1.14(1.12-1.16)	p=<0.01
	50-60	2853	1.32(1.26-1.38)	p=<0.01
	>60	440	1.28(1.13-1.45)	p=<0.01
Index of Multiple Deprivation	**1**	15635	1	
	2	17956	1.03(0.99-1.06)	p=<0.01
	3	21134	1.04(1.01-1.07)	p=<0.01
	4	22885	1.08(1.05-1.12)	p=<0.01
	5	24280	1.16(1.13-1.19)	p=<0.01
Charlson category	**1**	49074	1	
	2	42777	1.84(1.81-1.88)	p=<0.01
	3	10048	2.56(2.49-2.63)	p=<0.01
Bariatric surgery	**No**	99388		
	Yes	2511	1.14(1.08-1.19)	p=<0.01
Lipase inhibitor	**Yes**	91807	1.23(1.19-1.27)	p=<0.01
	No	10092	1	
Antidepressants	**Yes**	83020	1.49(1.46-1.52)	p=<0.01
	No	18879	1	
Cardiovascular disease	**Yes**	101087	1.57(1.45-1.52)	p=<0.01
	No	812	1	
Obstructive sleep apnea	**Yes**	100905	1.31(1.21-1.41)	p=<0.01
	No	994	1	
Cerebrovascular disease	**Yes**	101469	1.57(1.42-1.74)	p=<0.01
	No	430	1	
Chronic Respiratory disease	**Yes**	91071	0.78(0.76-0.79)	p=<0.01
	No	10828	1	

3 – 4 – 5. Mortality

Overall, there was an 8,534/180,560 (4.7%) all-cause mortality rate documented within the CPRD for our cohort (Figure 8). A Kaplan-Meier survival curve was constructed (Figure 2). When compared, the all-cause mortality for the metabolically healthy obese was 4,795/128,191 (3.7%) versus 3,739/52,369 (7.1%) in the non-metabolically healthy obese. The overall mean time from baseline diagnosis to mortality was 64.47 (SD 33.71) months.

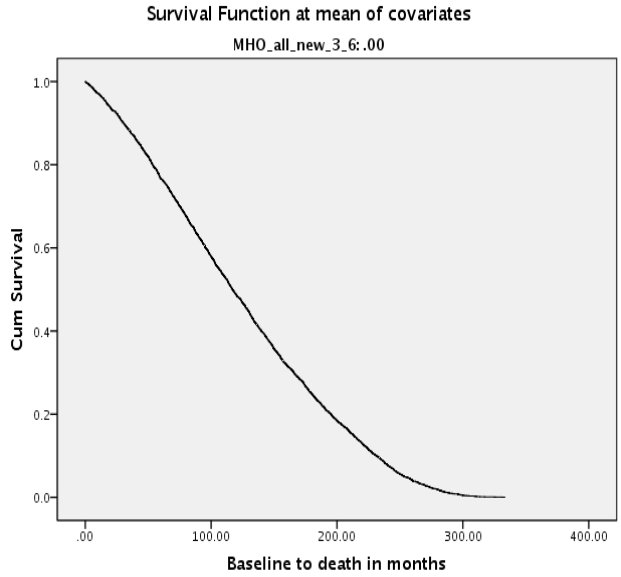


Figure 8: Cumulative survival timeline from baseline to death (months)

3 – 5. Discussion

The long-term outcomes of being metabolically healthy obese remain controversial. Dispute surrounds how the MHO state should be considered and its relevant practical implications for managing this in the obese population. It is unclear whether patients with MHO are simply in a temporary state that will later convert to metabolically unhealthy obesity, or whether they are actually in some way genetically able to function without still developing the sequelae that are observed in other obese patients. This is an important distinction for clinicians, as it may have implications for early intervention, how aggressively weight loss is followed up, and how long-term risks of excess weight are specifically outlined for these individuals. Some studies have demonstrated that MHO individuals have a diminished prospect of developing cardiovascular disease compared with the unhealthy obese individuals,(186) and not at increased risk when compared to metabolically healthy normal weight individuals.(102,179) In an 11-year follow-up study, Meigs et al. established that MHO was associated with a 3- to 4-fold risk of developing Type 2 Diabetes Mellitus or cardiovascular disease events, accounting for 2-3% of these events in the population.(179) The strongest predictor of both MHO and MUO was previously reported as baseline BMI.(187) This was also demonstrated in our study on univariate and multivariate analysis, reflecting the higher BMI category predicted a quicker transition to comorbidity and metabolic syndrome. The overall risk of transition to metabolic comorbidities on medium to long-term follow-up was increased in our study and there was found to be a steady decrease in metabolically healthy prevalence annually (Table 1).

An American longitudinal study similarly reported two-thirds of healthy obese individuals, during 10 years of follow-up, established metabolic syndrome (188) and highlighted a decreasing prevalence of MHO in 11 years of subsequent surveillance.(107) Another cohort reported 42% of their subjects with MHO developed the metabolic syndrome within 10 years.(189) The study reports an initial prevalence of 71%, of which 55.8% of remained healthy

on long-term follow-up. All obese patients were followed up until a final outcome within database to a restricted range of up to 300 months (25 years) which remains the longest follow-up period in UK published literature. A recent published study from the larger European Prospective Investigation into Cancer and Nutrition concluded that those in the metabolically healthy group were at greater risk of coronary heart disease.(190) Lassale et al. reported a 12-year follow-up to a European population study; however, I could not monitor the evolution of the subjects' metabolic health along time. This study also reports the steady metabolic progression of a cohort followed up through long-term community monitoring. It was quite apparent that there was a steady decline in metabolic health annually; this was demonstrated at a steady rate ranging between 5-9% annually. This does suggest, despite the limitations of this large clinical database perhaps, that metabolic health in the presence of obesity is impermanent. To the author's knowledge, this has not been reported in the literature on such a large obese population in the UK.

The authors relate the slightly higher prevalence due to a few factors but mainly due to the already explained limitations of a large database and specifically the CPRD database. This study aimed to recreate a modified definition, as epidemiologically as possible, of metabolic health. This has been feasible in other studies as well as this, but limitations were encountered. This may not be possible to confirm on an individual patient basis. However, some variability in completeness of data is possible; restriction to those with complete data may result in biased analyses.(150,191) Nevertheless, our definition defined the metabolically healthy at a specific time point which was the first reference point of a diagnosis of BMI 35Kg/m^2. This would be a cross sectional non dynamic representation of the population with epidemiologically defined criteria suitable for the CPRD, not a dynamic true reflection.

The criteria used to define metabolic health relied on diagnosis and treatment for individual comorbidities but relied heavily on documentation and accuracy of diagnostic codes. From our

experience this could vary, and we found several medcodes for similar diagnoses and therapies. Other factors would be associated with the geographical representation of CPRD within the UK, despite Campbell et al evidence with regards to metabolically health distribution could deem an untrue representation. I realised that this is a relatively high prevalence compared to the world published evidence, as demonstrated in chapter 1, however the data and results have been interrogated three times for confirmation according to author definitions declared in chapter 2.

This data is from a unique large UK clinical community database, interrogating longitudinal outcomes of the metabolically healthy obese by use of established criteria. The results are original to the UK and the CPRD data used extends over a period from 1987-2016, which provides a large coverage representative of the UK population as reported previously by Campbell et al. (172).

These results suggest that there is a reasonably steady transition into an unhealthy state as years go by; nevertheless, maintaining a healthy state can possibly be prolonged by regular weight and BMI measurements, weight control advice, early obesity intervention, and rigorous follow-up. This is supported by the longer median duration to transition in the lower BMI group (35-40 kg/m^2). The data demonstrates that the presence of metabolic risk identifies BMI and age sub phenotypes, amongst other predictors, to progression to an unhealthy state. These predictors were: male gender, a higher baseline BMI category and age category, a higher index of multiple deprivation, and smoking. Population-based data on the prevalence within various BMI sub phenotypes are few, and different definitions for metabolic risk allow only indirect comparisons.

3 – 6. Conclusion

Our study proves that metabolic health status is a stable condition with a steady annual decline. Around half of these entities will progressively transition into unhealthy status on long-term follow-up. This large population analysis of obese patients concludes that the UK population is prevalently metabolically healthy. Being female, aged 30-40 years at baseline, of a lower BMI category, lower index of multiple deprivation, a non-smoker, free of any other associated comorbidities at baseline, and being on lipase inhibitors decreases the relative risk of transitioning into an unhealthy state.

Chapter 4

Mortality in the metabolically healthy obese

(A study from the Clinical Practice Research Datalink)

Mortality in the metabolically healthy obese

4 – 1. Introduction

Obesity, as defined by a body mass index (BMI) greater than 35 kg/m^2, is associated with a significant health burden for both the individual and health care systems.(192,193) Obesity is associated with an increased risk of a number of diseases, including type II diabetes, hypertension, ischaemic heart disease and cancer.(194–198) The continued rise in the prevalence of obesity over the past 50 years consequently presents a challenge to health systems globally.(199) In the United States, the number of adults who are now obese stands at around 35%, having grown by more than 2% over a decade.(200) In the United Kingdom, 7 out of 10 people are projected to be either overweight or obese by 2020.(194)

Previous high impact meta-analyses have been conducted to elucidate the effect of BMI on all-cause mortality.(7,201,202) From these, a J-shaped curve has been identified. Patients with a BMI between 20 kg/m^2 and 25 kg/m^2 have the lowest relative risk of all-cause mortality, whilst underweight and overweight patients are at increased risk, and patients at the highest extremes of BMI are at the most risk. The impact of obesity on health is not just a result of weight alone but also the metabolic sequelae that are propagated by increased adiposity. A previous analysis of the (CPRD) from the (UK) between 1988 to 1998 identified factors which are associated with increased risk of death in a severely obese population; these include age, type 2 diabetes mellitus, male sex and smoking.(203) The CPRD collects data from primary care physicians, and accounts for 8.9% of the UK population, leading to robust retrospective analysis, as previously described.(172)

Since the previous analysis, a number of new patients with obesity have been entered into the CPRD, allowing for an analysis of a modern cohort of patients, who are subject to a heavily

'obesogenic' environment.(204) The aim of this study was to therefore evaluate the risk factors for all-cause mortality within the obese population of the United Kingdom.

4 – 2. Methods

4 – 2 – 1. Study Design and Database

A case-controlled analysis was conducted of a population of patients with obesity (BMI≥35kg/m^2) from the CPRD. The CPRD is a record of coded data from over 625 primary care practices in the UK, representing over 12 million patients. The CPRD has previously been verified as a representative sample of the UK population.(150,172) Cases of all-cause mortality were identified from mortality data registered in the CPRD. These were analysed against controls that were still alive at data extraction.

4 – 2 – 2. Patient and Data Selection

Patients with a BMI≥35kg/m^2 were identified from the CPRD via clinical coding provided by general practitioners. The date at which the patients were first identified as obese was found by interrogation of the datalink. In addition to this, the clinicopathological characteristics of each patient at baseline were extracted from the CPRD. BMI was calculated from height and weight and compared against BMI values inputted by primary care physicians into the CPRD. Where these did not agree, calculated values were used in preference to coded BMI. It was also identified whether patients had ever been a smoker of tobacco products. Patients who underwent bariatric surgery in the following years were also identified from the CPRD. Those who were eligible for bariatric surgery according to National Institute of Care and Excellence (NICE) guidelines were identified. Finally, patients were linked to index of multiple deprivation (IMD) scores. As mentioned above, the IMD is a surrogate score of the socio-

economic background of a neighborhood, considering the following factors: income, employment, health deprivation and disability, educational attainment, barriers to housing and services, crime, and living environment.(205)

4 – 2 – 3. Statistical Analysis

Demographic factors were analysed by either Student's t-test, Mann-Whitney test or chi-squared test depending on whether they were continuous variables, or categorical. Means are displayed alongside the standard deviation, whilst median values are provided with the range. Statistical significance was set at p-value <0.05. A Cox proportional hazard model was conducted to identify the hazard ratios (HRs) for risk of death associated with several categorical variables, via a univariate analysis. Variables with HRs that were calculated to have a p-value <0.05 were included in a multivariate analysis. Significance of the multivariate analysis was again set at p-value <0.05. Missing data values were removed from univariate and multivariate analysis. Data was read and analysed using Statistical Package for the Social Sciences (SPSS) [IBM Statistics version 24 SPSS Inc., New York, USA].

4 – 2 – 4. Results

On primary CPRD interrogation, up until July 2017, 231,399 patients were identified as obese. After restricting for patients with a BMI ≥35kg/m^2 and BMI <80kg/m^2, there were 231,316 patients remaining. After controlling for extremes of age, 180,560 remained for final quantitative analysis. The median follow-up time from first diagnosis of BMI≥35kg/m2 until final patient visit or patient death was 98.0 months (range: 3.0-1095.0 months). Of those included, 8,534 (4.7%) were identified as having died over the study period. The median time from baseline obesity diagnosis until death was 137.0 (range: 3.0-628.7 months).

A comparison of the deceased within the metabolically healthy and metabolically unhealthy groups throughout were performed from baseline health status (Table 5). Overall there was 3,739/52,369 (7.1%) of the metabolically unhealthy deceased versus 4,795/123,396 (3.7%) of the metabolically healthy obese deceased comparatively. The recorded BMI measurements were compared and were 37.39 (SD 3.73) kg/m^2 versus 37.57 (SD 3.57) kg/m^2 relatively.

The deceased patients who were metabolically unhealthy were older at baseline diagnosis (mean: 51.14 ± 7.69 vs 48.16 ± 9.32; p<0.001). Deceased patients who were metabolically unhealthy were also more likely to be male (46.9% vs 40.5%; p<0.001). In higher BMI individuals mortality was lower in the metabolically unhealthy (37.79 ± 4.29 vs 38.19 ± 4.49; p<0.001). Of those who died during follow-up, only 14 (0.4%) metabolically unhealthy and 31 (0.6%) metabolically healthy received bariatric intervention.

Table 5 – Clinicopathological characteristics of study participants at baseline of obesity and mortality characteristics

	Non-Deceased	**Deceased**	**P-value**
Subjects (n)	178,406	8,655	
Age	39.72 ± 11.48	49.40 ± 8.79	p<0.001
Sex			p<0.001
Male	56449 (31.6%)	3746 (43.3%)	
Female	121950 (68.4%)	4909 (56.7%)	
BMI at baseline (kg/m^2)	38.80 ± 4.43	39.86 ± 5.46	p<0.001
BMI category			p<0.001
35-40 kg/m^2	131454 (73.7%)	5643 (65.2%)	
40-45 kg/m^2	30943 (17.3%)	1786 (20.6%)	
45-50 kg/m^2	10481 (5.9%)	716 (8.3%)	
50-55 kg/m^2	3526 (2.0%)	293 (3.4%)	
55-60 kg/m^2	1241 (0.7%)	126 (1.5%)	
>60 kg/m^2	761 (0.4%)	91 (1.1%)	
IMD			p<0.001
1	16081 (15.5%)	600 (12.4%)	
2	18349 (17.7%)	792 (16.4%)	
3	21561 (20.8%)	969 (20.1%)	
4	23268 (22.4%)	1150 (23.8%)	

5	24517 (23.6%)	1311 (27.2%)	
Hypertension	22210 (12.4%)	1612 (18.6%)	p<0.001
Diabetes Mellitus	9213 (5.2%)	932 (10.8%)	p<0.001
Hyperlipidemia	3355 (1.9%)	203 (2.3%)	p=0.002
IHD	1480 (0.8%)	217 (2.5%)	p<0.001
OSA	1674 (0.9%)	102 (1.2%)	p=0.030
Cerebrovascular Disease	760 (0.4%)	112 (1.3%)	p<0.001
Chronic Respiratory Disease	18549 (10.4%)	1115 (12.9%)	p<0.001
Bariatric Surgery	3822 (2.1%)	47 (0.5%)	p<0.001
Tobacco Use	65335 (36.6%)	3147 (36.4%)	p=0.622

BMI – Body Mass Index, IMD – Index of Multiple Depravation, IHD – ischemic heart disease, OSA – obstructive sleep apnea

4 – 2 – 5. Univariate analysis

A Kaplan-Meier survival analysis was performed to comparatively evaluate factors associated with survival in the metabolically healthy and unhealthy. The following factors were all found to be associated with an increased likelihood of prolonged survival on univariate analysis: female gender in both groups, age of 40-50 years in unhealthy and <30 years in healthy, BMI of 40-50kg/m^2 in both groups; an index of multiple deprivation of 3 in the unhealthy and 1 in the healthy were the significant independent factors for longer survival in both cohorts. Table 6 displays the estimated median survival and 95% confidence intervals.

Table 6 – Univariate analysis of prognostic factors for all-cause mortality

Variable	n	HR (95% CI)	p-value
Age			
18-30	43,781	1	
31-40	46,029	2.989 (2.656-3.365)	p<0.001
41-50	49,775	10.020 (8.991-11.168)	p<0.001
51-60	42,230	26.443 (23.806-29.373)	p<0.001
Sex			
Female	123,455	1	
Male	58,353	2.136 (2.047-2.229)	p<0.001
BMI category			
35-40 kg/m^2	133,359	1	
40-45 kg/m^2	31,780	1.222 (1.158-1.288)	p<0.001
45-50 kg/m^2	10,843	1.663 (1.538-1.797)	p<0.001

50-55 kg/m^2	3,684	2.174 (1.933-2.445)	p<0.001
55-60 kg/m^2	1,330	2.870 (2.405-3.424)	p<0.001
>60 kg/m^2	819	2.828 (2.295-3.486)	p<0.001
IMD			
1	16,261	1	
2	18,685	1.144 (1.029-1.272)	p=0.013
3	21,954	1.239 (1.119-1.372)	p<0.001
4	23,758	1.399 (1.267-1.544)	p<0.001
5	25,130	1.559 (1.415-1.717)	p<0.001
Hypertension			
Absent	158,447	1	
Present	23,368	5.416 (5.130-5.719)	p<0.001
Diabetes Mellitus			
Absent	171,891	1	
Present	9,924	7.079 (6.612-7.579)	p<0.001
Hyperlipidemia			
Absent	178340	1	
Present	3475	4.159 (3.617-4.781)	p<0.001
IHD			
Absent	180,163	1	
Present	1,652	7.173 (6.268-8.208)	p<0.001
OSA			
Absent	180,093	1	
Present	1,722	4.548 (3.739-5.533)	p<0.001
Cerebrovascular Disease			
Absent	180,953	1	
Present	862	7.478 (6.205-9.011)	p<0.001
Chronic Respiratory Disease			
Absent	162,677	1	
Present	19,138	1.445 (1.357-1.539)	p<0.001
Tobacco			
Non-user	114,940	1	
Smoker	66,875	1.057 (1.011-1.104)	p=0.014
Bariatric Surgery			
No Surgery	177,973	1	
Surgery	3,842	0.196 (0.146-0.259)	p<0.001

BMI – Body Mass Index, IMD – Index of Multiple Depravation, IHD – ischemic heart disease, OSA – obstructive sleep apnea

4 – 2 – 6. Multivariate analysis

The results of the subsequent multivariate analysis are included within Table 7. There was an increased risk of all cause mortality multiplied with increasing age category HR 18.074

(15.721-20.778) p<0.001, HR male gender 1.805 (1.702-1.914) p<0.001, BMI category of 55-60Kg/m^2 HR 3.233 (2.572-4.063) p<0.001 and Index of multiple deprivation HR 1.633 (1.481-1.801) p<0.001 on multivariate analysis. There was also an increased risk of all cause mortality with the presence of morbidity at initial time of diagnosis, factoring for other variables. The risk was higher when obese patients were associated with diabetes HR 2.766 (2.552-2.998) p<0.001, obstructive sleep apnea HR 2.095 (1.593-2.755) p<0.001 and hypertension HR 2.108 (1.953-2.276) p<0.001. BMI was the only dependent finding of prolonged survival in the unhealthy group within the examined cohort.

Table 7 – Multivariate analysis of prognostic factors for all-cause mortality

Variable	n	HR (95% CI)	p-value
Age			
18-30	43,781	1	
31-40	46,028	2.757 (2.363-3.216)	p<0.001
41-50	49,772	8.141 (7.063-9.383)	p<0.001
51-60	42,227	18.074 (15.721-20.778)	p<0.001
Sex			
Female	123,455	1	
Male	58,353	1.805 (1.702-1.914)	p<0.001
BMI category			
35-40 kg/m^2	133,357	1	
40-45 kg/m^2	31,776	1.328 (1.235-1.427)	p<0.001
45-50 kg/m^2	10,842	1.735 (1.561-1.929)	p<0.001
50-55 kg/m^2	3,684	2.277 (1.946-2.664)	p<0.001
55-60 kg/m^2	1,330	3.233 (2.572-4.063)	p<0.001
>60 kg/m^2	819	2.541 (1.922-3.360)	p<0.001
IMD			
1	16,261	1	
2	18,685	1.115 (1.003-1.240)	p=0.045
3	21,953	1.179 (1.065-1.306)	p=0.002
4	23,757	1.311 (1.186-1.448)	p<0.001
5	25,130	1.633 (1.481-1.801)	p<0.001
Hypertension			
Absent	158,443	1	
Present	23,365	2.108 (1.953-2.276)	p<0.001
Diabetes Mellitus			

Absent	171,885	1	
Present	9,923	2.766 (2.552-2.998)	p<0.001
Hyperlipidemia			
Absent	178,333	1	
Present	3,475	1.641 (1.362-1.979)	p<0.001
IHD			
Absent	180,156	1	
Present	1,652	1.503 (1.336-1.692)	p<0.001
OSA			
Absent	180,086	1	
Present	1,722	2.095 (1.593-2.755)	p<0.001
Cerebrovascular Disease			
Absent	180,946	1	
Present	862	1.755 (1.354-2.274)	p<0.001
Chronic Respiratory Disease			
Absent	162,673	1	
Present	19,135	1.286 (1.180-1.402)	p<0.001
Tobacco			
Non-user	114,937	1	
Smoker	66,871	1.212 (1.141-1.287)	p<0.001
Bariatric Surgery			
No Surgery	177,966	1	
Surgery	3,842	0.487 (0.343-0.691)	p<0.001

BMI – Body Mass Index, IMD – Index of Multiple Depravation, IHD – ischemic heart disease, OSA – obstructive sleep apnea

4 – 3. Discussion

Obesity is well known to increase the likelihood of all-cause mortality at an earlier age compared to people with a normal BMI.(7,201,202) When patients are first identified as obese it is common for them to concurrently experience the metabolic sequelae of obesity at the same time. In the group of metabolically unhealthy patients from this analysis 12.7%, 5.5% and 1.9% of patients had hypertension, type II diabetes and hyperlipidemia respectively at baseline. However, it is not clear which factors at baseline place the patients at greatest risk of all-cause mortality. The results from this analysis indicate that a number of individual independent risk factors that are prevalent amongst the obese population are prognostic of overall survival. Those most heavily associated with an increased risk of death appear to be a high BMI, late

age at diagnosis and male gender. However, those patients who had bariatric surgery were also at reduced risk of all-cause mortality.

These results suggest that increasing obesity beyond BMI≥35kg/m^2 is independently associated with increased risk of death, especially if metabolically healthy at baseline. Survival was a median of 148.04 months compared to 116.76 months if metabolically unhealthy ($p<0.001$) on univariate Kaplan-Meier analysis. Multivariate analysis identified that the highest BMI categories are at greatest risk of all-cause mortality, despite controlling for a number of other disease parameters that were also independently associated with a heightened risk of mortality. The risks of obesity were traditionally believed to be due to developing metabolic sequelae that increase cardiovascular disease risk, as well as increasing risk of cancer and other chronic health conditions.(206,207) These findings run contrary to that hypothesis. The most likely reason behind this finding is that increasing BMI places an increasing disease burden upon patients that cannot be accounted for in the present analysis. However, recent findings have demonstrated a trend between obesity and risk of mortality independent of those sequelae. These patients are otherwise referred to as the 'metabolically healthy obese'. These patients have a risk between that of metabolically healthy normal weight persons and metabolically unhealthy obese individuals.(208) In addition to initial baseline risk, around 30% of these patients become metabolically at risk after being previously healthy.(70) The reason behind why some patients remain metabolically healthy is unclear and is thought to be due to an interplay between genetic and environmental factors.(208) Regardless, it is important to encourage weight loss in all obese patients regardless of their metabolic status due to the increased risk it places on them.

This study also indicates that the socio-economic environment in which a person lives is important for determining future risk of mortality. There is an 'obesity paradox' which exists within developed countries in which those who live closer to the poverty line are at increased risk of obesity.(209) The largest proportion of this obese population is similarly derived from areas of the UK with the highest levels of deprivation (IMD=5). The patients from these areas were similarly found to be at increased risk of all-cause mortality. This is corroborated by research that has identified health inequalities between different communities depending on socio-economic factors.(210) Altogether, these results highlight the importance of public health initiatives to improve access to healthcare and of health education to reduce inequality in health outcomes.

In addition to these, a number of metabolic comorbidities were associated with all-cause mortality when present at baseline diagnosis. All those factors that have been previously demonstrated to lead to worse outcomes (hypertension, type II diabetes, hyperlipidemia) in obese patients showed a significant correlation with all-cause mortality in the non-metabolically healthy obese.(197,211–213) This is not only due to poorer cardiovascular outcomes. Demissie et al. have previously described that hypertension and insulin resistance in particular play a role in premature ageing.(212) This highlights that obese patients with comorbidities are at increased risk. Importantly, effective treatments are available for these conditions and when they are well controlled can lead to improved outcomes.(214–216) Subsequently, it is important these are identified early in the obese in order to initiate appropriate therapy.

An interesting finding of this study is that those patients who underwent bariatric surgery were

at reduced risk of all-cause mortality (HR=0.487 (0.343-0.691)). The most recent meta-analysis on the topic demonstrated similar findings. The evidence in support of bariatric surgery in regards to primary endpoints of reduced mortality is becoming increasingly convincing. This is in addition to long-standing evidence supporting its effects on type II diabetes and hypertension, as well as its cost-effectiveness.(217–219) It is clear from this analysis, however, that bariatric surgery is not widely utilised within the obese population in the UK. Out of those patients for who were eligible for bariatric surgery, only 4.1% of patients went on to have an intervention. Welbourn and colleagues have previously highlighted both national and global discrepancies in access to bariatric surgery due to a number of barriers along the referral pathway.(220,221) A survey questionnaire of primary care staff in the UK identified that whilst 86% would use the bariatric service they encountered barriers such as 'remote location', 'insufficient awareness', 'fear of complications' and 'lack of information'.(222) A recent report form the Royal College of Surgeons also identified that 3% of Clinical Commissioning Groups have policies that do not follow national guidelines and subsequently restrict access to bariatric surgery. Meanwhile, a recent analysis by Bhanderi et al. identified factors that may reduce access to bariatric procedures, including geographic variability and local deprivation.(223) Reduction of such barriers to bariatric surgery would most likely therefore help improve all-cause mortality in the obese population in the UK.

The present study reports on a large population of obese patients from the CPRD, a database that has been previously demonstrated to be representative of the UK population.(150,172) The number of patients involved significantly adds to the strength of the study and allows the results to be generalisable across the population as a whole as it is carried out in a real-life setting. A limitation of database research is that the quality of information is reliant on the accuracy of recording. To minimise the risk of misclassification, extremes of BMI beyond 80 kg/m^2 were

removed. This only removed 83 patients from the analysis, but helped improve accuracy of the patient coding by eliminating outliers. To further eliminate misclassification of BMI, I used values calculated from height and weight in preference to clinical coded values, as previous reports have identified that the coded BMI values are recorded less frequently.(224) The reported prevalence of comorbidities in the present study is lower than reported in series that are not reliant on coded data.(207)

Additionally, in comparison to Office of National Statistics data the CPRD has been shown to record deaths later than their actual date (median 5 days). This however has limited impact on the present analysis which is conducted across the timescale of months to years. However, I do recognise this as a drawback to the recorded date of death on CPRD and more importantly as lack of actual cause of death. In this study we could only use the strictly recorded CPRD death variables which do not specify primary or secondary causes of death and wether this could be contributed to obesity related morbidity. This could be addressed and verified by database linkage with the Office of National Statistics to highlight cause of death which would be a beneficial source of pre-empting obesity related comorbidities. This will be addressed as further future work.

Another factor that limits the results are inconsistencies in follow-up. Without a structured follow-up protocol, the process is reliant upon patients presenting to their primary care practitioner to enable diagnoses to be made. To reduce the effect of this bias, all comorbidities were taken at baseline diagnosis. This would subsequently again cause the results to tend towards the null, rather than overstate the findings. Finally, it is important to recognise that whilst multivariate analysis aims to identify the individual effect size of different risk factors, it is not able to control for all possible confounders.

4 – 4. Conclusion

The results from this study suggest a number of factors are associated with a poorer prognosis in the obese, most notably: high BMI, late age at diagnosis, and a higher index of multiple deprivation. In addition to this, bariatric surgery is associated with improved survival; however, it is under utilised in the obese population of the United Kingdom. Effective public health campaigns, as well as improved access to bariatric surgery, could improve outcomes in the obese.

Chapter 5

Outcome of bariatric surgery within the metabolically healthy obese

(A descriptive study from the Clinical Practice Research Datalink)

Bariatric surgery in the metabolically healthy obese

5 – 1. Introduction

As noted above, obesity is one of the most important public health conditions worldwide. Bariatric surgery in obesity is an effective treatment that results in the improvement and remission of many obesity-related comorbidities, as well as providing sustained weight loss and improvement in quality of life.

In the mid-1960s, Edward Mason reported for the first time that weight loss can be achieved effectively by means of a restrictive and malabsorptive gastrointestinal procedure — the gastric bypass. Laparascopic sleeve gastrectomy was first described as the initial step in a proposed two-stage approach to Roux-en-Y gastric bypass or Bilio-pancreatic diversion, in an effort to reduce the morbidity and mortality of performing a these procedures in high-risk patients with extreme obesity (specifically, patients with BMI >50 kg/m^2).(24) However, data began to show that LSG is an effective primary bariatric operation without the need for a second-stage conversion to RYGB. By the late 2000s, the LSG had established itself as another primary bariatric operation.

Evidence for the effectiveness of bariatric surgery is primarily based on the results of rando-mised trials.(7–10) However, trials simultaneously measuring the effects of different surgical methods are scarce, and it is unclear how evidence from trials translates to population-based healthcare. As bariatric surgery is now being offered more to people with T2DM, the effectiveness of treatment in these patients needs to be better defined. We therefore used data from the UK CPRD to characterise the association between bariatric surgery and weight, BMI, and a wide range of relevant clinical outcomes including diabetes, cardiovascular diseases, and mortality.

5 – 2. Aim

The aim of this study was to interrogate the bariatric surgery group for medium- to long-term outcomes, specifically when classified into metabolic health groups as is the intention of the entirety of this thesis. This will allow me to understand the interventions and outcomes of this variably understood cohort within the obese.

5 – 3. Results

The whole cohort entailed 180,560 patients who had a BMI of 35kg/m^2 and above from the start of the study until the end. Two thirds of the cohort 122,570 (67.9%) were female. our manuscript reports the prevalence and longevity of the metabolically healthy obese in the UK earlier in this thesis.(225) Mortality, was examined in the general obese population in the UK,(225) as well as specifically in the metabolically healthy obese.

There were 3,822 patients who underwent bariatric surgery within this cohort in the UK, 3,033 (79.4%) of which were female, and the largest proportion was demographically represented in London 632/3819 (16.5%). It was commonest to be in the 30-40 years age and BMI 35-40 kg/m^2 categories. More patients in the higher index of multiple deprivation category had surgery and the the commonest was index 5, 575 (15%) procedures. Patient descriptives can be found in Table 8. Furthermore, understandibly there was a significant difference in BMI loss from 4.71 (SD 4.72) Kg/m^2 to 10.59 (SD 7.29) Kg/m^2 $p<0.002$, between non bariatric surgery and Bariatrc surgery.

Table 8: Descriptive of patients that underwent bariatric surgery in the metabolically healthy obese

	Minimum	Maximum	Mean	Std Deviation
Age (years)	18	60	36.45	9.869
BMI change	0.00	44.00	10.5862	7.2932
Relative BMI	0.00	124.65	27.9528	19.33912
Baseline to death	0.00	294.57	1.8566	18.41578
First BMI to	0.00	300.52	1.9257	19.01470
Last BMI to death	0.00	87.62	0.1981	2.90070
Weight	68.40	216.70	106.6122	16.09901
Weight	69.00	263.20	135.9273	27.27831
First recorded	35.00	72.60	38.1759	4.02546
Last recorded	35.00	79.90	48.7621	8.35043

The first BMI (standard deviation) recording above 35 kg/m^2 averaged 38.18 (SD 4.03) kg/m^2 and the average first weight recorded was 106.6 (16.1)kg. Bariatric procedures were undertaken in 982 (25.7%) of the metabolically unhealthy and 2,840 (74.3%) in the healthy. Of the unhealthy, 28.6% had 2 or more comorbidities. The number of patients who underwent bariatric surgery is found in Table 9.

Table 9. Bariatric surgery within the metabolically healthy obese

Metabolically	Bariatric surgery	Frequency	Percent	Cumulative
Unhealthy	No	51387	98.1	98.1
	Yes	982	1.9	100.0
	Total	52369	100	
Healthy	No	125351	97.8	97.8
	Yes	2840	2.2	100.0
	Total	128191	100	

Frequency of bariatric surgery occurrences within the metabolically health cohort and generally was performed more in the metabolically healthy than unhealthy, 2.2% vs 1.9%. The database was split for comparison according to the metabolically healthy cohort versus unhealthy. Unhealthy metabolic obese non-bariatric surgery group was commonest in the age category 50-60 years and in the healthy group non-surgery was commonest between 40-50

years ($p < 0.001$). In the metabolically healthy, when comparing categories through the Chi-squared test, the non-surgery was greatest in the age group less than 30 years old versus 40-50 years of age in the surgery group ($p < 0.001$).

Lipase inhibitor use was more than twice prescribed in the bariatric surgery cohort than the non-surgery one: 36.6% versus 63.4% and 33.9% and 66.1% ($p < 0.002$). Smoking was commoner in the non-metabolically healthy group: 39.7% versus 35.7% ($p < 0.001$).

Death was examined amongst both groups comparatively along the duration of the database; in the unhealthy group without bariatric surgery mortality was 7.2%, whilst with surgery it was 1.4% ($p < 0.001$). In the healthy group death was 3.8% amongst the non-bariatric surgery group versus 1.1% in the surgery group ($p < 0.001$). Median survival was non-significantly prolonged by bariatric surgery on Kaplan-Meier survival from time to bariatric surgery until death, and more so for the metabolically healthy obese group: ($p = 0.409$, $p = 0.684$ respectively). Metabolically healthy obese survival is plotted in Table 10.

Table 10 Survival within the Metabolically healthy obese

		Median (months)	**Std Error**	**Mean (95% Confidence interval)**	
Metabolically healthy obese	Bariatric surgery			Lower bound	Upper bound
Unhealthy	No	124.532	1.214	122.153	126.911
	Yes	146.710	16.720	113.938	179.482
	Overall	124.617	1.211	122.243	126.990
Healthy	No	148.245	1.156	145.979	150.511
	Yes	168.013	11.202	146.057	189.969
	Overall	148.370	1.151	146.113	150.626

On Cox regression analysis, bariatric surgery remained a nonsignificant independent factor of survival within both the metabolically healthy and unhealthy obese. Figures 9,10 and 11 display Kaplan Meir curves for time to transition to unhealthy and mortality after Bariatric surgery.

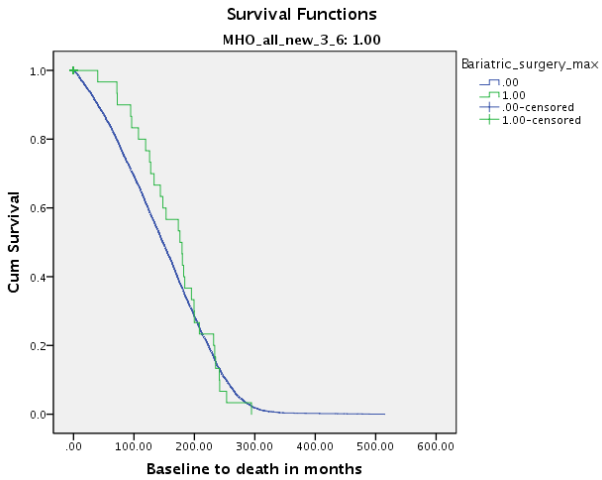


Figure 9: Kaplan Meir curves to transition for metabolically healthy group when exposed to surgery

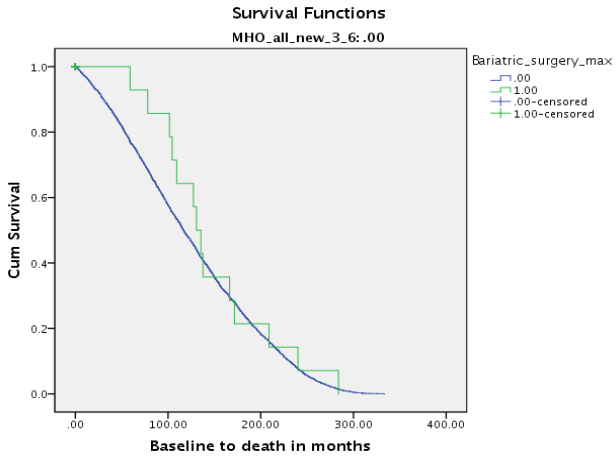


Figure 10: Kaplan Meir curves to transition for metabolically unhealthy group when exposed to surgery

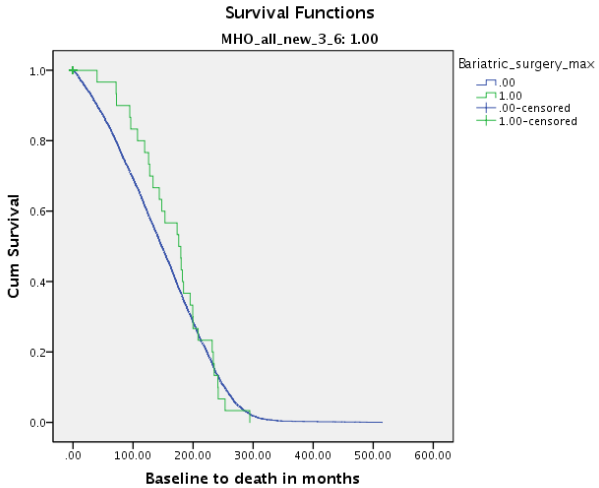


Figure 11: Kaplan Meir survival curve after Bariatric surgery

5 – 4. Discussion

Bariatric surgery offers the most effective treatment option for obesity, and the number of weight loss surgeries has increased dramatically in the past 15 years. By contrast, the evidence base for bariatric surgical procedures has expanded rapidly over this time, and it has yielded important short- and long-term data on the efficacy and safety of surgical treatment for obesity and related metabolic disorders.

Given the absence of long-term randomised controlled trials comparing bariatric procedures with non-surgical treatment of obesity. The evidence started with current knowledge with long-term results of bariatric surgery from the Swedish Obese Subjects (SOS) study. This study began in 1987 as a prospective trial of 2,010 people undergoing bariatric surgery compared with 2,037 usual care controls who were matched on 18 clinical and demographic variables.(217)

Several studies have been published with a low perioperative mortality rate (0.18%) and a long-term reduction in all-cause mortality of 41% in patients receiving bariatric surgery compared to non-operated obese controls. The two observational studies, that is, the Bariatric Outcomes Longitudinal Database and the Longitudinal Assessment of Bariatric Surgery, showed a perioperative mortality risk of 0.1% and 0.3%, respectively.(65,66) These findings are supported by those of previous meta-analyses.(17–20) Maggard et al. reported pooled mortality rates that ranged from 0.02%, in case series, to 1.0%. Several studies have evaluated the long-term mortality rates of patients with obesity after BS. Data from registries have shown long-term mortality rates after BS ranging from 1.5% to 6.1% during a mean follow-up of 8 to 10.9

years; one of these studies by Telemet et al. reported a significantly lower mortality in patients receiving BS than in the general population (1.5% vs 2.1%, respectively).(67–69) Furthermore, one study summarising the estimate effects of 140 treatment arms, which involved 19,928 patients from RCTs and observational studies, reported a total mortality at 30 days to 2 years of 0.35%.(18) Other meta-analyses studies have reported a global mortality reduction (OR,0.48-0.55) in patients receiving BS compared to non-operated obese controls.(21,70,7)

In conclusion, our study suggests that BS is a safe therapeutic option for weight loss. The current body of evidence from RCTs estimates a short-term all-cause mortality after BS of 0.18% (95% CI, 0.04%-0.38%). We found a reduction in long-term mortality of 41% (HR, 0.59; 95% CI, 0.52-0.67) among patients receiving BS compared to non-operated obese controls. Thus, the evidence suggests that BS may improve the long-term survival of obese patients and possibly decrease cardiovascular and cancer-related mortality, but these effect estimates were pooled from lower quality studies (ie, observational studies). Therefore, prospective studies are needed to firmly establish whether benefits concerning cardiovascular and cancer mortality can be observed. In addition, future studies should address the predictors of long-term mortality, as some patients (e.g., those with diabetes) appear to benefit more than others in terms of survival.

Obesity management surgery demonstrates lower mortality and morbidity rates and shorter length of hospital stay.(226) Miras et al. also proved that there might be underreporting of complications and postoperative deaths (e.g., due to loss of follow-up, when patients change healthcare providers), the 0.07% mortality and overall 2.6% complication rate from the NBSR and this also proves obesity surgery to be one of the safest major elective surgical

procedures.(226) The low in-hospital mortality reported in the NBSR is also coherent with the Hospital Episode Statistics (HES) mortality data collected in the NHS in England.(227)

Recently Douglas et al., similarly to this study, examined mortality within the Clinical Practice Research Datalink amongst other short- and long-term outcomes of Bariatric surgery in the UK.(149) The post hoc analysis for mortality, stratified on follow-up period, found an HR of 1.10 (95% CI 0.59–2.06) for the first year after surgery and 0.77 (95% CI 0.48–1.24) after the first year. In the analysis of mortality within 30 days of surgery, fewer than five surgery patients (0.08%) were recorded as deceased, compared with no records in the non-surgical group (because of CPRD restrictions around patient anonymity, counts of less than five cannot be given precisely). Mortality in the no surgery group was recorded in 50/3,774 (1.4%) cases and in the surgery group 53/3,714 53 (1.4%), hazard ratio 0.97 (0.66–1.43) (p=0.87).(149)

This is the only documented mortality from the Clinical Practice Research Datalink for obesity surgery comparison to a propensity-matched cohort within the UK. Similarly, mortality was examined amongst both groups comparatively; in the unhealthy group without bariatric surgery mortality was 7.2%, whilst with surgery it was 1.4% ($p<0.001$). In the healthy group death was 3.8% amongst the non-bariatric surgery group versus 1.1% in the surgery group ($p<0.001$). Median survival was non-significantly prolonged by bariatric surgery on Kaplan-Meier survival from time to bariatric surgery until death, and more so for the metabolically healthy obese group. (p=0.409, p=0.684). This demonstrates a significant difference in mortality between both healthy and unhealthy when exposed to bariatric surgery, but not, however, on time to death on Kaplan-Meier and Cox regression analysis with time from first diagnosis of obesity to time of recorded death being the dependent factor. Previously in this thesis, all-cause mortality for the morbidly obese examined 187,061 patients with super obesity from the CPRD

with a median follow-up of 137.0 (range: 3.0–628.7 months). Of those included, 8,655 (4.6%) were recorded as deceased over the study period.

As well as mortality, obesity surgery has demonstrated other beneficial outcomes on physical, psychological, and quality of life improvements. Obesity surgery has been found to have major beneficial associations with several clinical outcomes, with reductions in risk seen for incident T2DM, hypertension, angina, myocardial infarction and obstructive sleep apnea.(226) Resolution of T2DM and hypertension was also seen.(228) There has also been a proven psychological impact and improvement of clinical depression for bariatric surgery in the United Kingdom.(229)

As part of another study from the CPRD for all-cause mortality for obesity, a total of 93,313 patients (49.9%) in both groups were eligible, on estimate, for bariatric surgery according to National Institute of Care and Excellence guidelines at baseline diagnosis of super obesity. Only 3,869 (2.1%), however, received surgical intervention for their obesity.(225) Of the bariatric procedures recorded, 982 (25.7%) were in the metabolically unhealthy group and 2,840 (74.3%) were in the healthy one.

5 – 5. Conclusion

This study supports results from other studies conducted around the world in favour of bariatric surgery and improvement in outcomes, especially amongst the metabolically unhealthy obese, to improve survival. Bariatric surgery should be more available and more easily accessible for improved overall medical and reduced cost years outcomes.

Chapter 6

Discussion and Conclusion

6 – 1. Transition of the metabolically healthy obese

From UK community retrospective cohort there lies a 71% MHO prevalence rate of which 55.8% remain healthy on long term follow up. In light of the improved outcomes in MHO patient compared to obese patients with comobidities, it is important to assess for contributing factors that affect how and when MHO patients develop comborbidities. Data from the Clinical Practice Research Datalink (CPRD) was utilised, with the intention of identifying the true picture that is representative of these conditions in obesity by applying information derived from actual subjects of obesity. Through the analyses of this database, I aimed to develop an understanding of the extent of metabolic health in patients who had been diagnosed with obesity, to establish the prevalence within these patients.

I defined metabolic health, as done so previously, as the absence of comorbidity or any drugs of metabolic significance to hypertension, diabetes, hyperlipidemia and obstructive sleep apnea, among other conditions, in an obese patient.(136) I applied this definition with the awareness that numerous definitions of metabolic health exist. For instance, according to various researchers, metabolic health is dependent on the physiological state of a patient, in the sense that it shifts with the diagnoses of different diseases (49,98,142). The selected definition of metabolic health was utilised as it would be achievable with current CPRD medical and therapeutic codes. This guided the conclusions and contribution to the discussion into transition from healthy into unhealthy obesity.

I identified that an important component in the development of metabolic abnormalities in an obese population is age. The MHO cohort were typically younger, however a clinically significant proportion of these patients developed the metabolic sequalaeas they aged. This is in keeping with findings from other studies.(230–232)

Mechanisms that could explain the favorable metabolic profile of MHO individuals are poorly understood. However, preliminary evidence suggests that differences in visceral fat accumulation, birth weight, adipose cell size and gene expression-encoding markers of adipose cell differentiation may favor the development of the MHO phenotype.(233) The most probable explanation for these findings may be the fact age impacts on a person's metbolic homeostasis mechanisms. That is to say that obese patients may be metabolically healthy at the time of diagnosis and continue to be healthy through their life. However, it is also probable that age impacts on metabolism, and thus as someone ages, their metabolic rate and status decreases, leading them from healthy obesity into the 'unhealthy' state of obesity, on the basis of their metabolic abilities. As a consequence, whilst some patients may persist with a MHO phenotype, most patients will be unable to sustain the chronically high levels of endogenous insulin and cholesterol production. This eventually results in the development of metabolic abnormalities (233) such as fat deposition rate shifts with age. As an individual progresses through life, their metabolic state is further influenced by the body fat content in adipose stores. (95)

The presence of these conditions in an already obese patient introduces cormobidity. As evidenced in the previous and subsequent sections, cormobidity is the determining factor in obese patients as it exposes them to increased chances of complications and quicker mortality on account of their overall physiological and metabolic state. At this point, morbidity as a study variable and contributing factor for incidence of MHO obesity was investigated with the intention of developing an understanding of the contribution of morbidity in MHO.

6 – 2. Morbidity in MHO

Out of the respondents of this study, the occurrence of obesity and the metabolic complications associated with it were measured. The researchers established a prevalence of 71.0% among the recruited obese patients. More specifically, this was 128,191 out of the 180,560 respondents. Through the follow-up period within which the findings of this study were developed, 55.8% of the respondents were still healthy, at the twenty-five year mark of follow-up after obesity diagnosis. We established a decreasing rate of non-healthy states of obesity annually from these establishments of follow-up. The independent factors developed for the study, including comorbidity, were assessed with the application of the Kaplan-Meier analysis. Bariatric surgery and treatment with a lipase inhibitor were used as the control tests for the study, so that it was discovered that a close relationship did exist between the presence of other infections and the level of metabolic health in an obese patient.(234,235)

6 – 3. Mortality in MHO

There were 8,534 deaths recorded out of the 180,560 patients recruited for this study. All-cause mortality was recorded for these cases. We demonstrated the most probable cause of this to be comorbidity that was found following an assessment of the cause of mortality. This opinion was developed by the comparison between the all-cause mortality of the metabolically healthy obese (3.7%) and that of the non-metabolically healthy obese (7.1%). The long term outcomes of being metabolically health even when obese were not quite established in this study. The manuscript attributed this uncertainty to the morality rate recorded in the obese patients. It was unclear whether the metabolically healthy patients were in a transition phase, so that at a future date, they would then enter the metabolically unhealthy obese category and thus also be predisposed to death in the long run. The researchers sought to explain these uncertainties with the application of findings from several studies, which demonstrated effectively that there may

be a possibility that MHO patients would either progress into Type 2 diabetes, or possibly grow into non-metabolically healthy obese patients, whose possibility of mortality was evidenced as higher.

With this background of information, the study preceded into an investigation of the mortality rates among the metabolically healthy obese people with no stated comorbidity. With a median follow-up period of 98 months, the manuscript used 187,061 records of MHO patients for analysis. Of these patients, 8,655 died in the course of the study. The bariatric control tests proved that metabolically healthy obese patients who underwent the surgery exhibited lesser chances of death compared to their counterparts who did not.

6 – 4. Bariatric surgery for metabolically healthy obese patients

We decided to take up this study to investigate the effect and outcome of bariatric surgery in the study participants to establish the impact and possibility of alleviating obesity-related mortality after bariatric surgery. Out of the 180,560 patients, 3,033 female patients underwent the surgery, with the majority of them coming from London. There were 982 metabolically unhealthy patients who underwent bariatric surgery, with 28.6% of them having two or more comorbidities, while 2,840 who underwent the surgery were metabolically healthy.

The rate of prescription of lipase inhibitors in the metabolically healthy was at 36.6% while that of the metabolically unhealthy was at 63.4%. Of the combined metabolically healthy and unhealthy groups, 33.9% had no bariatric surgery whilst the remaining 66.1% were in the surgery group. The study also shows that 39.7% of the non-metabolically healthy had a link to smoking as compared to 35.7% of the metabolically healthy. Mortality in both groups was rated at 7.2% for the non-surgery unhealthy group versus 1.4% for the unhealthy surgery group. Otherwise was 3.87% for the non-surgery group as opposed to a 1.1% for the surgery group.

The metabolically healthy experienced no significant improvement in the rate of survival from the procedures. Obese individuals can now look to bariatric surgery as a safe and effective therapeutic treatment method for weight loss.(236,237) Long-term mortality has been reduced by 41% for patients undergoing bariatric surgery, thereby concluding that BS may in theory decrease cardiovascular and cancer-related mortality.(238,239)

In the UK, 788 patients with a BMI below 35 kg/m^2 underwent bariatric surgery between 2009 and 2014. Of these, 77.1% had no cases of comorbidities prior to surgery while the rest exhibited one or more such cases. The average weight and BMI before surgery was 93kg & 33.0kg/m^2 respectively.

6 – 5. Findings with regard to study hypotheses and objectives

The main aim of the study was to investigate the the outcome of metabolically healthy patients within the United Kingdom through primary health database.

Objective 1: Provide data that would aid a United Kingdom based database to easily determine short- and long-term outcomes of healthy individuals when compared to unhealthy obesity.

The findings of this study did find that various factors exist that impact and influence metabolic health in obese patients. According to the secondary data utilised by this study and the findings of the actual investigations conducted by the researchers, data has been presented that relates to mortality as a result of MHO or absence of metabolic health. The study, as was intended, utilised the UK database (CPRD) that sought to define obesity on the basis of body mass index and the comparison of health between metabolically healthy obese patients and metabolically unhealthy normal individuals. Consequently, the study has provided findings that seek to explain the factors that predispose obese patients to earlier death and increased morbidity. Some of these factors include the incidence of dyslipidaemia, diabetes and hypertension in

these patients. These findings provide a critical reference point on the short- and long-term impacts of metabolic health, or the absence thereof, in obesity. As such, the study findings, as relates to the assistance of a better database for these patients, do fulfil the first objective of the study.

Objective 2: Explore the existing scarcity of community follow-up among obese patients worldwide on a long-term basis using one of the largest community databases in the world (CPRD)

The researchers found that the follow-up criteria for obesity was generally faulty around the world. The main motivating factor for the researchers towards this objective was the awareness that there is great ignorance about the possible existence of metabolically healthy obesity amongst obese people.

As relates to this objective, the study observes full follow-up of all obese patients from the date of diagnosis for a substantial period of 98 months. During the entire period within which the study coordinators progressed with the follow-up of the patient, the aim was to identify the changes in etiology and the onset of actual symptoms associated with obesity. Owing to the minimal follow-up on obesity patients, possible changes are missed through the process, making it difficult to identify the specific issues related to obesity that result from gaps in monitoring and evaluation of obesity and metabolic capacities. The study fulfilled this objective in that it did achieve the hypothesised follow-up period to review mortality, comorbidity and metabolic health as progressive changes that occur in obese patients. As the findings of the study dictated, the achievement of this objective also contributed to the development of findings that would promote the body of knowledge upon which subsequent scholars in the field could develop their studies.

Objective 3: Evaluate the relevance of data related to BMI as developed from CPRD

The study found that BMI developed and reported in the CPRD found that BMI is an overall representative form of the obese population.

Findings as relates to the study hypotheses

Model 1 – Are the characteristics associated with the transition from the metabolically healthy obese state to the unhealthy one predictable

The main aim was to understand, from the reviewed database, whether or not it is possible to predict characteristics that predispose an obese patient to unhealthy obesity. From the evaluated databases and the findings of the study project through the follow-up period, the researchers present that it is indeed possible to predict some predisposing factors of unhealthy obesity. These may be inferred effectively from the associated factors of mortality; namely dyslipidaemia, diabetes or hypertension.

Model 2 – Is metabolic 'healthiness' a surrogate of survival in the obese

Essentially, the context within which this study presented the concept of MHO may show that it is possible for metabolic healthiness to put off death from obesity. As was demonstrated by databases on mortality (Chapter four) it is possible that there is not essentially a replacement of the eventual effects of obesity, even in the presence of metabolic 'healthiness'. Hence, as relates to this hypothesis, we conclude that it is not necessarily true that being metabolically healthy exclusively protects obese people and promotes their survival, even though it does reduce the progression of symptoms or the incidence of comorbidity.

Model 3: Are perioperative bariatric surgery outcomes comparable within the metabolically healthy obese

The large UK databases do provide a basis for discussion of bariatric surgery and its perceived importance for obese patients. The databases, with the information about BMI that they

presented the study with, do show a positive correlation between metabolic health and obesity complications. Bariatric surgery outcomes of the patients who participated in the process did provide an effective basis of control for the study. However, medical weight loss, for which bariatric surgery is mainly intended, did not provide possible grounds of result comparison as the study provides from the findings.

6 – 6. Summary of findings and conclusions on the project

The findings of this study may be developed into worthwhile single spelled-out conclusions as relates to the research objectives and hypotheses and how well they are achieved. However, even though singly described, these conclusions need linkage to previous sections of the study in order to be understood by an independent reader. This section contains the concluding concepts presented by the author of this thesis.

Metabolically healthy obesity has been the subject of controversial debate as regards to health in obese patients. It is evident from the findings developed from the large UK databases that the conditions that develop in an obese patient are majorly dependent on their metabolic health. The individuals who have a BMI high enough to be classified as obese may be healthier than people with a lesser BMI, on basis of their metabolic rates and index. As is presented by the data on obesity by the NBSR, having a BMI of up to 25.5kg/m^2 does not essentially mean that an individual is healthy and exempted from the chances of being described as metabolically unhealthy and obese.

The major development that I wish to bring forth is that a close relationship between the metabolic index of an individual and their BMI status does exist, so that the complications associated with obesity vary in complexity based on individuals' metabolic health.

The author felt it would be beneficial to this thesis to summarise in bullet point form the main summary points of the chapters:

Prevalence of MHO
In the UK population was 128,191/180,560 (71.0%)
71,485/128,191 (55.8%) remained healthy (p=<0.01) with a mean follow-up of 68.2 months
Life table analysis initial 26% transition in first year then 7% annual cumulative increase over 10-year FU
Multivariate: Quicker transition, BMI>60, age 50-60, Male, North west England
Slower transition (protective) Bariatric surgery, Lipase inhibitor

MHO mortality
Same cohort, 180,560
Mortality 3,739/52,369 (7.1%) unhealthy vs 4,795/123,396 (3.7%) MHO
BMI median 37.39(3.73) kg/m^2 versus 37.57(3.57) kg/m^2
Age (mean: 51.14 ± 7.69 vs 48.16 ± 9.32; p<0.001)
Male gender (46.9% vs 40.5%; p<0.001)
Increased risk of death high BMI, late age at diagnosis and male gender
Early identification to initiate early appropriate therapy

Bariatrics in the MHO
180560, 3822 Bariatrics, 3033 (79.4%) female
London 632/3819 (16.5%)
Highest in 30-40 years age and BMI 35-40 Kg/m^2 categories
Higher index of multiple deprivation index 5, 575 (15%)
982 (25.7%) were unhealthy and 2,840 (74.3%) MHO
Frequency was 2.2% in MHO vs 1.9% unhealthy within whole population
Median survival was non-significantly prolonged by surgery on Kaplan-Meier survival from time to bariatric surgery until death, (p = 0.409, p = 0.684)
Surgery nonsignificant independent factor of survival within both the metabolically healthy and unhealthy obese
Reduction in long-term mortality of 41% (HR, 0.59; 95%CI, 0.52-0.67) among patients receiving BS compared to non-operated obese controls

Final Conclusion
Obesity is a worldwide epidemic
MHO is a vital sub cohort of obesity that needs to be further investigated and epidemiologically defined
From UK community retrospective cohort there lies a 71% MHO prevalence rate of which 55.8% remain healthy on long term follow up
There was a 3.7% mortality rate in MHO vs unhealthy 7.1% with an increased risk of death appear to be a high BMI, late age at diagnosis and male gender.

Frequency of bariatric surgery occurrences within the metabolically health cohort and generally was performed more in the metabolically healthy than unhealthy, 2.2% vs 1.9%. On Cox regression analysis, bariatric surgery remained a nonsignificant independent factor of survival within both the metabolically healthy and unhealthy

6 – 7. Contributions of the study

6 – 7 – 1. Contributions to Theory

This research project extensively utilised the databases on obesity follow-up in communities in the United Kingdom, with the main intention being to develop an understanding of the reasons why extensive follow-up is not maintained for such cases. Hypothesis Three of this study was that the CPRD database is reflective of the true picture of events for obesity related to healthy metabolism and comorbidity. By virtue of this context, the study has critically reviewed the largest database on community obesity in the UK, consequently updating information related to the study topic, in ways that can be harnessed by future scholars in the field.

6 – 7 – 2. Contribution to literature

This study evidently presents critical findings on metabolically healthy obesity, comorbidity and the practice of bariatric surgery for weight loss or alleviation of complications related to obesity. As such, the study does contribute to the field of knowledge related to these health topics, which as is clear from the reviewed literature (Chapter one) is interestingly underexplored. The findings of this study provide conclusions that may be effectively used by students, professionals and scholars in the field of health, medicine, nutrition, and health promotion among others. The findings of this study are also critical for policy makers, who may appreciate the new knowledge that this study has presented on metabolically healthy obesity.

6 – 7 – 3. Contribution to community medicine and health

The findings of this study utilise information derived from communities regarding obesity and its associated complications. As the researchers have established, and by virtue of the gap they intended to fill, community knowledge may be developed by the findings of this study. Awareness of bariatric surgery, and its chances of saving obese patients from impending death and reducing complications associated with obesity may be created by applying the findings that this study presents.

6 – 7 – 4. Implications of the study and recommendations for further research

Evidently, it is possible to conclude from the various findings of this study that mortality associated with obesity is dependent on the underlying condition of a patient's physiology. The implication of this is that a diagnosis of obesity as an independent factor for immediate determination of death or impending complications. It is imperative that the body mass index of an obese patient is laid side by side with their metabolic rate indices and the presence of any underlying conditions. Similarly, patients with obesity may essentially be required to understand that a progression from 'metabolic healthiness' into 'metabolic non-healthiness' is possible. The findings of this study show that obesity with unhealthy metabolism is an indicator for death, as are the presence of such conditions as hypertension and diabetes in obesity.

On the grounds of these conclusions, the researchers recommend further studies into the pathophysiology of metabolically unhealthy obesity, with a close reference to the presence or absence of comorbidity. I wish to pose an awareness of the gap in knowledge related to what happens in the transition period between 'healthy' obesity and 'non-healthy' obesity. It is also the intent of the researchers to present recommendations that future scholars look into the exact impacts of bariatric surgery on the body composition and metabolism of obese individuals, and

whether the long run impact of bariatric surgery on obese patients predisposes them to complications associated with medical weight loss.

On the basis of this thesis and data cohort, it was felt that already published work can be a platform to exapnd this resourceful database. I inititated and constructed a novel Imperial study group for obesity related morbidity and outcomes, this has been formed primarily by clinical researchers but aims to expand with further and more extensive collaboration in the future. This has been named the I'OBES - Imperial Obesity and Bariatric Epidemiology Syndicate.

The main aims of this study group are:

Bariatric surgery remains the treatment that has provided long term weight loss and resolution of co-morbidities, while also reducing the risk of obesity related malignancy. This project aims to develop the use of routinely collected primary and secondary care data as a means of quantifying safety and longevity of obesity related complications when associated with obesity surgery. The incidence and prevalence of this cohort in the UK would be used for future research in various aspects of care. This would drive improvements in quality and safety in Obesity surgery in the years to come. This would be an introduction to further larger database collaborations and larger trials for outcomes associated on retrospective cohort studies undertaken with large databases. This I'OBES can help define the health cost to the individual and to the public. We have already investigated the morbidity and outcomes related to obesity itself but the economic cost using CPRD can be further explored.

CPRD provides a unique opportunity to describe the patient pathway following surgery, and whether is beneficial in terms of cost and burden to primary care. In particular current decisions about which surgery is most beneficial to the individual does not consider the impact on resources following surgery. The group is currently undergoing our first cost analysis on impact

of bariatric surgery on the burden of GP visits for specific comorbidities that have been shown to improve after surgery. Studies will be mainly based as descriptive studies, retrospective cohort timeline analysis and retrospective case controlled matched comparative studies.

Imperial College Hospital is a renowned, well-established, centre for the management of obesity, associated with a widely respected institution with access to many different academic resources. However, the epidemiological study of obesity is relatively in its infancy. Despite this we have managed to publish 8 articles and presented 13 poster presentations and 7 oral presentations in international meetings over the last 4 years. There are 10 currently ongoing projects by junior clinicians and academic as well as BSc students. By formalising this study group with the inclusion of other specialities, statisticians and Imperial College London, we would expect to further increase output and prestige of this department. Ultimately we would like to translate the epidemiological work to clinical studies and trials. This study group will nurture further research and opportunities for BSc and PhD projects as well as further grants for more complex projection studies.

The outstanding proposed ideas include:

1. Survival of the super obese (BMI>50) in the United Kingdom: A Clinical Practice Research Datalink - BSc
2. Effect of bariatric surgery on long-term cardiovascular outcomes in patients with obesity: a nation-wide nested cohort study.
3. Long-term effect of bariatric surgery on cerebrovascular outcomes in patients with obesity.
4. Long-term impact of bariatric surgery on venous thromboembolic risk: a matched cohort study.
5. Long-term effect of bariatric surgery on the incidence and outcomes of obesity-related peripheral vascular disease.
6. Bariatrics surgery outcomes in the Metabolically healthy obese –
7. Validity of CPRD – ONS

8. Obstructive sleep apnea in the super obese
9. Hepatocellular carcinoma in the obese
10. GP consultations before and after Bariatric surgery in the community – Health cost-analysis
11. Impact of bariatric surgery on atherosclerotic cardiovascular disease burden in patients with Type 2 diabetes

There have been other ideas currently under feasibility review phase to determine bigger researcher involvement in weeks and months to come, namely:

MHO related

1. Retrospectively establishing BMI, age and prevalence MHO on yearly ANOVA to determine effect of that on the transition into unhealthy
2. Elicit exact cause of death and determine obesity related deaths link to ONS
3. RCT for bariatric intervention for medium to long term outcomes between MHO and non-MHO

Data related

1. Elicit individual effects of MHO on various outcomes such as OSA, depression, CVS, liver and renal disease
2. Elicit predisposition to cancers between MHO and non MHO
3. Data linkage to HES for short term complication rate and outcomes

There have been very promising reports this month, a paper giving an overview of the CPRD Aurum database has been published in the International Journal of Epidemiology. Like CPRD GOLD, CPRD Aurum holds routinely collected primary care data, but collected from practices using a different GP IT system. The paper describes the September 2018 CPRD Aurum build, with over 19 million patients in England, of whom 7 million were alive and currently contributing. The key strengths of CPRD Aurum are its size and coverage (complementing CPRD GOLD), longitudinal follow-up, representativeness, and standard linkages to national secondary care databases as well as deprivation and death registration data.

Since September, CPRD Aurum has continued to grow and includes additional practices from Northern Ireland. Data held by CPRD in the CPRD GOLD and recently introduced CPRD Aurum databases now encompasses over 35 million patient lives, including 11 million currently registered patients.

I have already collaborated with several specialities so far, including:

- Cardiology (Royal Brompton) – Professor Peter Collins
- Vascular surgery (St Mary's) – Usman Jaafar
- Ear, nose and throat (Charing cross and Royal national hospital of ENT) – Neil Tolley, Bhik Kotecha
- Psychiatry (St Mary's) – Samantha Scholtz

6 – 8. Conclusion

This study has been an intricate process of critical analysis and the reviewing of a database for the establishment of the required results. I have taken time to effectively guide the objectives of the research so that an understanding of the intended findings was realised. The conclusive findings of the study, as has been discussed in this chapter, have effectively fitted into the study hypothesis. This thesis did find a deficiency in the information that exists on MHO and bariatric surgery; a gap which the study has attempted to fill with the critical analysis of the data as presented. Despite the challenges of the limitations pointing to the gaps in follow-up of obesity patients, it is possible to conclude that the manuscript did achieve their intended findings, as they demonstrate in this thesis. Even though the suggested and potential areas of further research associated with the current study are challenging to undertake, the researchers show that it is especially worthwhile, owing to the satisfaction attained from achieving seamless results.

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Appendices

Medcodes
Original Extraction of obesity medcodes

medcode	clinicalevents	referralevents	readcode	readterm
70898	4	0	C38z.00	Obesity and other hyperalimentation NOS
16196	3499	152	1444	H/O: obesity
104129	0	0	C380600	Adult-onset obesity
38799	252	2	C380000	Obesity due to excess calories
59780	2233	104	222A.00	O/E - obese
11461	140320	778	66C..00	Obesity monitoring
104421	2	0	C380700	Lifelong obesity
22695	1647	6	C380400	Central obesity
22556	30626	221	22K7.00	Body mass index 40+ - severely obese
25968	192	2	C380500	Generalised obesity
13278	210854	709	22K5.00	Body mass index 30+ - obesity
38059	207	3	C380200	Extreme obesity with alveolar hypoventilation
7984	23373	755	22A5.11	O/E - obese
430	423461	23391	C380.00	Obesity
8854	10312	612	C380300	Morbid obesity
3176	8842	1047	66C4.00	Has seen dietician - obesity
10728	1336	91	ZC2CM00	Dietary advice for obesity
11401	782	22	C38z000	Simple obesity NOS

Original Extraction of Cardiovascular disease medcodes

medcode	clinicalevents	readcode	readterm
55137	48	G311011	MI - myocardial infarction aborted
14898	530	G305.00	Lateral myocardial infarction NOS
4017	10536	G32..00	Old myocardial infarction
39655	4	G311.12	Impending infarction
41221	168	G30y200	Acute septal infarction
12139	1655	G300.00	Acute anterolateral infarction
61072	56	G311000	Myocardial infarction aborted
23579	93	G310.00	Postmyocardial infarction syndrome
46017	319	G30yz00	Other acute myocardial infarction NOS
14658	79510	G30z.00	Acute myocardial infarction NOS
8935	1504	G302.00	Acute inferolateral infarction
63467	50	G306.00	True posterior myocardial infarction
102917	530	9hM1.00	Exc myocar infarction quality indicators: patient unsuitable
23892	704	G304.00	Posterior myocardial infarction NOS

40429	104	G301000	Acute anteroapical infarction
241	220657	G30..00	Acute myocardial infarction
34803	252	G30y.00	Other acute myocardial infarction
7783	433	323..00	ECG: myocardial infarction
1678	12225	G308.00	Inferior myocardial infarction NOS
96838	2	Gyu3400	[X]Acute transmural myocardial infarction of unspecif site
100437	61	9hM..00	Exception reporting: myocardial infarction quality indicator
32854	59	G30B.00	Acute posterolateral myocardial infarction
46166	11	G35X.00	Subsequent myocardial infarction of unspecified site
68748	12	G38z.00	Postoperative myocardial infarction, unspecified
9507	892	G307000	Acute non-Q wave infarction
68357	18	G31y100	Microinfarction of heart
12229	18954	G30X000	Acute ST segment elevation myocardial infarction
1677	84525	G30..15	MI - acute myocardial infarction
17689	429	G30..17	Silent myocardial infarction
99991	4	Gyu3600	[X]Subsequent myocardial infarction of unspecified site
38609	48	G351.00	Subsequent myocardial infarction of inferior wall
45809	54	G350.00	Subsequent myocardial infarction of anterior wall
109035	1	Gyu3500	[X]Subsequent myocardial infarction of other sites
100139	425	14AT.00	History of myocardial infarction
10562	53781	G307100	Acute non-ST segment elevation myocardial infarction
14897	3069	G301z00	Anterior myocardial infarction NOS
5387	2054	G301.00	Other specified anterior myocardial infarction
39449	86	G312.00	Coronary thrombosis not resulting in myocardial infarction
29758	168	G30X.00	Acute transmural myocardial infarction of unspecif site
46112	6	G380.00	Postoperative transmural myocardial infarction anterior wall
41835	32	G384.00	Postoperative subendocardial myocardial infarction
26974	4	3231	ECG: no myocardial infarction
72562	9	G353.00	Subsequent myocardial infarction of other sites
46276	21	G381.00	Postoperative transmural myocardial infarction inferior wall
106812	1	G383.00	Postoperative transmural myocardial infarction unspec site
32272	205	G38..00	Postoperative myocardial infarction
18842	318	G35..00	Subsequent myocardial infarction
16408	352	G32..11	Healed myocardial infarction
17464	1297	G32..12	Personal history of myocardial infarction
30421	183	G30..13	Cardiac rupture following myocardial infarction (MI)
105216	343	14AW.00	H/O acute coronary syndrome
11983	27577	G311500	Acute coronary syndrome

Original Extraction of Bariatric surgery medcodes

medcode	clinicalevents	referralevents	readcode	readterm
97691	193	1	7613600	Maintenance of gastric band
90454	513	34	761A500	Removal of gastric band
18863	3048	156	7613200	Laparoscopic adjustable gastric banding
89259	738	4	7611500	Sleeve gastrectomy NEC
93378	56	0	7611400	Sleeve gastrectomy and duodenal switch
89148	775	2	7611600	Laparoscopic sleeve gastrectomy
95929	3347	33	7616600	Laparoscopic gastric bypass
92957	18	0	7616013	Mason high gastric bypass
97014	201	4	ZV45P00	[V]Presence of gastric bypass
48417	30	0	7616015	Printer high gastric bypass
107267	3	0	14NE.11	History of bariatric operative procedure
102486	519	74	14NE.00	H/O: bariatric operative procedure

Original Extraction of Chronic Obstructive Pulmonary Disease medcodes

medcode	clinicalevents	referralevents	readcode	readterm
5710	62774	1082	H3z..00	Chronic obstructive airways disease NOS
12166	1260	17	H3y..00	Other specified chronic obstructive airways disease
104608	127	0	H3A..00	End stage chronic obstructive airways disease
1446	206896	4269	H312200	Acute exacerbation of chronic obstructive airways disease
998	210976	12959	H3...11	Chronic obstructive airways disease
103760	6	0	9kf2.11	COPD structured smoking assessment declined
11026	82988	5	9h51.00	Excepted from COPD quality indicators: Patient unsuitable
11266	56967	3	9h52.00	Excepted from COPD quality indicators: Informed dissent
98283	49	0	9kf2.00	COPD structured smoking assessment declined - enh serv admin
11019	16910	203	8H2R.00	Admit COPD emergency
104169	2902	6	661N300	COPD self-management plan review
18717	3341	4	9h5..00	Exception reporting: COPD quality indicators
28743	174205	11	66Yf.00	Number of COPD exacerbations in past year
104710	45	0	9NgP.11	On COPD (chr obstruc pulmonary disease) supportv cre pathway
103558	230	3	8CeD.00	Preferred place of care for next exacerbation of COPD
104265	739	0	9e03.00	GP OOH service notified of COPD care plan
46036	1427	4	66Yi.00	Multiple COPD emergency hospital admissions
18501	144999	482	66YI.00	COPD self-management plan given
103758	626	373	8Hkw.00	Referral to COPD community nursing team
18476	36049	382	66YL.11	COPD follow-up

97800	327	1	9kf..00	COPD - enhanced services administration
98284	73	0	9kf1.00	Refer COPD structured smoking assessment - enhanc serv admin
35303	18896	0	9N4W.00	DNA - Did not attend COPD clinic
104117	4218	34	661M300	COPD self-management plan agreed
19003	11954	11	66Ye.00	Emergency COPD admission since last appointment
103864	23	0	9kf0.11	COPD patient unsuitable for pulmonary rehabilitation
19106	12618	2	66Yd.00	COPD accident and emergency attendance since last visit
103400	3	0	9kf1.11	Referred for COPD structured smoking assessment
99948	5389	0	9kf0.00	COPD patient unsuitable for pulmonary rehab - enh serv admin

Original Extraction of Obstructive Sleep Apnea medcodes

medcode	clinicalevents	referralevents	readcode	readterm
2329	72397	2495	Fy0..00	Sleep disorders
2506	32275	9275	R005311	[D]Sleep apnoea syndrome
8148	25815	1339	Fy03.11	Obstructive sleep apnoea
7603	16408	2567	Fy03.00	Sleep apnoea
12072	4284	119	8Q0..00	Sleep management
93615	7095	29	9Nk0.00	Seen in sleep clinic
23779	2863	276	H5B..00	Sleep apnoea
20748	1486	21	H5B0.00	Obstructive sleep apnoea
15407	1207	19	R005z00	[D]Sleep dysfunction NOS
36301	921	59	R005300	[D]Hypersomnia with sleep apnoea
20438	283	62	R005312	[D]Syndrome sleep apnoea
28473	248	14	A86..11	Sleeping sickness
48539	102	2	R005100	[D]Insomnia with sleep apnoea
27649	93	3	E274z00	Non-organic sleep disorder NOS
104005	17	2	9b9Y.00	Sleep studies - specialty
982	8512	1399	R060400	[D]Apnoea

Original Extraction of Diabetes medcodes

medcode	clinicalevents	referralevents	readcode	readterm
91943	1	0	C10EC11	Type I diabetes mellitus with polyneuropathy
101311	2	0	C10EC12	Insulin dependent diabetes mellitus with polyneuropathy
32193	300	12	C11y000	Steroid induced diabetes
64668	93	0	C10FJ11	Insulin treated Type II diabetes mellitus
106061	1	0	C10FP11	Type II diabetes mellitus with ketoacidotic coma
13279	13	0	C104y00	Other specified diabetes mellitus with renal complications
101801	134932	31	66At100	Type II diabetic dietary review

43951	707	0	66AK.00	Diabetic - cooperative patient
13103	4236	27	2BBS.00	O/E - left eye preproliferative diabetic retinopathy
36633	41	0	C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
106738	653	3	9Oy0000	Diabetic foot screening invitation
52236	46	21	C10A.00	Malnutrition-related diabetes mellitus
11149	20210	148	R102.11	[D]Prediabetes
8836	137123	3930	66AR.00	Diabetes management plan given
18167	12017	86	66AT.00	Annual diabetic blood test
28769	14112	20	66AV.00	Diabetic on insulin and oral treatment
105937	14	18	8IEQ.00	Referral to community diabetes specialist nurse declined
107452	38	7	66o..00	Further diabetic monitoring
17262	110	26	C109600	Non-insulin-dependent diabetes mellitus with retinopathy
18642	10	0	C10EH00	Type 1 diabetes mellitus with arthropathy
47649	20	2	C10E100	Type 1 diabetes mellitus with ophthalmic complications
62674	68	0	C10FA00	Type 2 diabetes mellitus with mononeuropathy
12675	57098	61	66AQ.00	Diabetes: shared care programme
5002	373	3	F372.11	Diabetic polyneuropathy
2342	8399	301	F372.12	Diabetic neuropathy
28622	3922	10	2126300	Diabetes resolved
95992	1	0	C108A11	Type I diabetes mellitus without complication
49884	406	3	6761	Diabetic pre-pregnancy counselling
34528	29	0	3882	Diabetes well being questionnaire
47584	116	1	F420500	Advanced diabetic retinal disease
42831	24	1	C10E200	Type 1 diabetes mellitus with neurological complications
9308	3338	4	ZV18000	[V]Family history of diabetes mellitus
20900	15385	50	9OLA.11	Diabetes monitored
6813	41987	1689	1434	H/O: diabetes mellitus
102767	183	4	67IJ100	Pre-conception advice for diabetes mellitus
61071	7	1	C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
10692	5404	100	C10EM00	Type 1 diabetes mellitus with ketoacidosis
69993	12	0	C10E600	Type 1 diabetes mellitus with gangrene
26054	4384	48	C10FL00	Type 2 diabetes mellitus with persistent proteinuria
93854	20799	4	9OLM.00	Diabetes structured education programme declined
47582	45	2	C10E000	Type 1 diabetes mellitus with renal complications
93878	6	0	C10E511	Type I diabetes mellitus with ulcer
100422	44	0	8HgC.00	Discharged from diabetes shared care programme
26666	740696	12	2G5E.00	O/E - Right diabetic foot at low risk
96235	12	0	C10E911	Type I diabetes mellitus maturity onset
110481	1	0	K081000	Acquired nephrogenic diabetes insipidus

94777	511	5	ZV13F00	[V]Personal history of gestational diabetes mellitus
39317	190	1	C106100	Diabetes mellitus, adult onset, + neurological manifestation
102768	1094	1	9NiZ.00	Did not attend diabetes foot screening
108005	55	0	C109312	Type 2 diabetes mellitus with multiple complications
45491	80	3	C10z.00	Diabetes mellitus with unspecified complication
13678	816	1728	ZL62600	Referral to diabetic liaison nurse
10098	8	0	C10yy00	Other specified diabetes mellitus with other spec comps
99231	1	0	C108B11	Type I diabetes mellitus with mononeuropathy
98616	2	0	C10F211	Type II diabetes mellitus with neurological complications
19203	5839	0	1I0..00	Diabetes mellitus excluded
66145	1	0	C10EN11	Type I diabetes mellitus with ketoacidotic coma
110056	2	0	9m0B.00	Excluded frm diab retinop screen as no currnt contct details
107597	3	0	9m0D.00	Excluded from diabetic retinopthy screen as learn disability
26605	1988	3	9OLB.00	Attended diabetes structured education programme
44260	7	2	C108F00	Insulin dependent diabetes mellitus with diabetic cataract
61470	204	7	66Al.00	Diabetic monitoring - higher risk albumin excretion
40023	8	0	C102000	Diabetes mellitus, juvenile type, with hyperosmolar coma
106778	3	0	9m0C.00	Excluded frm diabetic retinopathy screen as terminal illness
62384	44	3	2G5V.00	O/E - right chronic diabetic foot ulcer
47011	25340	2972	8Hj0.00	Referral to diabetes structured education programme
44443	212	3	C108500	Insulin dependent diabetes mellitus with ulcer
35385	192	5	C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
18505	8060	314	C108.11	IDDM-Insulin dependent diabetes mellitus
56448	18	0	C108A00	Insulin-dependent diabetes without complication
43453	33	0	C10C.00	Diabetes mellitus autosomal dominant
40401	11	1	C109500	Non-insulin dependent diabetes mellitus with gangrene
105484	757	0	66Az.00	High risk of diabetes mellitus annual review
49074	112	3	C10F400	Type 2 diabetes mellitus with ulcer
18662	208	19	8HBH.00	Diabetic retinopathy 6 month review
1323	92377	7920	F420.00	Diabetic retinopathy
107739	14	0	679L211	Advice about diabetes and driving
24363	937	195	8A13.00	Diabetic stabilisation
101430	2780	0	1252000	Family history of diabetes mellitus type 1
61523	58	0	C106y00	Other specified diabetes mellitus with neurological comps
32999	103	2	Q440.00	'Infant of a diabetic mother' syndrome
65062	7	0	C103z00	Diabetes mellitus NOS with ketoacidotic coma
42505	343	8	C101z00	Diabetes mellitus NOS with ketoacidosis
18142	276	7	N030000	Diabetic cheiroarthropathy

12455	519	4	C10E.11	Type I diabetes mellitus
98392	6	0	C10C.12	Maturity onset diabetes in youth type 1
46624	196	9	C10C.11	Maturity onset diabetes in youth
1407	12322	77	C10FJ00	Insulin treated Type 2 diabetes mellitus
63357	52	1	C107100	Diabetes mellitus, adult, + peripheral circulatory disorder
21983	5	0	C108012	Type 1 diabetes mellitus with renal complications
46533	424	12	13Y1.00	Diabetic association member
18747	10324	40	8I6F.00	Diabetic retinopathy screening not indicated
107414	1420	12	8I94.00	Diabetes structured education programme not available
108360	2	0	C10P000	Type I diabetes mellitus in remission
35399	3517	28	C107.00	Diabetes mellitus with peripheral circulatory disorder
31171	47910	20	2G5G.00	O/E - Right diabetic foot at high risk
95093	168	1	8I83.00	Did not complete DESMOND diabetes structured educat program
18311	184710	8723	68A7.00	Diabetic retinopathy screening
32739	2073	28	9N0n.00	Seen in community diabetes specialist clinic
31240	23667	5	9OL7.00	Diabetes monitor.verbal invite
17886	5524	2	66AM.00	Diabetic - follow-up default
55123	106	0	66AO.00	Date diabetic treatment stopp.
47370	198	77	8HLE.00	Diabetology D.V. done
102704	6793	7	66At000	Type I diabetic dietary review
25041	571	1	ZC2CA00	Dietary advice for type II diabetes
18278	3951	26	C109J00	Insulin treated Type 2 diabetes mellitus
52041	148	0	2BBl.00	O/E - left eye stable treated prolif diabetic retinopathy
43857	32	2	C10M.00	Lipoatrophic diabetes mellitus
11433	69115	151	2BBP.00	O/E - right eye background diabetic retinopathy
13097	2685	15	2BBT.00	O/E - right eye proliferative diabetic retinopathy
50527	12	0	C10FB11	Type II diabetes mellitus with polyneuropathy
100033	5	0	U60231E	[X] Adverse reaction to insulins and antidiabetic agents NOS
65684	13	0	U602311	[X] Adverse reaction to insulins and antidiabetic agents
106722	201	0	9Oy0300	Diabetic foot screening invitation second letter
99716	2	0	C10EE12	Insulin dependent diabetes mellitus with hypoglycaemic coma
94956	104	0	8I84.00	Did not complete XPERT diabetes structured education program
107701	2	0	C10FK11	Hyperosmolar non-ketotic state in type II diabetes mellitus
97809	6	0	8I82.00	Did not complete DAFNE diabetes structured education program
11551	1297	24	C10B.00	Diabetes mellitus induced by steroids
22487	120	4	C10N.00	Secondary diabetes mellitus
60499	10	2	C108600	Insulin dependent diabetes mellitus with gangrene

37806	68	2	C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
758	821388	11818	C10F.00	Type 2 diabetes mellitus
36695	336	4	C10D.00	Diabetes mellitus autosomal dominant type 2
24693	5	0	C109G00	Non-insulin dependent diabetes mellitus with arthropathy
3837	21908	383	F420400	Diabetic maculopathy
10099	777	90	F420300	Advanced diabetic maculopathy
59903	24	0	C106.11	Diabetic amyotrophy
7795	8881	194	C106.12	Diabetes mellitus with neuropathy
16491	64	0	C106.13	Diabetes mellitus with polyneuropathy
46301	31	0	C10EC00	Type 1 diabetes mellitus with polyneuropathy
51756	29	0	C10FP00	Type 2 diabetes mellitus with ketoacidotic coma
69278	13	0	C109E00	Non-insulin depend diabetes mellitus with diabetic cataract
18683	44	1	C10E500	Type 1 diabetes mellitus with ulcer
54600	5	0	C10E412	Unstable insulin dependent diabetes mellitus
49949	7	1	C10E411	Unstable type I diabetes mellitus
18390	7981	41	C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
36855	260	17	2BBG.00	Retinal abnormality - non-diabetes
10418	464	9	C10ED00	Type 1 diabetes mellitus with nephropathy
62352	1	0	C108H11	Type I diabetes mellitus with arthropathy
58604	21	5	C109611	Type II diabetes mellitus with retinopathy
42762	16	1	C109612	Type 2 diabetes mellitus with retinopathy
64357	113	0	C10zz00	Diabetes mellitus NOS with unspecified complication
12703	760	95	3881	Education score - diabetes
95351	10	0	C10FA11	Type II diabetes mellitus with mononeuropathy
37315	303	9	F3y0.00	Diabetic mononeuropathy
31790	1357	34	F372.00	Polyneuropathy in diabetes
46577	73	11	66AX.00	Diabetes: shared care in pregnancy - diabetol and obstet
13067	154459	7479	66AZ.00	Diabetic monitoring NOS
60046	11	0	C135.12	Diabetes insipidus - pituitary
104639	19	0	C10FF11	Type II diabetes mellitus with peripheral angiopathy
7045	187	60	14F4.00	H/O: Admission in last year for diabetes foot problem
95539	5	0	C10FS00	Maternally inherited diabetes mellitus
16881	388	536	ZV65312	[V]Dietary counselling in diabetes mellitus
22189	2386	0	ZV18011	[V]Family history of diabetes mellitus (DM)
53238	142	0	66AG.00	Diabetic drug side effects
50960	217	5	L180500	Pre-existing diabetes mellitus, insulin-dependent
61670	10	0	889A.00	Diab mellit insulin-glucose infus acute myocardial infarct
102112	6	0	C10E611	Type I diabetes mellitus with gangrene
109051	1	0	C10E612	Insulin dependent diabetes mellitus with gangrene

95641	5	3	8Hj1.00	Family/carer referral to diabetes structured education prog
68792	7	0	C10z000	Diabetes mellitus, juvenile type, + unspecified complication
56268	2	0	C109D11	Type II diabetes mellitus with hypoglycaemic coma
31157	168293	40	2G5F.00	O/E - Right diabetic foot at moderate risk
64446	3	1	C108G00	Insulin dependent diab mell with peripheral angiopathy
59725	2	0	C109111	Type II diabetes mellitus with ophthalmic complications
95813	20	0	9N1o.00	Seen in multidisciplinary diabetic clinic
62613	2	0	C10EA11	Type I diabetes mellitus without complication
6125	1740866	1630	66AS.00	Diabetic annual review
12307	26948	13	66AU.00	Diabetes care by hospital only
9881	2491	203	M271200	Mixed diabetic ulcer - foot
50175	29076	100	66AW.00	Diabetic foot risk assessment
101190	32	0	66AQ100	Declined consent for diabetes year of care programme
94955	1061	0	9NiE.00	Did not attend XPERT diabetes structured education programme
24694	1	0	C108B00	Insulin dependent diabetes mellitus with mononeuropathy
34268	170	3	C10F200	Type 2 diabetes mellitus with neurological complications
34912	227	4	C109400	Non-insulin dependent diabetes mellitus with ulcer
28574	4479	1	9h4..00	Exception reporting: diabetes quality indicators
38129	1538	9	9N0o.00	Seen in community diabetic specialist nurse clinic
108634	3	0	9NJy.00	In-house diabetic foot screening
13078	7356	16	13AC.00	Diabetic weight reducing diet
105302	220	10	K08yA00	Proteinuric diabetic nephropathy
93631	1208	0	9OLL.00	XPERT diabetes structured education programme completed
25591	180	5	C10FQ00	Type 2 diabetes mellitus with exudative maculopathy
47954	832	6	C10F900	Type 2 diabetes mellitus without complication
98954	3568	0	3883	Diabetes treatment satisfaction questionnaire
11348	101532	4	9h42.00	Excepted from diabetes quality indicators: Informed dissent
51957	10	1	C108511	Type I diabetes mellitus with ulcer
35316	4471	26	2G5H.00	O/E - Right diabetic foot - ulcerated
102434	13764	8	66Au.00	Diabetic erectile dysfunction review
38617	28	1	C101y00	Other specified diabetes mellitus with ketoacidosis
14049	83	152	42WZ.00	Hb. A1C - diabetic control NOS
18185	1767	40	2G5D.00	Foot abnormality - non-diabetes
57723	905	100	8HHy.00	Referral to diabetic register
66675	3	0	C10A000	Malnutrition-related diabetes mellitus with coma
65025	76	3	C107z00	Diabetes mellitus NOS with peripheral circulatory disorder
34283	165	0	C105z00	Diabetes mellitus NOS with ophthalmic manifestation

13057	63947	798	679L.00	Health education - diabetes
24571	190	4	F372200	Asymptomatic diabetic neuropathy
11041	72100	5	9h41.00	Excepted from diabetes qual indicators: Patient unsuitable
102435	108	1	8CE0000	Gestational diabetes information leaflet given
104374	10800	3	67D8.00	Provision of diabetes clinical summary
18766	2180	13	212H.00	Diabetes resolved
107824	10	0	C10P100	Type II diabetes mellitus in remission
12247	14859	13	8I6G.00	Diabetic foot examination not indicated
46850	17	0	C108811	Type I diabetes mellitus - poor control
45914	3	0	C108812	Type 1 diabetes mellitus - poor control
98723	21	0	C10FD11	Type II diabetes mellitus with hypoglycaemic coma
107361	721	0	679L200	Education about diabetes and driving
85660	3461	73	66An.00	Diabetes type 1 review
13069	13124	2	66A8.00	Has seen dietician - diabetes
17067	2313	59	F171100	Autonomic neuropathy due to diabetes
63412	5544	11	8CR2.00	Diabetes clinical management plan
107603	144	0	C10P.00	Diabetes mellitus in remission
96823	2	0	L180400	Diabetes mellitus in pueperium - baby previously delivered
52212	100	1	Cyu2.00	[X]Diabetes mellitus
99822	273	0	38DK.00	Finnish diabetes risk score
57389	2043	2	93C4.00	Patient consent given for addition to diabetic register
28873	89962	159	66Ai.00	Diabetic 6 month review
66475	431	0	66Ak.00	Diabetic monitoring - lower risk albumin excretion
102163	1	0	C10ED12	Insulin dependent diabetes mellitus with nephropathy
32619	9325	26	66Af.00	Patient diabetes education review
91942	4	0	C10E311	Type I diabetes mellitus with multiple complications
45276	13	0	C10E312	Insulin dependent diabetes mellitus with multiple complicat
57333	29	1	N030011	Diabetic cheiropathy
106953	183	0	8IEa.00	Referral to DAFNE diabetes structured educn prog declined
101177	210022	42	66At.00	Diabetic dietary review
106723	1891	0	9Oy0200	Diabetic foot screening invitation first letter
46963	29	1	C108000	Insulin-dependent diabetes mellitus with renal complications
10755	12551	25	F420600	Non proliferative diabetic retinopathy
101172	39	0	C135000	Cranial diabetes insipidus
32556	115	17	C107.12	Diabetes with gangrene
32403	269	49	C107.11	Diabetes mellitus with gangrene
6509	244	41	C108700	Insulin dependent diabetes mellitus with retinopathy
59253	49	2	C10FG00	Type 2 diabetes mellitus with arthropathy

104588	186	1	66Ay.00	Gestational diabetes mellitus annual review
35288	320	28	C10E800	Type 1 diabetes mellitus - poor control
5234	536519	362	6872	Diabetes mellitus screen
68105	9	0	C10EB00	Type 1 diabetes mellitus with mononeuropathy
32770	80	9	44V3.00	Glucose tol. test diabetic
34450	498	12	C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
37648	22	3	C109J11	Insulin treated non-insulin dependent diabetes mellitus
18264	51	4	C109J12	Insulin treated Type II diabetes mellitus
47341	228	18	8A12.00	Diabetic crisis monitoring
47144	31018	0	2BBM.00	O/E - diabetic maculopathy absent both eyes
18425	227	4	C10FB00	Type 2 diabetes mellitus with polyneuropathy
21472	29	0	Q441.00	Neonatal diabetes mellitus
7328	657	74	M037200	Cellulitis in diabetic foot
11930	2462	15	9NN9.00	Under care of diabetes specialist nurse
47032	61621	2233	8CS0.00	Diabetes care plan agreed
102946	3	0	C10E012	Insulin-dependent diabetes mellitus with renal complications
109837	1	0	C10E011	Type I diabetes mellitus with renal complications
9958	24143	8302	42W..00	Hb. A1C - diabetic control
48192	11	3	C109E11	Type II diabetes mellitus with diabetic cataract
22871	59	4	C10EP00	Type 1 diabetes mellitus with exudative maculopathy
57621	18	0	C108D00	Insulin dependent diabetes mellitus with nephropathy
16230	12345	55	C106.00	Diabetes mellitus with neurological manifestation
70316	36	0	C109112	Type 2 diabetes mellitus with ophthalmic complications
10824	17465	249	9N1i.00	Seen in diabetic foot clinic
11359	950	30	L180.00	Diabetes mellitus during pregnancy/childbirth/puerperium
106332	2487	0	9m00.00	Eligible for diabetic retinopathy screening
66872	7	0	C108D11	Type I diabetes mellitus with nephropathy
57278	4	0	C10F011	Type II diabetes mellitus with renal complications
38103	2471	3	9N0m.00	Seen in diabetic nurse consultant clinic
12030	83645	643	9OL6.00	Diabetes monitoring 3rd letter
104453	89	0	66At011	Type 1 diabetic dietary review
64571	5	1	C109C11	Type II diabetes mellitus with nephropathy
24836	10	1	C109C12	Type 2 diabetes mellitus with nephropathy
63762	50	0	C10z100	Diabetes mellitus, adult onset, + unspecified complication
85991	4	0	C10FM11	Type II diabetes mellitus with persistent microalbuminuria
65616	4	0	C108H00	Insulin dependent diabetes mellitus with arthropathy
17313	54	1	F440700	Diabetic iritis
64384	40	1	L180z00	Diabetes mellitus in pregnancy/childbirth/puerperium NOS
11471	230737	239	8B3l.00	Diabetes medication review

13070	21323	103	66A1.00	Initial diabetic assessment
93380	93	1	C10N100	Cystic fibrosis related diabetes mellitus
11663	1850	139	M271100	Neuropathic diabetic ulcer - foot
1045	3039	190	C135.00	Diabetes insipidus
50609	44	2	L180600	Pre-existing diabetes mellitus, non-insulin-dependent
95094	72	13	8I81.00	Did not complete diabetes structured education programme
55842	14	0	C109200	Non-insulin-dependent diabetes mellitus with neuro comps
67664	16	1	ZRBa.00	Education score - diabetes
31053	50	2	R054300	[D]Widespread diabetic foot gangrene
30294	445	5	C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria
65267	33	2	C10F300	Type 2 diabetes mellitus with multiple complications
13104	166663	1	2BBK.00	O/E - no left diabetic retinopathy
99628	2	1	Kyu0300	[X]Glomerular disorders in diabetes mellitus
35105	93	1	C104100	Diabetes mellitus, adult onset, with renal manifestation
69676	53	1	C10EA00	Type 1 diabetes mellitus without complication
33254	1586	24	C105.00	Diabetes mellitus with ophthalmic manifestation
17095	5332	49	2G5A.00	O/E - Right diabetic foot at risk
18056	766	229	2G5C.00	Foot abnormality - diabetes related
15690	348	57	C103.00	Diabetes mellitus with ketoacidotic coma
22967	1782	11	2BBF.00	Retinal abnormality - diabetes related
109520	4	0	9m03.00	Eligibility permanently inactive for diabetic retinop screen
41389	86	0	C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation
105207	200	499	8HTE100	Referral to community diabetes clinic
101802	2143	0	1252100	Family history of diabetes mellitus type 2
107423	1434	11	661N400	Diabetes self-management plan review
62146	9	2	C109300	Non-insulin-dependent diabetes mellitus with multiple comps
23005	49553	2	1253	FH: Diabetes mellitus in first degree relative
26604	7669	3	66AY.00	Diabetic diet - good compliance
10977	146669	121	66Ac.00	Diabetic peripheral neuropathy screening
13195	181278	1327	9OL5.00	Diabetes monitoring 2nd letter
100292	2	0	Cyu2300	[X]Unspecified diabetes mellitus with renal complications
108993	121	0	661M400	Diabetes self-management plan agreed
65704	14	2	C109412	Type 2 diabetes mellitus with ulcer
55075	19	1	C109411	Type II diabetes mellitus with ulcer
41716	11	0	C108C00	Insulin dependent diabetes mellitus with polyneuropathy
104323	1	0	C10F511	Type II diabetes mellitus with gangrene
13099	4424	33	2BBR.00	O/E - right eye preproliferative diabetic retinopathy
61829	6	0	C108212	Type 1 diabetes mellitus with neurological complications

49146	1	0	C108211	Type I diabetes mellitus with neurological complications
30970	95	0	Q44B.00	Syndrome of infant of mother with gestational diabetes
93491	195	0	9OLJ.00	DAFNE diabetes structured education programme completed
7777	8848	16878	8H4F.00	Referral to diabetologist
30477	71	0	F420700	High risk proliferative diabetic retinopathy
107881	3	0	K08yA11	Clinical diabetic nephropathy
1038	34457	2142	C100011	Insulin dependent diabetes mellitus
83532	49007	296	66Ao.00	Diabetes type 2 review
108013	2	0	ZC2CB00	Dietary advice for gestational diabetes
52237	12012	1	9360	Patient held diabetic record issued
53392	224	0	C10F911	Type II diabetes mellitus without complication
99719	2	0	C10EA12	Insulin-dependent diabetes without complication
94383	7	0	C10N000	Secondary diabetes mellitus without complication
35383	14676	3	9OLD.00	Diabetic patient unsuitable for digital retinal photography
41686	4	0	Cyu2000	[X]Other specified diabetes mellitus
82474	2701	3707	8Hl4.00	Referral to community diabetes specialist nurse
109521	3	0	9m02.00	Eligibility temporarily inactive for diabetic retinop screen
107793	39	0	9Oy0400	Diabetic foot screening invitation third letter
13194	794847	6953	9OL4.00	Diabetes monitoring 1st letter
105741	6033	2	2G5e.00	O/E - Right diabetic foot at increased risk
2475	3130	137	C104.11	Diabetic nephropathy
101735	1	0	C10E212	Insulin-dependent diabetes mellitus with neurological comps
34541	38	58	8HVU.00	Private referral to diabetologist
95159	1427	2	9NiD.00	Did not attend DESMOND diabetes structured education program
49276	16	0	C108100	Insulin-dependent diabetes mellitus with ophthalmic comps
24327	2214	197	M271000	Ischaemic ulcer diabetic foot
40682	73	1	C10E900	Type 1 diabetes mellitus maturity onset
6791	424	19	C108800	Insulin dependent diabetes mellitus - poor control
46917	101	2	C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
49559	39	2	L180300	Diabetes mellitus during pregnancy - baby not yet delivered
2379	1185513	3246	9N1Q.00	Seen in diabetic clinic
18824	17687	1	8I3W.00	Diabetic foot examination declined
61461	701	0	9M00.00	Informed consent for diabetes national audit
106679	3161	0	8OA3.00	Provision of written information about diabetes and driving
16490	11032	57	66AH.00	Diabetic treatment changed
66965	9	0	C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
95124	15879	7	9Oy0.00	Diabetes screening invitation

3550	2051449	15730	66A..00	Diabetic monitoring
30648	27382	15	9N4p.00	Did not attend diabetic retinopathy clinic
47650	30	0	C10E300	Type 1 diabetes mellitus with multiple complications
43139	29	0	C102100	Diabetes mellitus, adult onset, with hyperosmolar coma
44312	35	0	9M10.00	Informed dissent for diabetes national audit
12640	1974	59	C10FC00	Type 2 diabetes mellitus with nephropathy
101834	180	0	9h43.00	Excepted from diabetes qual indicators: service unavailable
93870	11803	1808	8Hj5.00	Referral to XPERT diabetes structured education programme
18230	3	1	C108J12	Type 1 diabetes mellitus with neuropathic arthropathy
60208	3	0	C108J11	Type I diabetes mellitus with neuropathic arthropathy
94699	689	0	ZRB5.00	Diabetes treatment satisfaction questionnaire
8414	47485	117	8CA4100	Pt advised re diabetic diet
13074	71551	339	13B1.00	Diabetic diet
44779	9	1	C109E12	Type 2 diabetes mellitus with diabetic cataract
608	438652	11531	66A2.00	Follow-up diabetic assessment
67635	14	0	L180000	Diabetes mellitus - unspec whether in pregnancy/puerperium
1684	208672	440	66A4.00	Diabetic on oral treatment
41049	9	0	C108712	Type 1 diabetes mellitus with retinopathy
38161	14	1	C108711	Type I diabetes mellitus with retinopathy
103902	17	0	C10FG11	Type II diabetes mellitus with arthropathy
54899	4	0	C109F11	Type II diabetes mellitus with peripheral angiopathy
60699	2	0	C109F12	Type 2 diabetes mellitus with peripheral angiopathy
72702	12	0	C10E812	Insulin dependent diabetes mellitus - poor control
105337	5	0	C10E811	Type I diabetes mellitus - poor control
19739	11729	1575	68A9.00	Diabetic retinopathy screening offered
44993	537	2	46Z0.00	Urine screening test for diabetes
106350	33	0	9m05.00	Excluded from diabetic retinopathy screening as moved away
106328	16	0	9m07.00	Excluded diabetc retinop screen as under care ophthalmolgist
22130	12156	5	9OL3.00	Diabetes monitoring default
13197	176602	9022	9OL1.00	Attends diabetes monitoring
16946	313	35	13L4.11	Diabetic child
11977	2011	1686	ZL62500	Referral to diabetes nurse
38078	26693	1	66A9.00	Understands diet - diabetes
105784	3	0	C109912	Type 2 diabetes mellitus without complication
109103	0	0	C109911	Type II diabetes mellitus without complication
11677	29106	2962	8H7r.00	Refer to diabetic foot screener
61557	10	3	8HKE.00	Diabetology D.V. requested

107560	304	0	67H9.00	Education about lifestyle for risk of diabetes
12507	3135	6	9N2i.00	Seen by diabetic liaison nurse
5905	25706	260	14O8.00	At risk of diabetes mellitus
101728	568	0	66As.00	Diabetic on subcutaneous treatment
103935	1	0	1IA..00	No evidence of diabetic nephropathy
54419	1561	1	918T.00	Diabetes key contact
10278	461	6	L180800	Diabetes mellitus arising in pregnancy
91164	5	0	ZRB4.11	CSQ - Diabetes clinic satisfaction questionnaire
53634	85	5	R054200	[D]Gangrene of toe in diabetic
50429	17	3	C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps
30323	509	5	C10EK00	Type 1 diabetes mellitus with persistent proteinuria
18777	205	16	C10F000	Type 2 diabetes mellitus with renal complications
10659	1519	106	F464000	Diabetic cataract
59365	56	2	C109C00	Non-insulin dependent diabetes mellitus with nephropathy
12736	51	4	C10F500	Type 2 diabetes mellitus with gangrene
23479	11	2	C350011	Bronzed diabetes
31141	31081	5	9OL8.00	Diabetes monitor.phone invite
33969	97	2	C10A100	Malnutrition-related diabetes mellitus with ketoacidosis
7069	77357	276	F420000	Background diabetic retinopathy
68714	6	1	SL23.00	Insulins and antidiabetic poisoning
93468	3	0	C10EG00	Type 1 diabetes mellitus with peripheral angiopathy
2471	273	7	K01x100	Nephrotic syndrome in diabetes mellitus
9835	3452	166	2BBL.00	O/E - diabetic maculopathy present both eyes
47816	7	3	C109H11	Type II diabetes mellitus with neuropathic arthropathy
61021	7336	41	68AB.00	Diabetic digital retinopathy screening offered
69748	6	0	C105000	Diabetes mellitus, juvenile type, + ophthalmic manifestation
67905	5	0	C109211	Type II diabetes mellitus with neurological complications
45919	15	0	C109212	Type 2 diabetes mellitus with neurological complications
50064	12	0	Q44y100	Transitory metabolic disturbance-infant pre-diabetic mother
102620	1	0	C10EL11	Type I diabetes mellitus with persistent microalbuminuria
27921	438	20	2G51000	Foot abnormality - diabetes related
43227	10	0	C10F311	Type II diabetes mellitus with multiple complications
33807	41	0	C107200	Diabetes mellitus, adult with gangrene
48078	141	4	F372000	Acute painful diabetic neuropathy
94330	283	369	8H4e.00	Referral to diabetes special interest general practitioner
30310	214	7	K081.00	Nephrogenic diabetes insipidus
102490	38309	8	66Av.00	Diabetic assessment of erectile dysfunction
22823	35560	84	66Ab.00	Diabetic foot examination

100436	1195	137	679L000	Education in self management of diabetes
106604	3476	4	C11y500	Pre-diabetes
58133	134	2	ZLD7500	Discharge by diabetic liaison nurse
49655	29	0	C10F611	Type II diabetes mellitus with retinopathy
93922	2	0	C104000	Diabetes mellitus, juvenile type, with renal manifestation
106528	2	0	C10FN11	Type II diabetes mellitus with ketoacidosis
26667	734045	20	2G5I.00	O/E - Left diabetic foot at low risk
10192	12152	305	1154200	No significant family history of diabetes
61344	6	0	C108011	Type I diabetes mellitus with renal complications
106218	28830	0	9m0A.00	Declined diabetic retinopathy screening
12677	2823	398	ZV77100	[V]Screening for diabetes mellitus
94011	603	5	9OLG.00	Attended XPERT diabetes structured education programme
2664	3594	63	L180900	Gestational diabetes mellitus
52283	8	0	C108200	Insulin-dependent diabetes mellitus with neurological comps
13102	10247	63	2BBW.00	O/E - right eye diabetic maculopathy
103743	32	0	8IE2.00	Diabetes care plan declined
47377	6	0	C105y00	Other specified diabetes mellitus with ophthalmic complicatn
26855	64	4	C108400	Unstable insulin dependent diabetes mellitus
22023	1412	34	66AJz00	Diabetic - poor control NOS
31310	551	20	C108900	Insulin dependent diabetes maturity onset
44982	143	3	C10FE00	Type 2 diabetes mellitus with diabetic cataract
4513	85864	1762	C109.00	Non-insulin dependent diabetes mellitus
24490	1448	50	C100000	Diabetes mellitus, juvenile type, no mention of complication
47321	74	1	C10F100	Type 2 diabetes mellitus with ophthalmic complications
1682	12378	2126	C101.00	Diabetes mellitus with ketoacidosis
107464	967	14	66AS000	Diabetes Year of Care annual review
103798	97	30	9b92000	Diabetic medicine
104287	307	446	8Hlc.00	Referral to community diabetes service
109878	1	0	ZC2C911	Diet advice for insulin-dependent diabetes
9013	903	99	66AJ.11	Unstable diabetes
16502	1387	100	C104.00	Diabetes mellitus with renal manifestation
26664	4793	47	2G5B.00	O/E - Left diabetic foot at risk
22573	256	1	C106z00	Diabetes mellitus NOS with neurological manifestation
68928	19	0	TJ23.00	Adverse reaction to insulins and antidiabetic agents
50972	583	7	C100z00	Diabetes mellitus NOS with no mention of complication
26665	335	3	2G51100	Foot abnormality - non-diabetes
106329	8	0	9m08.00	Excluded from diabetic retinopathy screening as blind
13108	10438	50	2BBX.00	O/E - left eye diabetic maculopathy

6795	848247	1437	1252	FH: Diabetes mellitus
64283	11	0	C10zy00	Other specified diabetes mellitus with unspecified comps
68390	15	0	C108512	Type 1 diabetes mellitus with ulcer
18066	5827	2	8CE0.00	Diabetic leaflet given
711	791926	38373	C10..00	Diabetes mellitus
64449	3	0	C108z00	Unspecified diabetes mellitus with multiple complications
61122	37	0	C10H.00	Diabetes mellitus induced by non-steroid drugs
35321	178	20	8H3O.00	Non-urgent diabetic admission
35785	396	8	F372100	Chronic painful diabetic neuropathy
24458	42	1	C109711	Type II diabetes mellitus - poor control
45913	40	1	C109712	Type 2 diabetes mellitus - poor control
17858	6162	177	C108.12	Type 1 diabetes mellitus
24423	787	17	C108.13	Type I diabetes mellitus
11018	4517	127	8HBG.00	Diabetic retinopathy 12 month review
50813	1	0	C109A11	Type II diabetes mellitus with mononeuropathy
102201	27	1	C10FC11	Type II diabetes mellitus with nephropathy
55431	79	0	L180X00	Pre-existing diabetes mellitus, unspecified
105740	6098	3	2G5d.00	O/E - Left diabetic foot at increased risk
39809	27	1	C108J00	Insulin dependent diab mell with neuropathic arthropathy
68818	574	0	ZRB5.11	DTSQ - Diabetes treatment satisfaction questionnaire
95343	11	0	C10E711	Type I diabetes mellitus with retinopathy
93875	6	0	C10E712	Insulin dependent diabetes mellitus with retinopathy
107508	21	1	66AH200	Conversion to insulin by diabetes specialist nurse
52303	16	2	C109000	Non-insulin-dependent diabetes mellitus with renal comps
97824	1	0	ZRB6.11	DWBQ - Diabetes wellbeing questionnaire
54008	57	0	C10EJ00	Type 1 diabetes mellitus with neuropathic arthropathy
44440	50	0	C108E00	Insulin dependent diabetes mellitus with hypoglycaemic coma
8618	5101	24	ZLA2500	Seen by diabetic liaison nurse
106351	5	0	9m09.00	Excluded from diabetic retinop screen as no longer diabetic
12262	22012	14	8I3X.00	Diabetic retinopathy screening refused
29979	245	6	C109900	Non-insulin-dependent diabetes mellitus without complication
45467	10	0	C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
3286	8459	106	F420100	Proliferative diabetic retinopathy
13071	57337	555	66AI.00	Diabetic - good control
32359	246	15	ZRbH.00	Perceived control of insulin-dependent diabetes
49554	20	0	C10EF00	Type 1 diabetes mellitus with diabetic cataract
68843	4	0	C103100	Diabetes mellitus, adult onset, with ketoacidotic coma
65463	36	0	F420800	High risk non proliferative diabetic retinopathy

11599	4661	12	7276	Pan retinal photocoagulation for diabetes
99277	54	0	9NiC.00	Did not attend DAFNE diabetes structured education programme
59288	3	0	C103y00	Other specified diabetes mellitus with coma
98978	113	6	38DM.00	Age, BP, clinical feat, duration, diabetes 2 stroke rsk scre
98704	1	0	C10E512	Insulin dependent diabetes mellitus with ulcer
21689	20144	45	13AB.00	Diabetic lipid lowering diet
68546	3081	1	ZRB4.00	Diabetes clinic satisfaction questionnaire
25636	1623	26	66Aa.00	Diabetic diet - poor compliance
7563	98377	564	66A3.00	Diabetic on diet only
8842	67254	162	66A5.00	Diabetic on insulin
106327	88	0	9m04.00	Excluded from diabetic retinopathy screening
70448	2	0	C107000	Diabetes mellitus, juvenile +peripheral circulatory disorder
106352	34	0	9m06.00	Excluded from diabetic retinopathy screening as deceased
26603	1690	5	9OL2.00	Refuses diabetes monitoring
40837	227	20	C10EN00	Type 1 diabetes mellitus with ketoacidotic coma
60107	4	0	C108411	Unstable type I diabetes mellitus
63371	8	0	C10y100	Diabetes mellitus, adult, + other specified manifestation
93657	15282	4754	8Hj4.00	Referral to DESMOND diabetes structured education programme
34152	218	15	G73y000	Diabetic peripheral angiopathy
34639	55	0	L180100	Diabetes mellitus during pregnancy - baby delivered
28856	89	5	8CP2.00	Transition of diabetes care options discussed
108724	1	0	C10EQ11	Type I diabetes mellitus with gastroparesis
97894	1	0	C10EP11	Type I diabetes mellitus with exudative maculopathy
106269	199	7	9m0..00	Diabetic retinopathy screening administrative status
105481	1973	409	14O8000	High risk of diabetes mellitus
2378	130408	8537	66AJ.00	Diabetic - poor control
17869	287	3	66AL.00	Diabetic-uncooperative patient
13191	9849	8	9OL..11	Diabetes clinic administration
2478	1044	267	66AJ100	Brittle diabetes
52104	11	1	C108300	Insulin dependent diabetes mellitus with multiple complicatn
46290	12	1	C108y00	Other specified diabetes mellitus with multiple comps
14803	13495	641	C100100	Diabetes mellitus, adult onset, no mention of complication
12506	342453	117	66AP.00	Diabetes: practice programme
106622	1835	0	38Gj.00	QDiabetes risk calculator
43921	46	0	C10E400	Unstable type 1 diabetes mellitus
18496	1758	41	C10F600	Type 2 diabetes mellitus with retinopathy
61210	44	0	TJ23z00	Adverse reaction to insulins and antidiabetic agents NOS
21482	215	34	C102.00	Diabetes mellitus with hyperosmolar coma

38130	322	0	ZRB6.00	Diabetes wellbeing questionnaire
39420	38	2	F381300	Myasthenic syndrome due to diabetic amyotrophy
50225	9	1	C109011	Type II diabetes mellitus with renal complications
32627	786	44	C10FN00	Type 2 diabetes mellitus with ketoacidosis
37036	862	0	ZV19800	[V]Family history of diabetes mellitus
12682	8595	633	679R.00	Patient offered diabetes structured education programme
8306	4946	2729	8H7f.00	Referral to diabetes nurse
51261	998	1	C10E.12	Insulin dependent diabetes mellitus
17910	590	0	13LZ.11	Diabetic relative
46521	2002	3	9N2d.00	Seen by diabetologist
17247	208	7	F35z000	Diabetic mononeuritis NOS
38986	2432	33	C100.00	Diabetes mellitus with no mention of complication
9897	2120044	8672	9OL..00	Diabetes monitoring admin.
96142	20154	8	38DE.00	Cong heart fail, hypertens, age, diab, stroke 2 risk score
102611	219	0	66At111	Type 2 diabetic dietary review
9974	68063	92	9N1v.00	Seen in diabetic eye clinic
35107	286	8	C104z00	Diabetes mellitus with nephropathy NOS
72345	7	0	C102z00	Diabetes mellitus NOS with hyperosmolar coma
58639	94	0	8I57.00	Patient held diabetic record declined
63017	1	0	C108911	Type I diabetes mellitus maturity onset
97446	2	0	C108912	Type 1 diabetes mellitus maturity onset
93727	38	0	C10FE11	Type II diabetes mellitus with diabetic cataract
5884	5865	165	C109.11	NIDDM - Non-insulin dependent diabetes mellitus
17859	44761	1132	C109.12	Type 2 diabetes mellitus
47315	82	0	C10F711	Type II diabetes mellitus - poor control
19381	4087	1030	8HTk.00	Referral to diabetic eye clinic
100964	4	0	C10F111	Type II diabetes mellitus with ophthalmic complications
98071	2	0	C10E112	Insulin-dependent diabetes mellitus with ophthalmic comps
99311	1	0	C10E111	Type I diabetes mellitus with ophthalmic complications
33343	66	1	C10y.00	Diabetes mellitus with other specified manifestation
31172	47191	18	2G5K.00	O/E - Left diabetic foot at high risk
47328	202	1	2BBk.00	O/E - right eye stable treated prolif diabetic retinopathy
106445	6	0	9m0E.00	Excluded from diabetic retinopathy screen physical disorder
51066	15	0	9OLC.00	Family/carer attended diabetes structured education prog
35116	4281	28	2G5L.00	O/E - Left diabetic foot - ulcerated
13192	75034	17	9OLA.00	Diabetes monitor. check done
13100	166503	5	2BBJ.00	O/E - no right diabetic retinopathy
69043	57	0	ZC2C900	Dietary advice for type I diabetes
62209	41	0	C10EM11	Type I diabetes mellitus with ketoacidosis

60796	59	0	C10FL11	Type II diabetes mellitus with persistent proteinuria
93390	218	0	9OLH.00	Attended DAFNE diabetes structured education programme
94186	581	55	9OLF.00	Diabetes structured education programme completed
49640	68	3	2G5W.00	O/E - left chronic diabetic foot ulcer
13101	2506	16	2BBV.00	O/E - left eye proliferative diabetic retinopathy
100347	1	0	C10A500	Malnutritn-relat diabetes melitus wth periph circul complctn
44033	44	3	F345000	Diabetic mononeuritis multiplex
94647	7622	14	9Oy..00	Diabetes screening administration
8403	1652	41	C109700	Non-insulin dependent diabetes mellitus - poor control
1647	23179	814	C108.00	Insulin dependent diabetes mellitus
72320	3	1	C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
97281	1807	0	9Nl4.00	Seen by general practitioner special interest in diabetes
109197	2	0	C10FH11	Type II diabetes mellitus with neuropathic arthropathy
95636	117	5	C10ER00	Latent autoimmune diabetes mellitus in adult
103597	136	0	1252111	Family history of diabetes mellitus type II
72333	2	0	8HME.00	Listed for Diabetology admissn
54856	37	2	C101100	Diabetes mellitus, adult onset, with ketoacidosis
2986	4339	31	F420200	Preproliferative diabetic retinopathy
96506	4	0	C10G000	Secondary pancreatic diabetes mellitus without complication
39070	82	1	C10EE00	Type 1 diabetes mellitus with hypoglycaemic coma
93704	851	119	8Hj3.00	Referral to DAFNE diabetes structured education programme
63690	161	5	C10FR00	Type 2 diabetes mellitus with gastroparesis
42567	6	0	C103000	Diabetes mellitus, juvenile type, with ketoacidotic coma
11626	1962	26	F420z00	Diabetic retinopathy NOS
97474	2	0	C108412	Unstable type 1 diabetes mellitus
16971	148	0	ZV77111	[V]Screening for diabetes mellitus (DM)
106441	11	0	9m01.00	Ineligible for diabetic retinopathy screening
11094	350830	396	9NND.00	Under care of diabetic foot screener
69163	147	83	8HTi.00	Referral to multidisciplinary diabetic clinic
110400	2	0	C108F12	Type 1 diabetes mellitus with diabetic cataract
17545	4	1	C108F11	Type I diabetes mellitus with diabetic cataract
18209	21	1	C109012	Type 2 diabetes mellitus with renal complications
50937	51	25	8HTe.00	Referral to diabetes preconception counselling clinic
42729	14	0	C108E11	Type I diabetes mellitus with hypoglycaemic coma
70766	2	0	C108E12	Type 1 diabetes mellitus with hypoglycaemic coma
47409	3	0	C109B11	Type II diabetes mellitus with polyneuropathy
109865	1	0	C109B12	Type 2 diabetes mellitus with polyneuropathy

106360	228	0	K27y700	Erectile dysfunction due to diabetes mellitus
14050	2055	310	42c..00	HbA1 - diabetic control
13241	471185	31	1228	No family history diabetes
14889	20650	2093	C100111	Maturity onset diabetes
13245	680	30	12G2.00	FH: Diabetes in pregnancy
100770	1	0	C10EF12	Insulin dependent diabetes mellitus with diabetic cataract
109133	1	0	L180700	Pre-existing malnutrition-related diabetes mellitus
70821	15	0	C10yz00	Diabetes mellitus NOS with other specified manifestation
11129	67892	41	2BBQ.00	O/E - left eye background diabetic retinopathy
46150	5	0	C109512	Type 2 diabetes mellitus with gangrene
62107	7	1	C109511	Type II diabetes mellitus with gangrene
12213	84079	41	8BL2.00	Patient on maximal tolerated therapy for diabetes
47058	185	4	8Hg4.00	Discharged from care of diabetes specialist nurse
91646	5	0	C10F411	Type II diabetes mellitus with ulcer
95994	160129	134	66Aq.00	Diabetic foot screen
107554	324	0	38Gv.00	Diabetes UK diabetes risk score
101456	4974	0	8IAs.00	Diabetic dietary review declined
45250	216	22	ZL22500	Under care of diabetic liaison nurse
95553	104	0	9NiA.00	Did not attend diabetes structured education programme
12225	5025	7410	8H7C.00	Refer, diabetic liaison nurse
26108	110	4	C10B000	Steroid induced diabetes mellitus without complication
10642	19733	414	ZC2C800	Dietary advice for diabetes mellitus
54846	118	0	9OL9.00	Diabetes monitoring deleted
6430	25446	405	9NM0.00	Attending diabetes clinic
9145	70164	32	9N4I.00	DNA - Did not attend diabetic clinic
8446	23439	120	L180811	Gestational diabetes mellitus
36669	674	1	66b1.00	Diabetic monitoring not required
18387	498	11	C10E700	Type 1 diabetes mellitus with retinopathy
51697	280	4	C10G.00	Secondary pancreatic diabetes mellitus
1549	84358	2069	C10E.00	Type 1 diabetes mellitus
102316	3451	51	1JL..00	Suspected diabetes mellitus
25627	1234	52	C10F700	Type 2 diabetes mellitus - poor control
64142	6513	3465	8Hl1.00	Referral for diabetic retinopathy screening
11848	28	6	C314.11	Renal diabetes
55239	253	3	C10EQ00	Type 1 diabetes mellitus with gastroparesis
18219	4749	124	C109.13	Type II diabetes mellitus
109628	1	0	C10P011	Type 1 diabetes mellitus in remission
52630	53	4	2BBo.00	O/E - sight threatening diabetic retinopathy
53200	86	4	C101000	Diabetes mellitus, juvenile type, with ketoacidosis

106927	2	0	PKyP.00	Diab insipidus,diab mell,optic atrophy and deafness
105585	1896	6	8CMW700	Diabetes clinical pathway
18143	1	0	C109G11	Type II diabetes mellitus with arthropathy
7059	1233	180	8H2J.00	Admit diabetic emergency
93529	1407	2	9OLK.00	DESMOND diabetes structured education programme completed
101455	1286	1	9OLN.00	Diabetes monitor invitation by SMS (short message service)
20696	11799	1	66AA.11	Injection sites - diabetic
108007	1	0	C108311	Type I diabetes mellitus with multiple complications
100533	23	1	66AQ000	Unsuitable for diabetes year of care programme
67853	74	0	C106000	Diabetes mellitus, juvenile, + neurological manifestation
102740	1	0	C108112	Type 1 diabetes mellitus with ophthalmic complications
27891	852	44	N030100	Diabetic Charcot arthropathy
54601	2672	11	9NN8.00	Under care of diabetologist
506	94101	4524	C100112	Non-insulin dependent diabetes mellitus
101881	5	0	2BBr.00	Impaired vision due to diabetic retinopathy
31241	18555	37	9OLZ.00	Diabetes monitoring admin.NOS
2340	589	43	F381311	Diabetic amyotrophy
13196	51207	252	66AD.00	Fundoscopy - diabetic check
22884	4414	11	C10F.11	Type II diabetes mellitus
59991	30	0	C10D.11	Maturity onset diabetes in youth type 2
49869	1	0	C109G12	Type 2 diabetes mellitus with arthropathy
97849	10	0	C10E912	Insulin dependent diabetes maturity onset
29041	562	5	66AN.00	Date diabetic treatment start
31156	165665	38	2G5J.00	O/E - Left diabetic foot at moderate risk

Original Extraction of Hypertension medcodes

medcode	clinicalevents	readcode	readterm
27511	40467	6628	Poor hypertension control
34744	179	G244.00	Hypertension secondary to endocrine disorders
4372	16093	G202.00	Systolic hypertension
5215	112639	9OI..00	Hypertension monitoring admin.
51635	46	G241z00	Secondary benign hypertension NOS
83473	490	G203.00	Diastolic hypertension
105989	8	G26..00	Severe hypertension (Nat Inst for Health Clinical Ex 2011)
799	2621185	G20..00	Essential hypertension
3425	47604	662O.00	On treatment for hypertension
5513	2299	8HT5.00	Referral to hypertension clinic
12680	2131	8CR4.00	Hypertension clinical management plan
30776	4382	6629	Hypertension:follow-up default

97533	6	Gyu2100	[X]Hypertension secondary to other renal disorders
31755	78	G240.00	Secondary malignant hypertension
13186	981322	662P.00	Hypertension monitoring
105487	90	G26..11	Severe hypertension
102458	3	Gyu2000	[X]Other secondary hypertension
24127	7317	9OIA.11	Hypertension monitored
18590	3665	662b.00	Moderate hypertension control
19070	389944	662d.00	Hypertension annual review
2666	142150	14A2.00	H/O: hypertension
3712	79730	G20z.11	Hypertension NOS
10818	147344	G20z.00	Essential hypertension NOS
105316	1167	G25..11	Stage 1 hypertension
21826	5626	662F.00	Hypertension treatm. started
105480	63	G27..00	Hypertension resistant to drug therapy
15377	3086	G200.00	Malignant essential hypertension
105274	976	G28..00	Stage 2 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
16059	460	G24z.00	Secondary hypertension NOS
4444	2643577	662..12	Hypertension monitoring
102406	4067	662P000	Hypertension 9 month review
1894	32795	G201.00	Benign essential hypertension
107704	11	G20..12	Primary hypertension
105371	803	G25..00	Stage 1 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)

Original Extraction of Hyperlipidemia medcodes

medcode	**clinicalevents**	**readcode**	**readterm**
637	320190	C324.00	Hyperlipidaemia NOS
856	15440	44O6.00	Lipids abnormal
5791	55143	C322.00	Mixed hyperlipidaemia
14781	398	44O4.00	Serum lipids high
16085	9292	1442	H/O: raised blood lipids
23125	54	44O3.00	Serum lipids borderline raised
26019	684	C320200	Hyperlipidaemia, group A
32244	3622	8BG2.00	Lipid lowering therapy indicated
33694	241	ZC2CJ00	Dietary advice for hyperlipidaemia
66240	61	Cyu8D00	[X]Other hyperlipidaemia
71747	15	8CR3.00	Hyperlipidaemia clinical management plan
95952	3294	C328.00	Dyslipidaemia
102390	276	C322000	Familial combined hyperlipidaemia