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Real-World Clinical and Service Outcomes of Pre-bariatric Weight Loss Interventions and Post-bariatric Outcomes among Patients with Insulin-treated Type 2 Diabetes Living in the UK: Public Health and Epidemiological Approach

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* *Shared first author.*
** *Conference was cancelled due to Covid-19 outbreak situation. However a decision was made by the Diabetes UK team to include all accepted abstracts and e-posters within a special edition of Diabetic Medicine publications.*
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ABSTRACT

In numerous countries globally, the morbid obesity pandemic is increasingly posing a major lifelong disorder. With one-in-four adults classed as obese, while two-thirds are overweight, obesity's prevalence in England is among the highest in Europe. The effect of obesity and obesity-related comorbidity on the UK's NHS public health budgets is second only to smoking, estimated to cost £44.7 billion annually. The official UK obesity management is attained via a commissioned service that adopts a four-tiered pathway. The first two tiers are outside of this study's remit, pertaining to environmental and population-wide schemes for obesity prevention and promotion of a healthy weight and nutritional balanced diet. Tier 3 is a Multidisciplinary Weight Management Service, aimed at those whose obesity is complex and/or is accompanied by medical needs; patients in this tier may be considered for Tier 4, namely bariatric surgery. Exposure to these two clinical tiers is the focused in this thesis, which evaluates the clinical effect and health outcomes of the commissioned clinical interventions.

To comprehend the comorbidities and metabolic status of individuals with severe obesity living in the UK, the Tier 3 and similar programmes were systematically reviewed. Furthermore, Tier 3 was supplemented by research conducted at a local clinic. This research extends to patients with a major comorbidity (i.e. insulin-treated T2D) and were at high risk of CV, nephropathy or hepatic disease (i.e. respectively microalbuminuria and NAFLD at baseline), who had been referred for bariatric intervention. Analysis of CV, metabolic and renal outcomes was undertaken.

Additionally, this thesis presents a chapter appraising the economic effect of surgical treatment provision for the morbidly obese. It assesses the costs involved in providing clinical care, laboratory tests and pharmacotherapy (typically, antihypertensives, aspirin, insulin, GLP-1 analogues, lipids lowering and oral antidiabetic drugs). Moreover, it evaluates the likelihood of T2D remission and insulin independency in post-bariatric intervention, alongside an in-depth analysis of composite obesity-related comorbidity events—including asthma, atherosclerosis, cancers (breast, bowel or uterine), chronic kidney disease, coronary heart disease, dementia, depression, gallstones or gallbladder disease, GORD, gout, hyperlipidaemia, hypertension, liver diseases, osteoarthritis, sleep apnoea and stroke.

Drawing on the systematic review results and local clinic study, a strong correlation was identified between those patients requiring Tier 3 services and their risk of developing serious comorbidities, profoundly with advanced T2D. Although subtle, the short- to mid-term effects of Tier 3 are statistically positive for patients with severe obesity. Bariatric patients with serious comorbidities (i.e. insulin-treated T2D), gained a longer-term protective effect against certain major elements of CV diseases and CKD events, while significant metabolic improvements were experienced by patients with NAFLD at baseline. Concerning the analyses of composite obesity-related comorbidities, the protective effect conferred by the Tier 4 bariatric intervention is significant, therefore justifying its cost effectiveness. Therefore, clinical interventions for preventing morbid obesity are effective in mitigating or resolving numerous comorbidities that affect patients with severe obesity living in the UK.

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Abbreviations

BMI	Body Mass Index
BNF	British National Formulary
BP	Blood Pressure
CB	Commissioning Body
CCGs	NHS Clinical Commissioning Groups
CG	Commissioning Group
CKD	Chronic Kidney Disease
CV/CVD	Cardiovascular/Cardiovascular Disease
DM	Diabetes Mellitus
eGFR	estimated Glomerular Filtration Rate
EU	European Union
FBS	Fasting Blood Sugar
GORD	Gastro-oesophageal reflux disease
GBP	Great Britain Pounds
GLP-1	Glucagon-like peptide-1
GP	General Practitioner
HbA1c	Glycated Haemoglobin
HDAS	Healthcare Databases Advances Search
HDL	High-Density Lipoprotein
HR (aHR)	Hazard Ratio (Adjusted Hazard Ratio)
HSE	Health Survey for England
LA	Local Authority
LAGB	Laparoscopic Adjustable Gastric Band
LDL	Low-Density Lipoprotein
LELD	Low-Energy Liquid Diet
MDT	Multi-Disciplinary Team
MDWMC	Multi-Disciplinary Weight Management Clinic
MI	Multiple Imputation

MWMS	Multidisciplinary Weight Management Service
MWMP	Multicomponent Weight Management Programme
NAFLD	Non-alcoholic Fatty Liver Disease
NASH	Non-alcoholic Steatohepatitis
NCDs	Non-communicable Diseases
NHS	National Health Service
NICE	National Institute for Clinical Excellence
OAD	Oral Antidiabetic Drugs
OR	Odds Ratio
PA	Physical Activity
PCTs	Primary Care Trusts
PHE	Public Health England
PS	Propensity-score
RCT	Randomised Clinical Trials
RWMP	Renal Weight Management Programme
RYGB	Roux-en-Y Gastric Bypass
SCGs	Specialised Commissioning Groups
SD/±	Standard Deviation
SES	Socioeconomic Status
SIGN	Scottish Intercollegiate Guidelines Network
SWM	Specialist Weight Management
SWMS	Specialist Weight Management Service
SWMP	Specialist Weight Management Programme
T1D	Type 1 Diabetes Mellitus
T2D	Type 2 Diabetes Mellitus
THIN	The Health Improvement Network
uACR	urine Albumin-to-Creatinine Ratio
UK	United Kingdom
UN	United Nations
WHO	World Health Organisation

Chapter One: Introduction

1.1 Obesity

Resulting from excessive increase in body fat, obesity is not only closely correlated with a string of chronic illnesses, but it also diminishes life expectancy and is an independent risk factor for mortality, which is why it is considered a major health problem [1,2]. Extensive research has been conducted on the implications that obesity has for health, including physical, psychological, and social implications [3-5]. The formation and abnormal increase in adipose tissue mass, which is the greatest energy storage in the human body, occur when the intake and consumption of energy are unequal [6]. In the UK, obesity is diagnosed based on the clinical guidelines issued by the National Health Service (NHS) Commissioning Board [7] and the National Institute for Health and Care Excellence (NICE) [8]. Thus, fitting to the Body Mass Index[1] (BMI), five categories of body weight have been identified, namely, healthy body weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), obesity class I (30-34.9 kg/m^2), obesity class II (35-39.9 kg/m^2), and obesity class III (≥40 kg/m^2). Nonetheless, the use of BMI can be a misleading measure between ethnicities especially within highly diverse populations.

At global level, the prevalence of obesity has increased nearly three-fold since 1975, with the proportion of adult individuals classified as overweight and obese being 39% and 13%, respectively [1]. This has prompted the World Health Organisation (WHO) to declare that obesity was among the non-infectious

[1] The body mass index is calculated by using an individual's body weight in kilograms divided by their height in meters squared.

pandemics that needed to be urgently addressed in every country [9]. In September 2011, the United Nations (UN) General Assembly held a high-level meeting regarding non-communicable diseases (NCDs), where the staggering increase in obesity levels worldwide was discussed and obesity was acknowledged as a difficult health problem confronting all countries [10]. However, that meeting did not translate into the formulation of public health policies for tackling obesity and type 2 diabetes (T2D) in any country [10]. Consequently, the battle to identify solutions for combating the increase in obesity among both adults and children continues [9,10]. **Figure 1.1** provides an overview of the prevalence of obesity at global level [2].

Among countries in Europe, obesity has a high prevalence, which has increased more than two-fold in the last ten years, especially in England, France, Germany, Italy, the Netherlands, Poland, Republic of Moldova, Slovenia, and Sweden [11]. The efforts made by countries have been ineffective at halting the increase in adult obesity in the period 2010-2016 [11]. Likewise, obesity levels among children are high. This determined a large number of countries with membership to the EU to publish an Action Plan document (2014-2020) [11]. However, of all the countries in Europe, obesity, defined as a BMI higher than 30 kg/m^2, is most prevalent in the UK, according to official statistics from the WHO (**Figure 1.2**) [12].

A 2016 Health Survey for England revealed that, since 1993, the rate of obesity among adult individuals nearly doubled, from 15% to 26% [11]. Furthermore, between the periods 2015-2016 and 2016-2017, there was an 18% increase in the

number of individuals admitted to hospital with obesity-related conditions, and of the 617,000 admissions, 72% were female individuals [13]. Similarly, the 2016-2017 UK National Childhood Measurement Programme reported that obesity occurred in almost 10% of children in the age range 5-6 years old and 20% of children in the age range 10-11 years old [11,13]. The 2007 Government's Foresight report anticipated that, by 2050, obesity could affect over 50% of adults in the UK, which would increase healthcare costs two-fold and extract £50 billion in broader societal and productivity costs every year [14]. This prediction suggested a stable rise of 12% compared to the forecast made by the McKinsey Global Institute, which conjectured that obesity was the second costliest public health problem, second to smoking, costing the NHS £44.7 billion every year [15].

Government initiatives, policies, and investment in awareness campaigns, surveillance, and research are critical in tackling obesity. However, instead of dealing with it themselves, most governments have relegated this challenge to individuals, the private sector, and non-governmental organisations [10]. The purpose of a multidisciplinary strategy for dealing with obesity is not merely limited to promoting weight loss through a negative energy balance [6], since there is more than one factor contributing to the onset of obesity, such as primary appetite control regulated by the brain, the force of dietary habits, physical exercise, and psychological factors [14]. All of these factors must be given due consideration if obesity is to be managed effectively. Additional factors must be taken into account in relation to severe obesity, including comorbidities, problems

of mobility or impairment, socioeconomic status, and access to healthcare services.

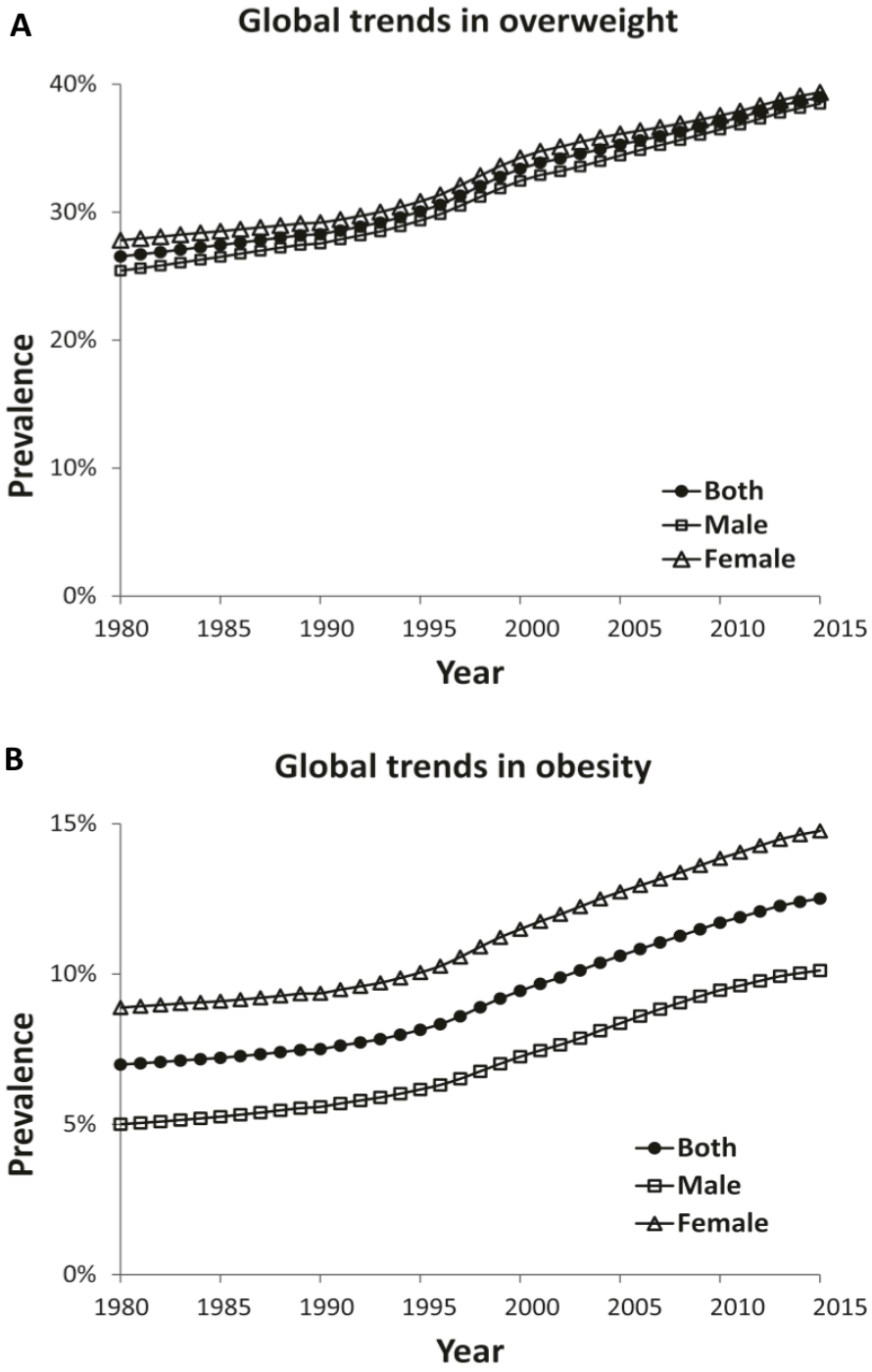

Figure 1.1 Global prevalence of overweight and obesity.
Age-adjusted worldwide prevalence of overweight (BMI 25–29.9 kg/m^2) (A) and obesity (BMI ≥ 30 kg/m^2) (A) among male and female individuals of adult age in the period between 1980 and 2015 [2].

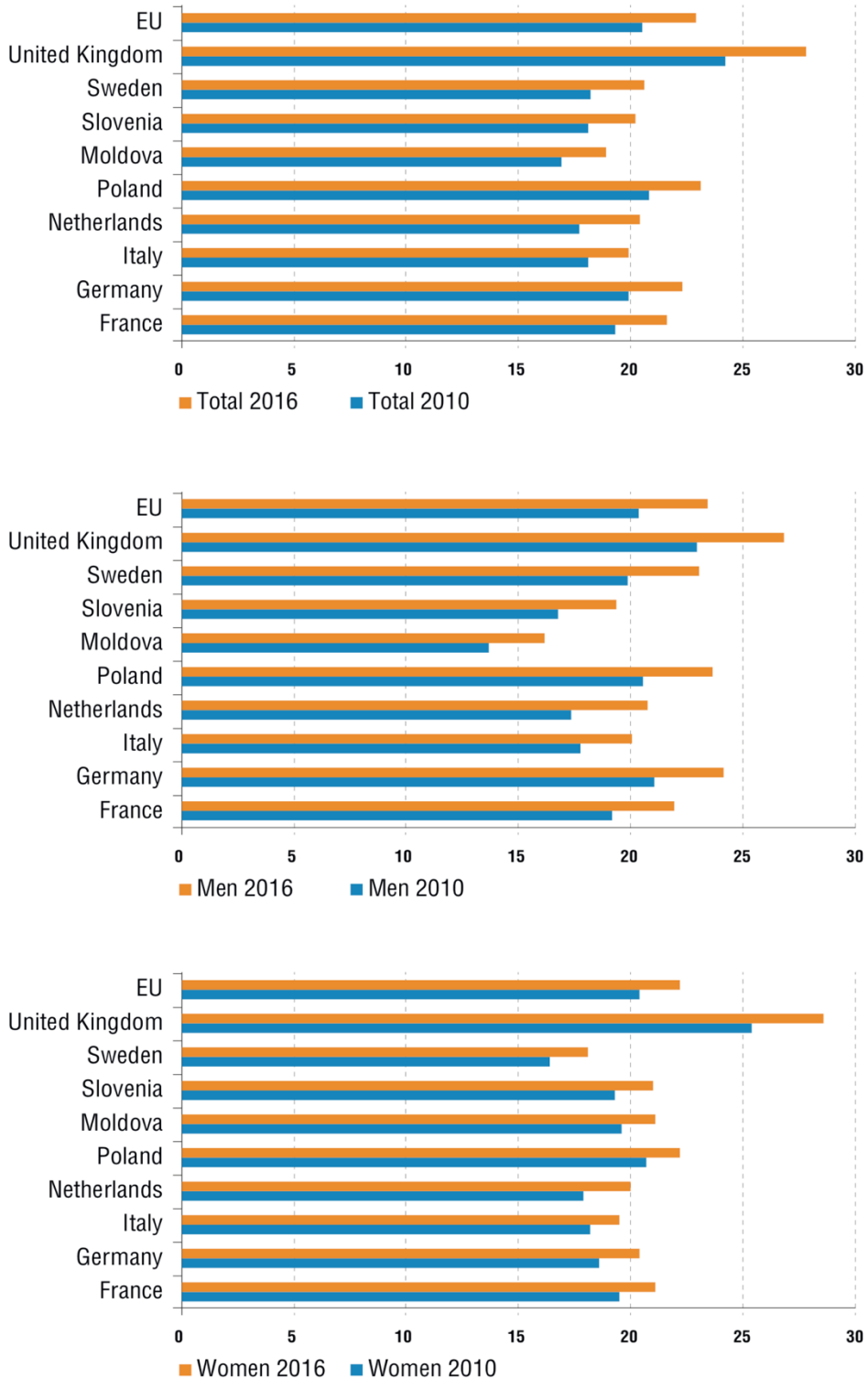

Figure 1.2 Prevalence of obesity in Europe.
The prevalence of obesity (BMI ≥ 30 kg/m^2) among adult individuals in European countries in the period 2010-2016 [11,12].

1.2 Type 2 diabetes

The series of metabolic diseases characterised by hyperglycaemia caused by impaired insulin secretion, or action, or both is known as diabetes [16,17]. Among the serious complications of diabetes-related chronic hyperglycaemia are long-term damage, improper function, and failure of a number of organs, particularly, the eye, kidney, neural system, and cardiovascular system [16].

The diabetes form of highest prevalence is T2D, formerly known as non-insulin dependent or adult-onset diabetes. T2D occurs as a result of suboptimal production of insulin and resistance to the pancreas-secreted hormone called insulin, which is responsible for controlling the levels of glucose in the blood. If untreated, diabetes gives rise to hyperglycaemia, which is significantly damaging to numerous body structures in the long term, particularly the neural and the vascular systems [17]. A progressive step-ladder increase in treatment is recommended by clinical guidelines for managing T2D, beginning with changes to lifestyle, such as healthier dietary habits, losing weight, and engaging in physical activity on a regular basis. If such changes are unsuccessful, the first-line monotherapy that is administered is Metformin, which may be supplemented with Sulphonylurea, if it cannot regulate glucose levels effectively on its own [18]. The complexity of the guidelines increases at this stage, as additional oral antidiabetic (OAD) drugs are administered, such as insulin [18]. This approach is justified by the lack of definitive evidence about the best medication to administer after Metformin to accelerate therapy [19]. Since insulin resistance occurs in both

obesity and T2D, insulin administration becomes necessary in numerous T2D cases over the long term to keep the levels of glucose normal [20]. However, it has been noted that insulin administration leads to an increase in body weight [21].

Unlike individuals with normal body weight, individuals with obesity are seven times more likely to develop T2D [21]. The heightened predisposition towards diabetes is significantly influenced by the manner in which fat is distributed around the body, but there are still uncertainties about how these two aspects are correlated exactly [22]. Furthermore, there is a lack of clarity as to why obesity does not always lead to T2D and why diabetes can be developed by individuals of normal weight [23]. There is variation among individuals in terms of independent factors such as age, lifestyle, socioeconomic status, ethnic background, and dietary habits. However, the mechanism of insulin resistance development is believed to be general, being activated by the production of pro-inflammatory chemicals by fat cells as a result of abdominal obesity, which interferes with the function of cells responsive to insulin [21]. The occurrence of insulin resistance may be further compounded by obesity by inducing alterations in metabolic activities, stimulating over-expression of fatty acids, glycerol, hormones, pro-inflammatory cytokines, and other factors by the adipose tissue [21]. The levels of glucose in the blood can no longer be regulated when insulin resistance occurs alongside improper function of the islet beta-cells of the pancreas [20].

In the UK, diabetes is becoming increasingly prevalent, affecting 4.7 million individuals in the period 2018-2019. Of those individuals, adults account for 3.9

million. This constitutes a two-fold increase from 1998 [24]. Furthermore, the actual number of people with T2D may be higher because around 25% of individuals have T2D without knowing it. Given the close correlation between obesity and T2D, diabetes will become more and more prevalent as obesity grows in prevalence [21]. More specifically, obesity is considered to be responsible for around a third of the increase in T2D prevalence, with additional contributing factors including ageing and changes in the ethnic structure of the British population [21].

1.3 Comorbidities

In addition to T2D, increased BMI is a key risk factor for numerous non-infectious comorbidities, such as micro- and macro-cardiovascular diseases (CVDs) [25], musculoskeletal disorders (e.g. osteoarthritis) [26], as well as several well-known types of cancers [27] (e.g. breast, ovarian, prostate, liver, gallbladder and colon cancers) [1]. Moreover, a close correlation exists between obesity and several serious health problems, including hypertension [28], gallbladder disease or gallstones [29], gout [30], sleep apnoea and/or asthma [31,32], high blood cholesterol and/or atherosclerosis, liver diseases (e.g. non-alcoholic fatty liver disease) [33], chronic nephropathy [34], gastro-oesophageal reflux disease (GORD) [35], as well as depression and/or dementia [36].

The clinical impact of obesity-related comorbidities and the need to meet health provisions and expectations are the causes of the economic strain placed by high obesity prevalence on health systems. Obesity is a complex health problem

stemming from multiple factors and often occurs alongside other health disorders, particularly T2D. Therefore, the comorbidities must be considered in any obesity prevention strategies, else these strategies will not be effective. In 2007, the NHS spent £4.2 billion on treating health problems associated to obesity and related comorbidities, and that figure is estimated to increase to £9.7 billion by 2050, with broader societal costs (e.g. productivity loss) expected to rise to £49.9 billion by 2050 [21]. Cancer Research UK and NHS, with funding from the Medical Research Council and the Health and Safety Executive, conducted the Million Women Study[2], which revealed that obesity was the reason that one in eight women of 50 years of age or older were admitted to hospital in England [37].

1.4 Obesity prevention

In the context of 'cradle-to-grave' welfare state social reforms fostered by the suggestions of the Beveridge Report in the aftermath of World War II, which peaked in the National Health Service Act of 1946 [38], the NHS was founded on July 5th, 1948, at the initiative of the Minister for Health Aneuryn Bevan under the Labour government of Clement Atlee. The NHS was intended to be open to all people living in the UK lawfully at no cost, with provision of services being contingent upon clinical needs rather than capability to pay. Public taxation remains the main basis of NHS funding, but some care services (e.g. eye tests, dental care, prescriptions) have become subject to extra charges [38]. Although

[2] The Million Women Study is a national study of women's health, involving more than one million UK women aged 50 years and over. It is a collaborative project between Cancer Research UK and the National Health Service, with additional funding from the Medical Research Council and the Health and Safety Exective.

the NHS was designed to eliminate regional inequalities in healthcare, this has not been entirely achieved, especially in terms of services for weight management [38].

Primary care is provided in the UK by general practitioners (GPs), who are therefore the initial point of contact for the majority of individuals requiring medical help. GPs and other community healthcare practitioners then refer patients to secondary care, which includes emergency care, elective planned specialist medical care or surgery [38]. Prior to April 2013, obesity management, commissioning of weight management services, and prevention initiatives were the remit of GP primary care trusts (PCTs), which could commission primary, care, secondary care or private sector professionals to tackle obesity cases of high severity or complexity [38]. By contrast, specialised commissioning groups (SCGs) were responsible for commissioning bariatric surgery at regional level [38].

SCGs were empowered to allocate particular specialised services to providers. In England, there were ten SCGs, which were involved in the formulation of national standards regarding service allocation, with emphasis on the implementation of a general strategy at local or regional level. The SCG commissioned bariatric surgery and the eligibility criteria were subsequently established at local level [38]. According to the NICE Clinical Guidance (CG No. 43), cases were eligible for bariatric surgery if they had a BMI ≥ 40 or ≥35 kg/m^2 alongside a comorbidity, such as hypertension, or if they had a BMI of 50 kg/m^2 or above [39]. Similar guidelines were issued in 2010 by the Scottish Intercollegiate Guidelines Network (SIGN), with

cases with a BMI of 35 kg/m^2 or above alongside comorbidity being eligible for bariatric surgery [40]. Nevertheless, there were some differences between regions, which enabled certain PCTs to refuse bariatric surgery in cases of severe and complex obesity or in cases with referral criteria that restricted access to this type of surgery, despite fulfilment of clinical needs [41]. Differences exist at national level as well, with Northern Ireland having no service of bariatric surgery [38].

Since its founding, the NHS has been most extensively restructured through the Health and Social Care Act of 2012. Although this restructuring maintained the core principle of patient-oriented care, it afforded greater authority to healthcare practitioners, especially GPs, to commission services based on clinical outcomes in the context of clinical commissioning groups [38]. Another consequence of the restructuring was the creation of local authority (LA) health and wellbeing boards. Whereas healthcare is governed at national level by Public Health England (PHE), it is governed by LAs at local level, where the majority of lifestyle weight management services are commissioned [38]. Hence, the allocation and influence of funds for weight management services has come to be dictated by elected (at local levels) individuals without appropriate medical expertise [38].

An independent NHS commissioning body (NHS CB) was established to supervise the daily operations of the restructured NHS, while PCTs and SCGs were dissolved in April 2013. However, the variation in bariatric surgery availability, the so-called ‘postcode lottery’, and other issues persisted [41]. The new NHS England

guidelines formulated by the NHS CB clinical reference group for obesity of high severity and complexity were introduced in the immediate aftermath of the NHS reorganisation [7]. Since April 2013, the NHS CB has been in charge of provision of guidelines on an England-wide contract for bariatric surgery delivery to be undertaken by a provider fulfilling the stringent requirements related to the intervention [38]. These guidelines specify sources of funding as well as eligibility criteria for bariatric surgery in England.

In keeping with the NICE CG43 BMI thresholds, the commissioning board has issued guidance about bariatric surgery eligibility, the procedures that can be offered through the NHS, and the clinical criteria that have to be satisfied to justify referral [38]. One contentious recommendation is that referral to surgery should be provided only after a year or two of 'medical management' administered in a Tier 3 non-surgical multidisciplinary team (MDT) clinic [38]. However, the available Tier 3 non-surgical MDT weight management services vary significantly owing to detailed suggestions regarding the anticipated provision of services [42].

Weight management services at every level are incorporated in obesity care in the UK, including public health campaigns, weight management programmes at community level, specialist MDT interventions, and bariatric surgery [38]. Interventions have been organised along three tiers according to the obesity model proposed by NICE (2006), namely, community weight management (Tier 1), specialist weight management (Tier 2), and bariatric surgery (Tier 3) [39]. Currently, however, NHS England implements a four-tier weight management

framework, which was proposed by NHS Rotherham, which won the 2009 Health and Social Care award for Excellence in Commissioning for its Healthy Weight Framework for individuals of all ages [43]. The four-tiered obesity management framework was further refined in an April 2014 report by a Department of Health working group concerned with 'Joined Up Clinical Pathways for Obesity' in adults. This document also offered guidance regarding the bodies that should be accountable for the four tiers and have the power to commission them [44].

1.4.1 Tier 1 and Tier 2

Tier 1 consists of behavioural or general interventions, such as public health initiatives for raising awareness about the importance of a healthy diet and physical exercise as well as dissemination of basic information. Such interventions are typically undertaken by various healthcare practitioners (e.g. GPs, nurses, health visitors, school nurses) alongside pharmacists, local leisure providers, and related agencies in the context of primary care at local and regional levels. Furthermore, besides basic public health interventions, Tier 1 is frequently concerned with identifying overweight or individuals with obesity and those who have the necessary motivation to gain the most from being referred to weight management services at local level [38].

Lifestyle weight management services offered for a restricted period of time are the focus of Tier 2. Such services are usually provided by local teams in a group context at community level and encompass guidance for making modifications to diet, nutrition, lifestyle, and behaviour [38]. It has been recently advocated that

Tier 2 interventions could be successfully commissioned by commercial providers, such as WeightWatchers™, Rosemary Conley, and Slimming World [45], and moreover, that such interventions can be an affordable approach for offering overweight or obese individuals without comorbidities with general guidance for managing their weight (**Figure 1.3**) [38].

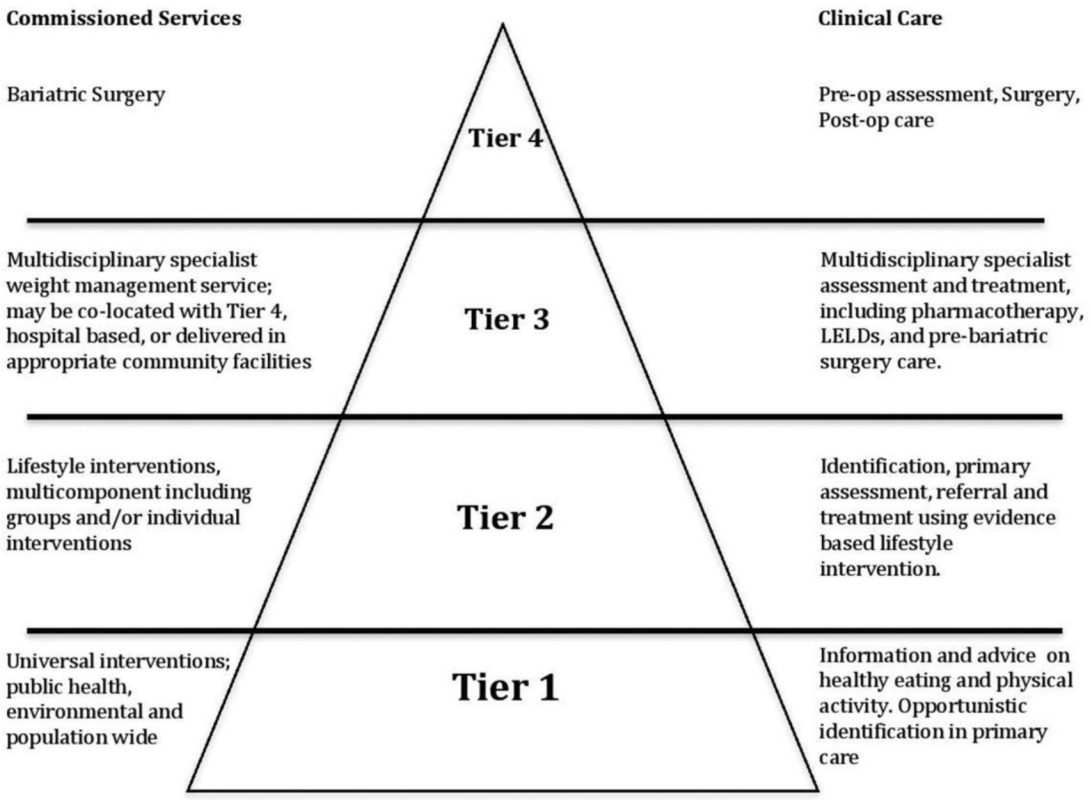

Figure 1.3 Four-tiered structure.
The implemented four-tiered weight management framework [46,47].

1.4.2 Tier 3 (MWMS)

Tier 3 constitutes a multidisciplinary weight management service (MWMS) delivered by a team made up of at least one bariatric physician, a dietitian, a specialist nurse, a clinical psychologist, and a liaison psychiatry professional with

access to physical therapy. Eligibility criteria for this tier include adult individuals with a BMI of 40 kg/m^2 or higher, a BMI of 35 kg/m^2 or higher alongside comorbidities (e.g. hypertension) or BMI of 30 kg/m^2 or higher coupled with T2D diagnosed in the last decade. Furthermore, Tier 3 is compatible with 'Weight Assessment and Management Clinic' offered by NHS primary or secondary care [47]. However, if a primary care clinic contributes to weight loss intervention, a clear differences from Tier 2 interventions should be enforced [47].

The bariatric physician is in charge of analysing excessive weight causes of a hormonal or genetic nature and associated comorbidities and disabilities. The dietitian should provide customised lifestyle and healthy eating guidance as well as an adequate physical activity plan in the context of the intervention devised for every patient. Furthermore, given the close correlation between obesity and various psychological disorders (such as anxiety, depression, self-harm, suicidal tendencies, eating disorders, borderline personality disorder, alcohol and substance abuse, problems stemming from a disadvantaged childhood, and obstacles to voluntary weight), every patient should be assessed for psychiatric comorbidities as well. Moreover, a treatment duration should be approximated by the psychiatrist for every patient, since more long-term support may be required by some [47,48].

After every obesity-related comorbidity has been effectively tackled and weight decrease has been achieved, the patients are referred by the MDT back to their GP. Advancement to Tier 4 bariatric surgery is offered to patients who have put in

serious effort in attending the clinic appointments, have a suitable MDT-outlined timeframe and the correct weight criteria, and are medically optimised for undergoing a surgical intervention. When making this decision, the MDT must take into account every contraindication of a medical, surgical, nutritional, psychological, and social nature. Additionally, patients must be appropriately informed regarding what the surgery involves from a nutritional perspective and have awareness about the life-long commitment necessary for post-surgery follow-up [47,49].

The identification of quantifiable outcomes for weight management programmes at community level and Tier 3 clinics should be prioritised by the local authorities and clinical commissioning groups [38]. This is necessary to determine how effective the relative expenditure is from a clinical and cost perspective by comparison to the proven effectiveness of bariatric surgery. In the UK, data on the performance of every surgeon can be openly accessed and this should be supplemented with similar data related to how effective the interventions at every tier are [38]. **Figure 1.4** provides an overview of the approach of identification and weight evaluation and management (Pathway).

1.4.3 Tier 4 (Bariatric)

Patients are prepared to be referred to Tier 4 bariatric surgery based on the Tier 3 recommendations of the MDT and once they have become physically and psychologically primed for the surgical intervention [47]. By comparison to obesity management through methods other than surgery, bariatric surgery not only

increases the amount of weight lost, but also leads to higher T2D remission rate and significantly diminishes reliance on medication for diabetes, antihypertensive, and lipid lowering, according to the findings of a meta-analysis of randomised controlled trials [50]. Furthermore, comorbidities associated with obesity in the analysed studies were unobserved. On the whole, a decrease of 25.9 kg (95%CI: -30.9 to -21.0) was the mean difference in weight loss among the analysed studies from all methods, except gastric band, of bariatric surgery utilised [50].

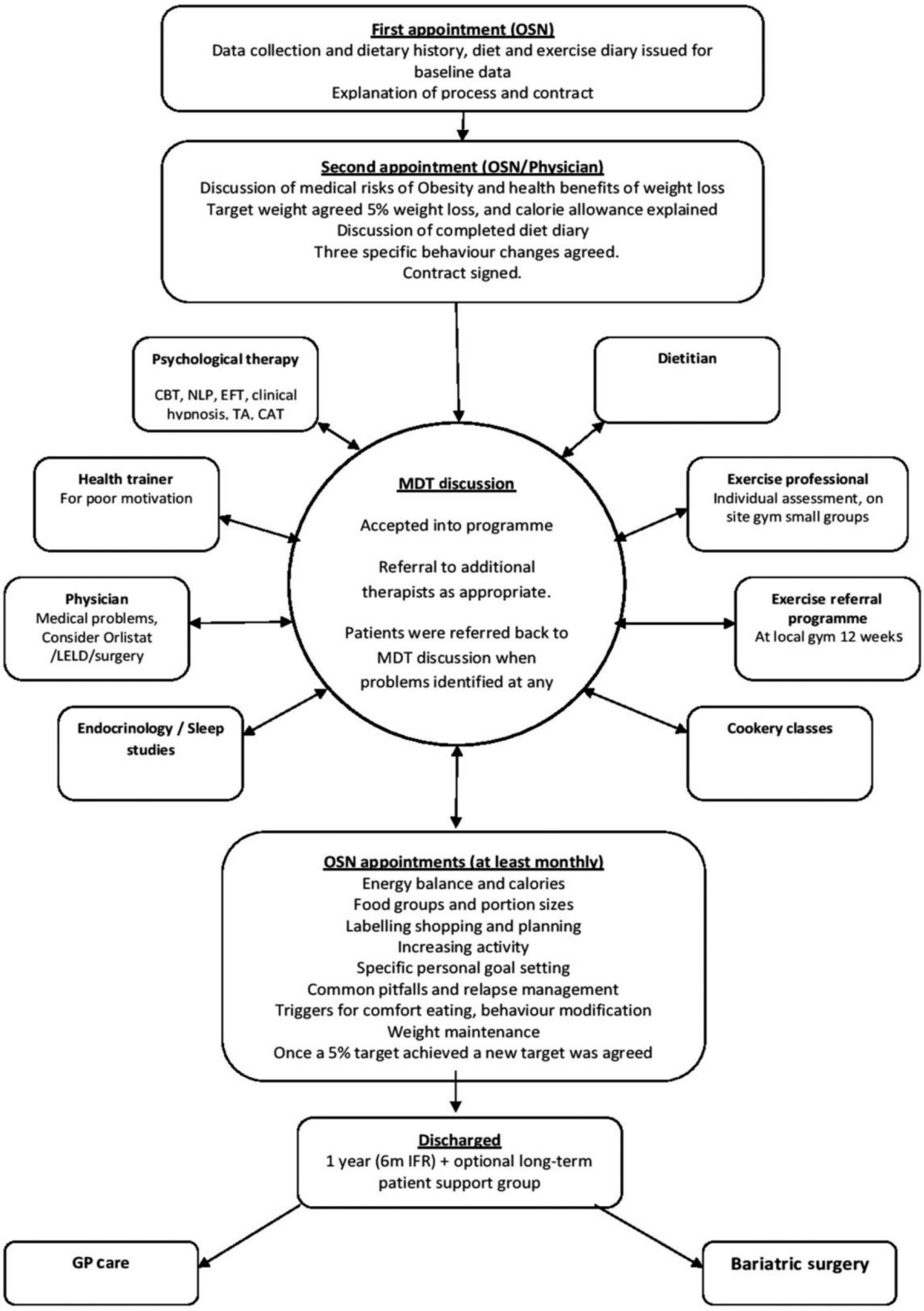

Figure 1.4 Obesity prevention pathway.
Model of care and patients' pathway promoted by the NHS [46].

The metabolic surgical interventions performed on the organs of the gastric system to regulate the amount of food that can be consumed are known under the term bariatric. These kinds of procedures are intended to reduce calorie consumption by inducing neurohormonal and biological changes [51]. In turn, the reduced calorie consumption improves or fully eliminates a large number of diagnosed comorbidities, whilst also diminishing the risk of dying and hospitalisation, and alleviating healthcare expenditure in the long run [4].

In the UK, the ability to offer bariatric surgery exceeds the existing demand, as there is evidence that over 2 million individuals may have eligibility for this surgical procedure [52]. Employing data from the Health Survey for England (HSE), Ahmad and colleagues investigated the criteria for bariatric surgery eligibility as well as the socio-demographic characteristics and the comorbidities displayed by eligible individuals among a research sample of 9,425 participants. The results showed that a proportion of 5.4% of adults in England satisfied the eligibility criteria for bariatric surgery, which was considerably greater than the available capacity for this intervention [52]. The proportion of eligible individuals is likely to increase further [53] as the eligibility threshold is set to be reduced by updated NHS guidelines [47] and the number of individuals with obesity continues to increase [13]. Nevertheless, a decline in the number of bariatric surgeries from 8,794 to 6,384 was recorded in the UK in the period 2011-2012 and 2014-2015, which are the lowest numbers of operations compared with the western European countries [52]. Moreover, bariatric surgery represents a much smaller part of data (less than

1% for 2017-2018) disclosed by the Statistics on Obesity, Physical Activity and Diet report [52,54].

Bariatric surgery pursues three major principles, depending on its mechanism. Thus it can be a restrictive procedure, whereby solid food intake is restricted by making the stomach smaller; it can be a malabsorptive procedure, whereby the size of the small intestine is reduced to restrict nutrient assimilation and therefore diminish surface area exposure to food; or it can be a combination of the previous two principles [51]. In the last two decades, the NHS has commissioned four kinds of bariatric surgery [47].

Gastric banding: The purpose of the Laparoscopic Adjustable Gastric Band (LAGB) (**Figure 1.5a**) is to restrict food intake by circumscribing the superior part of the stomach and thus forming a small pouch. This brings about a sensation of satiety with minimal food intake [55].

Sleeve gastrectomy: This bariatric procedure (**Figure 1.5b**) is designed to decrease the stomach size by around three-quarters. It involves a superior-inferior vertical division of the stomach, which produces a banana-shaped pouch along the internal curve and the pyloric valve at the inferior side of the stomach. In this way, the stomach emptying into the small intestine is controlled, without altering the function of the stomach [55].

Gastric bypass: This type of bariatric intervention (**Figure 1.5c**) can be conducted in several different ways, the Roux-en-Y gastric bypass (RYGB) being preferred in

the UK. The RYGB procedure involves formation of a small pouch by stapling off the superior part of the stomach and creation of a new exit from the pouch into a 'Y' loop from the small intestine, thus preventing assimilation of food by the previous stomach and a small intestine portion of 100-150 cm. Careful thought is given to how big the stomach pouch should be and how much of the small intestine should be bypassed to allow sufficient food intake to meet the needs of the body at regular weight [55].

Duodenal switch: Malabsorption is the main mechanism underpinning this type of bariatric intervention (**Figure 1.5d**), which can be undertaken via two routes, namely, an open operation route by making a midline incision from the breastbone base or a laparoscopic route. From a technical perspective, the procedure has a high level of complexity and can last 5-7 hours. After surgery, the patient must typically remain hospitalised for 4-6 days. The procedure involves the removal of a small portion of the duodenum at the bottom of the stomach, which is linked to the second half of the small intestine. The next step is reconnecting the bypassed small intestine portion for the transport of bile and juices from the pancreas to the other portion of the small intestine close to its junction with the large intestine [55].

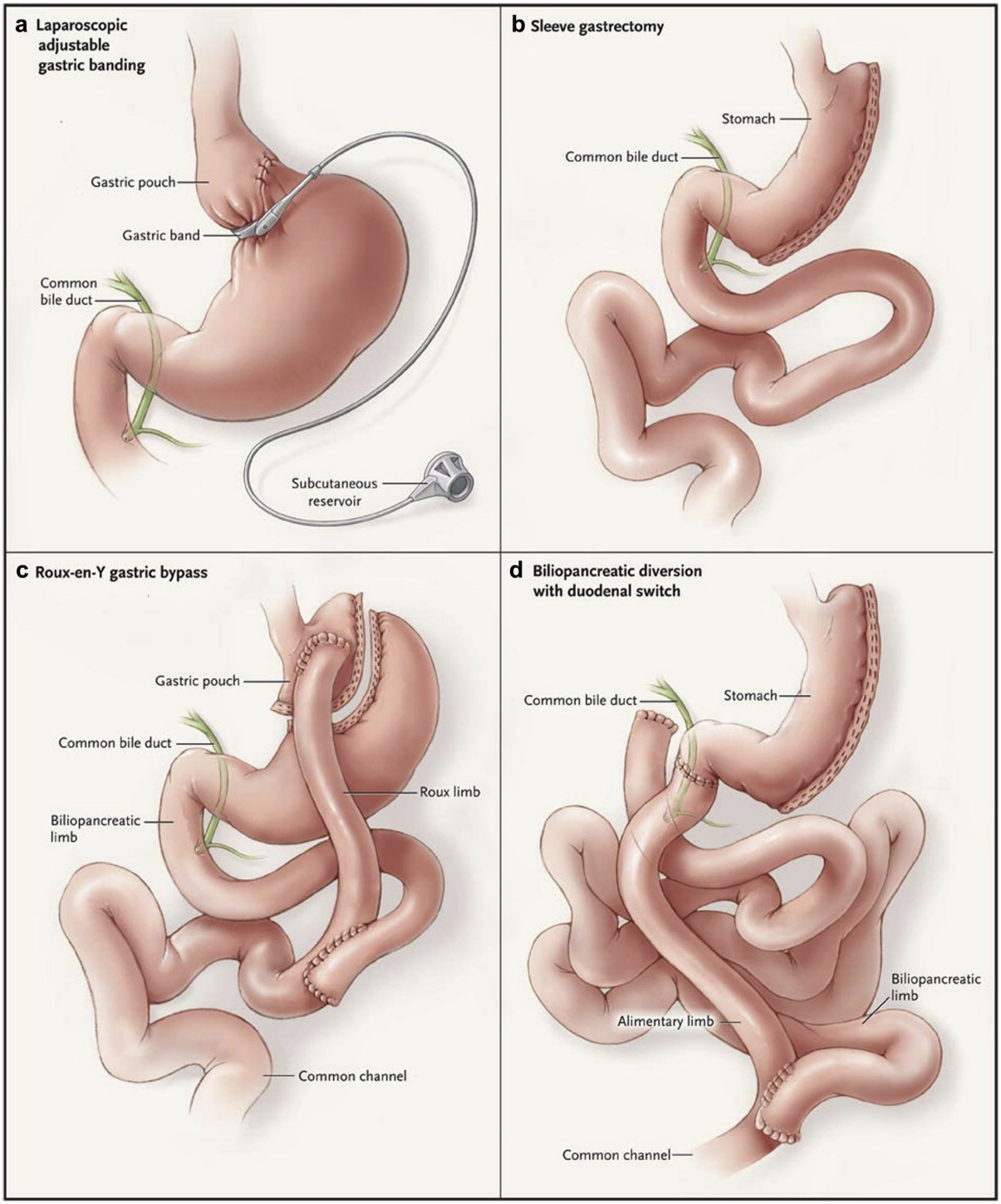

Figure 1.5 Bariatric surgery procedures.
(a) Laparoscopic adjustable gastric banding, (b) laparoscopic sleeve gastrectomy, (c) Roux-en-Y gastric bypass, (d) duodenal switch [34].

1.4.4 Bariatric surgery complications

Similar to numerous other major surgical interventions, bariatric surgery has a few limitations. However, unlike the average patient undergoing general surgery, the patient undergoing bariatric surgery may not present obvious manifestations of complications due to the fact that their body habitus and incompatibility of fit with most diagnostic examination tables make assessment challenging. Thus, deterioration may occur quickly and the patient may be inadequately equipped to cope [51].

Another issue related to bariatric surgery is the significant variation in the technical competence possessed by bariatric surgeons. One study reported that, when the intervention was performed by highly-skilled surgeons, there was a lower proportion of complications after surgery and fewer patients were required to undergo surgery or hospitalisation again or had to present to the emergency department [56]. Birkmeyer and colleagues developed a surgical skill scale, whereby the rates of complications (14.5% vs 5.2%, $P < 0.001$), mortality (0.26% vs. 0.05%, $P = 0.01$), operation duration (137 minutes vs 98 minutes, $P < 0.001$), and reoperation and readmission (6.3% vs. 2.7%, $P < 0.001$) were all higher in the bottom quartile than in the top quartile of surgical skill [56].

Among patients with a BMI lower than 50 kg/m^2 and below the age of 55, the mortality rate is less than 1% [57]. However, this rate increases to 2–4% among patients with a BMI exceeding 60 kg/m^2 and who have comorbidities as well [51]. Besides surgical skill, a positive correlation exists between reduced morbidity and

mortality risk and several factors, including surgical volume at the clinic, surgery in a tertiary care setting, gender, age, and respiratory status [58]. On average, the rate of complications associated with bariatric surgery is below 10% [59]. Outcome improvement can be most effectively achieved in the initial 6-12 hours, with fast increase in the likelihood of morbidity and mortality after 24 hours [51]. In spite of this, bariatric surgery remains a suitable option for managing severe obesity [59]. Nevertheless, long-term data about the impact of weight reduction on the comorbidities associated with obesity are necessary, as highlighted by evidence from a decade-long prospective study, which revealed that continuous weight reduction did not have a favourable effect on every risk factor related to obesity [59].

Anastomotic or staple line leakage may be among the first complications after bariatric surgery. Post-RYGB anastomotic leakage occurs in 1.2–3% of cases [60]. The physician must examine the matter closely as the clinical presentation can be subtle. Constant symptoms include sustained tachycardia, particularly a heart rate persistently over 120 bpm, tachypnoea, as well as fever. Identification of anastomotic leakage via upper gastrointestinal series and computed tomography occurs in just 22% of cases and the skill of the operator is highly influential [60]. The leakage is managed via immediate surgery and follow-up examination via diagnostic laparoscopy or laparotomy [60].

An additional complication of bariatric surgery occurring in 3.1% of cases is post-operative bleeding [61]. Such bleeding stops on its own in 22% of cases, but

necessitates blood transfusion and surgery in 55% and 22% of cases, respectively [61]. It is usually in the first six hours after surgery that active bleeding occurs, taking the form of secretion of bright red blood from the mouth, rectum or abdomen, which can be accompanied by low blood pressure and tachycardia. Active bleeding is managed through immediate surgery or endoscopy. On the other hand, delayed bleeding typically occurs a number of days after surgery and manifests as dark blood in the surgical drains or leaking from the mouth or rectum [61]. Although no signs or hemodynamic instability are associated with delayed bleeding, assessment via radiology, haematology, and endoscopy can facilitate detection [51].

Another possible complication of bariatric surgery is band erosion or dislocation, which may manifest as signs of proximal gastric outlet blockage, such as dysphagia, nausea, vomiting, intolerance to solids, and pain or discomfort in the abdomen, as well as immoderate weight loss [51]. The suggested course of action is to refer such cases to a bariatric surgeon. Furthermore, LAGB can also result in port or band tubing leak, which manifests as an initial sensation of post-prandial fullness, followed by subsiding of this sensation and greater tolerance for a greater amount of solid food after a couple of days. This can lead to renewed increase in weight or inadequate weight loss [51].

The formation of scar tissue in the context of healing may be accompanied by anastomotic stricture, which may be the reason why patients who have recently undergone surgery lose their tolerance to oral intake and start to gradually feel

nauseous and vomit when they ingest solid food and are capable of minimal fluid intake in one go. The suggested course of action is to refer such cases to a qualified dietitian and bariatric surgeon [51].

In cases of RYGB, unsuccessful or partial separation of the pouch through stapling may lead to the formation of gastrogastric fistulae [62]. This can manifest as the ability to eat great amounts of solids, absence of restriction or sensation of fullness, the ability to eat foods with textures that are not normally tolerated post-surgery, renewed increase in weight, or suboptimal weight loss. The suggested course of action is to refer such cases to a bariatric surgeon [51].

When bariatric surgery is performed via a malabsorptive principle (i.e. reduction of nutrients absorption) or a combination of restrictive and malabsorptive, dumping syndrome can develop. This is defined as food going straight into the small intestine, without going first into the stomach [51]. Initial signs may occur in the first half hour after food ingestion and are caused by rapid passage of food and liquid into the small intestine. They may encompass nausea, vomiting, stomach pain or cramps, diarrhoea, sensation of fullness or bloating, and elevated heart rate [51]. Meanwhile, delayed signs occur within 1-3 hours of food ingestion and are caused by alteration in the blood levels of insulin and sugar, which is known as reactive hypoglycaemia. Among the delayed signs are flushing or sweating, pressing need to lie down, sensation of weakness or dizziness, sensation of nervousness or shakiness, or a decline in blood pressure [51].

Nausea or vomiting, excess or loose skin, blockage of the small intestine, and ulcers are potential complications of bariatric surgery as well. In the majority of cases, nausea or vomiting can be alleviated by educating patients about which foods to eat and how to eat [51]. However, stricture and blockage evaluation should be conducted in cases where vomiting persists. Such cases should also be subjected to screening for thiamine deficiency and should be administered supplements if neurologic symptoms are identified [49]. When patients lose a significant amount of weight, they are often left with excess or loose skin, which can interfere with their ability to move and care for themselves, as well as promote the development of infections and skin ulcerations. The course of action suggested is to refer such cases to a bariatric physician or occupational or physical therapist [51]. Abdominal bloating or cramps, pain that can reach a high level of severity, nausea, and vomiting are possible symptoms of small intestine blockage, which may be caused by adhesions, internal hernia or severe constipation [51]. Upper epigastric pain or burning with possible radiation to the back, nausea, vomiting, and lack of tolerance to food may be symptoms of stomach ulcers or marginal ulcers (anastomosis). Chronic ulcers are typically accompanied by anaemia stemming from iron insufficiency [63]. It is important to evaluate patients' longer term health conditions, including self-harm, substance abuse, mental health as well as the persisting problem of weight regain.

1.5 Thesis narrative, objectives and hypothesis

The purpose of this overview is to emphasise how important it is to investigate the long-term advantages of weight loss and its ability to minimise or fully eradicate the impact of comorbidities associated with obesity. From a clinical perspective, the aim here is to examine the health outcomes of interventions in the pre- and in the post-bariatric surgery, taking specific consideration of the evidence from the extant literature as well as from a local service provision. In addition, this thesis establishes the extent to which the comorbidities have spread across the adult population and the impact of bariatric surgery. The analysis will heavily be based upon data originating from local clinics and the British primary care database. Based on an economic standpoint and identifying T2D as the primary comorbidity in the most extreme obesity cases, this thesis will initiate an exploration into the effectiveness of bariatric surgery. The objectives have been inspired or developed on light of the 2017 Commissioning Guide (Subsection 7.1 Research Recommendations) issued by the British Obesity and Metabolic Surgery Society [47].

By adopting an evidence-based research design, data analysis is performed using information from quantitative databases in conjunction with a qualitative approach in the form of a systematic review (refer to **Chapter 2**). The objective of this approach is to conduct a detailed exploration into comorbidities associated with obesity. In addition, this approach uses the metabolic results gained in previous research into severe obesity. However, due to its qualitative nature, the

systematic review may not provide an impartial perspective of the observational studies under evaluation. This could be attributed to the nature of qualitative typical approaches and the relatively increased risk of subjectivity.

This thesis focuses upon addressing a series of research questions regarding the benefits of clinical and service outcomes of the before and after bariatric surgery in cases of severe obesity associated with a range of major comorbidities. Emphasis will be placed on cardiometabolic effect, and CKD and CV risks in cases with or without microalbuminuria, as well as the positive or negative implications of the procedures where the risk of liver disease is high.

A number of key goals form the foundation of this thesis: determining the practicality of the clinical aspect of the four-tiered framework implemented in the UK for obesity prevention and weight loss promotion in terms of addressing the main comorbidities associated with obesity; determining the efficiency of surgery to improve patient health for those suffering from T2D and other comorbidities; determining the benefits of bariatric surgery in terms of minimising costs and enhancing long-term patient health; and determining areas of health most positively impacted by bariatric surgery.

The clinical aspects of Tier 3 interventions and comorbidity data relating to extreme cases of obesity will be the focus of **Chapter 2** and **Chapter 3**. **Chapter 2** includes a literature review related to Tier 3 and similar interventions and an overview of the comorbidities reported by the examined studies. **Chapter 3** explores Tier 3 local clinics, with a view to gaining insight into the development of

actual comorbidities by individuals with severe obesity. Within mind, the thesis will proceed asking whether Tier 4 bariatric surgery is effective in alleviating or eradicating the primary comorbidities throughout the following three chapters. Using the data sources employed in the fourth, fifth, and sixth chapters, the seventh chapter will comprehensively explore the effectiveness of Tier 4 bariatric surgery from a cost perspective. In addition to health utilisation, this chapter will evaluate composite risk of developing several comorbidities related to severe obesity – which were not fully covered in the previous chapters.

The hypothesis is that commissioned clinical interventions for morbid obesity are effective long-term measures, protecting patients from the risk of developing obesity-related comorbidities, such as risk of CVDs, CKD, and liver diseases. A key benefit of these clinical interventions is the potential cost saving, reducing the overall pressure on the national budgets. Thus, this thesis has six main objectives:

i. Systematically review and summarise obesity-related comorbidities within pre-operative weight loss interventions.

ii. Characterise non-surgical weight loss intervention and patients' comorbidities within local clinics (i.e. Tier 3 multidisciplinary weight management service).

iii. Investigate the cardiometabolic effect of bariatric (Tier 4) intervention on patients with major comorbidities (i.e. insulin-treated T2D).

iv. Investigate the development of CKD in bariatric (Tier 4) intervention for patients with increased risk of diabetic nephropathy (i.e. baseline microalbuminuria in patients with insulin-treated T2D).

v. Explore the metabolic outcomes of diabetic patients with a high risk of liver disease (i.e. NAFLD) in the post-bariatric (Tier 4) intervention.

vi. Establish a health utilisation (i.e. cost effectiveness) comparison of post-bariatric (Tier 4) intervention and explore composite obesity-related comorbidity differences.

Chapter Two: Systematic Review of Tier 3 Services and Pre-bariatric MWMPs

2.1 Summary

Background and Aim: NHS England has recommended a multidisciplinary weight management services (MWMS—Tier 3 services) for patients requiring specialised management of obesity, including bariatric surgery, but clinical and measurable health-related outcomes from these services remains fragmented. This systematic review was undertaken to explore the evidence base of effect on body weight loss and comorbidities outcomes of Tier 3 or UK pre-bariatric Multicomponent Weight Management Programmes (MWMPs).

Methods: AMED, CINAHL, EMBASE, HMIC, MEDLINE, PsycINFO, PubMed, HDAS search and Google Scholar were searched from January 2000 to September 2017 in a free-text fashion and crossed-references of included studies to identify potential illegibility. Inclusion criteria were as follows: (a) published Tier 3 original study abstracts/articles; (b) intervention studies with before and after data; (c) studies that included any sort of MWMPs conducted within the UK for patients with obesity (BMI ≥30 kg/m^2); and (d) studies included T2D measurements in MWMPs.

Results: In total, 19 studies met the inclusion criteria. The total number of participants analysed was N = 11,735. Baseline accumulative average BMI was calculated at 42.54 kg/m^2, weight 117.88 kg and waist circumference 126.9 cm. And at 6 months, 40.73 kg/m^2, 112.17 kg and 120.3 cm, respectively. Secondary outcome variables were as improved with reduction in HbA1c, fasting blood sugars, insulin usage and blood pressure. Physical activity increased at 3 months then declined after 6 months. Little or no significant changes in cholesterol levels throughout.

Conclusion: Tier 3 and MWMPs have a short to mid-ranged positive effect on patients with severe obesity living in the UK regarding accumulated reduction in body weight, glycaemic control, blood pressure and with subtle improvements in physical activity.

2.2 Background

Morbid obesity is an increasing lifelong chronic condition that no country has yet succeeded to tackle [48]. In England, the prevalence of obesity is among the highest in Europe [7]. Two-thirds of adults are overweight and one in four are obese BMI of >30 kg/m^2) [64]. McKinsey Global Institute reported that, second to smoking, obesity has the largest impact on the public health budget with an estimated annual cost to the UK's NHS of £44.7b [15]. The importance of a range of obesity prevention initiatives comes from the increasing number of health complications and their related high cost. High Blood Pressure (BP), T2D, heart attacks, strokes, cancers and other health issues, for instance, are evidently associated to the conditions of being overweight or obese [47].

Even though bariatric surgical intervention is a proven effective approach for treating chronic obesity, access and eligibility for bariatric surgery remains low [65]. The reasons for this are multifactorial, but may include a lack of developed infrastructure for medical assessment and services, unclear referral procedures, as well as uncertainties regarding costs and long-term outcomes [66]. In England, the rate of bariatric surgical operations dropped by 31% between 2011-2012 and 2014-2015 (from 8,794 to 6,032 operations, respectively) [47]. It is much worse in Scotland and Wales, and there is no NHS bariatric surgery performed in Northern Ireland. Provision of bariatric intervention by NHS is, therefore, less than 1% of the national need [67].

In the UK, obesity is managed through a 4-levels tiered pathway. Tiers 1 and 2 are focused on universally environmental and population-wide prevention services [47,68]. Following this, individuals with more complex obesity and/or medical needs are considered for Tier 3 MWMS, [69] which may lead to a Tier 4 service for consideration of bariatric surgery [70]. Tier 3 MWMS consists of a (bariatric) physician, a dietitian, a specialist nurse and a clinical psychologist with access to physical therapy. All adults identified with a BMI of ≥40 kg/m^2, or ≥35 kg/m^2 with comorbidities are eligible for bariatric surgery following assessment and input from involvement in Tier 3 services[3]. Tier 3, in this context, could also apply to a "Weight Assessment and Management Clinic" provided by primary or secondary care [47].

Within a Tier 3 service, strategies are implemented to make critical changes about eating and physical activity habits to improve overall health and identify risk factors so that the planned intervention addresses and improves all elements comprehensively. Screening for hormonal or genetic causes of excessive weight as well as all related comorbidities and disabilities are conducted by the bariatric physician and each individual patient should have their own tailored lifestyle and healthful eating advice provided by a specialist dietitian [47].

Although our understanding of the benefits of a Tier 3 service is growing—based on our appraisal of current literature [70,71], current evidence remains fragmented and needs to be synthesised to produce a more comprehensive

[3] This criteria is slightly different between local clinics across England.

picture which will help to translate to a safe and cost-effective approach to the management of morbid obesity in the UK.

2.3 Aims

To explore the evidence base of effect and magnitude on body weight loss in addition to other health-related outcomes of adults with severe obesity undergoing a Tier 3 or pre-bariatric MWMPs in the UK. We included adults with obesity (i.e. with BMI ≥30 kg/m^2) living in the UK who have been enrolled in a Tier 3 service or in any form of MWMP for losing weight.

2.4 Methods

2.4.1 Literature search

A free-text literature search of articles published from January 2000 through September 2017 was performed. The search used the Healthcare Databases Advances Search (HDAS) via the National Institute for Health and Care Excellence's (NICE) evidence services with access to the following electronic bibliographical databases: AMED, CINAHL, EMBASE, HMIC, MEDLINE, PsycINFO and PubMed (an example of search strategy is available in **Appendix 10.1**). An extended search was conducted using Google Scholar after reviewing additional studies that were included by Brown et al (2017) systematic review [72]. Terms used were related to "obesity" and "overweight" in conjunction with geographical restrictions to the UK (e.g. England, Wales, Scotland, North Ireland). Terms related to MWMS, Specialist Weight Management (SWM) and Tier 3 (e.g. weight management services, weight

reduction programmes, weight management interventions, multidisciplinary weight loss initiatives and multicomponent weight loss schemes) were utilised on the titles and abstracts search. In addition, I screened reference sections of all included studies to identify potentially illegible articles that meet the inclusion criteria of this review. See **Figure 2.1** flow chart.

2.4.2 Study selection

This review used a similar pragmatic selection approach to Brown et al (2017) [72]. Tier 3 studies for adults (18 years and over with no upper age limit) with a mean baseline BMI of ≥40 or ≥35 kg/m^2 with a comorbidity or ≥30 kg/m^2 with T2D are included. In addition, all UK multicomponent pre-bariatric weight loss interventions that were planned and delivered for adults with BMI ≥30 kg/m^2 published since January 2000 until September 2017 were screened for potential inclusion. Inclusion criteria follow: (a) published Tier 3 original study abstracts and/or articles; (b) weight reduction intervention studies with before and after data; (c) studies including any sort of MWMP planned for patients with morbid obesity living in the UK; and (d) studies that included T2D measurements in a MWMP for overweight adults. The review excluded studies on children or adolescents and all studies conducted within non-British weight reduction intervention programmes. The decision to include or exclude studies was initially made based on the article title, then abstract and finally by reviewing the article in full-text.

2.4.3 Data extraction

The included studies were projected to extract four major elements of data contributions: (a) descriptive to study design and intervention; (b) sample size and demographic characteristics; (c) assessed measurements; and (d) health outcome records at baseline followed by points of time intervals.

In the descriptive of study design and intervention, I included the following: setting, study design, aim, type of intervention, a brief description of intervention, inclusion and exclusion criteria, duration and lost-to-follow-up or drop-out data rate. In the demographics: sample size (N), age (years), gender (female, %), ethnicity, socioeconomic status (SES), education level, marital status and type of financial support. On the assessed measurements (n, %): mental disorder, anxiety, depression, sleep apnoea, hypertension, CVD, ischaemic heart disease, hyperlipidaemia, diabetes mellitus (DM), impaired fasting glucose, insulin use, oral hypoglycaemic and incretin based.

For the baseline, 3, 6, 12, 18 and 24 months, I extracted (or calculated) the following variables of health outcome results: BMI (kg/m^2), body weight (kg), waist circumference (cm), 5% or more weight loss achieved, 10% weight loss achieved, lost ≥5 kg (reported in proportion), lost ≥10 kg (reported in proportion), lost 0 to ≤5 kg (reported in proportion), lost 5 to ≤10 kg (reported in proportion), lost 10 to ≤15 kg (reported in proportion), lost 15 to ≤20 kg (reported in proportion), lost ≥20 kg (reported in proportion), mean weight loss (kg), percentage of body weight lost, BP (systolic and diastolic), hypertension, insulin usage, Fasting Blood Sugar (FBS)

(mmol/L), glucose (mmol/L), HbA1c[4] (% and mmol/mol), cholesterol (mmol/L), HDL and LDL (mmol/L), total cholesterol, triacylglycerol and levels of physical activity.

It was not feasible to extract food intake observations because of heterogeneity of stratification methods used by a number of studies in addition to concerns of related recall bias. This review supports Brown's et al (2017) decision regarding the difficulty in producing a meta-analysis in reviewing Tier 3 and all MWMPs due to heterogeneity [72]. The increased rate of patient drop-out and apparent risk of bias are also preventive factors to a meta-analysis. Thus, narrative synthesis was carried out.

[4] Observed and calculated HbA1c results in this review were converted to mmol/mol.

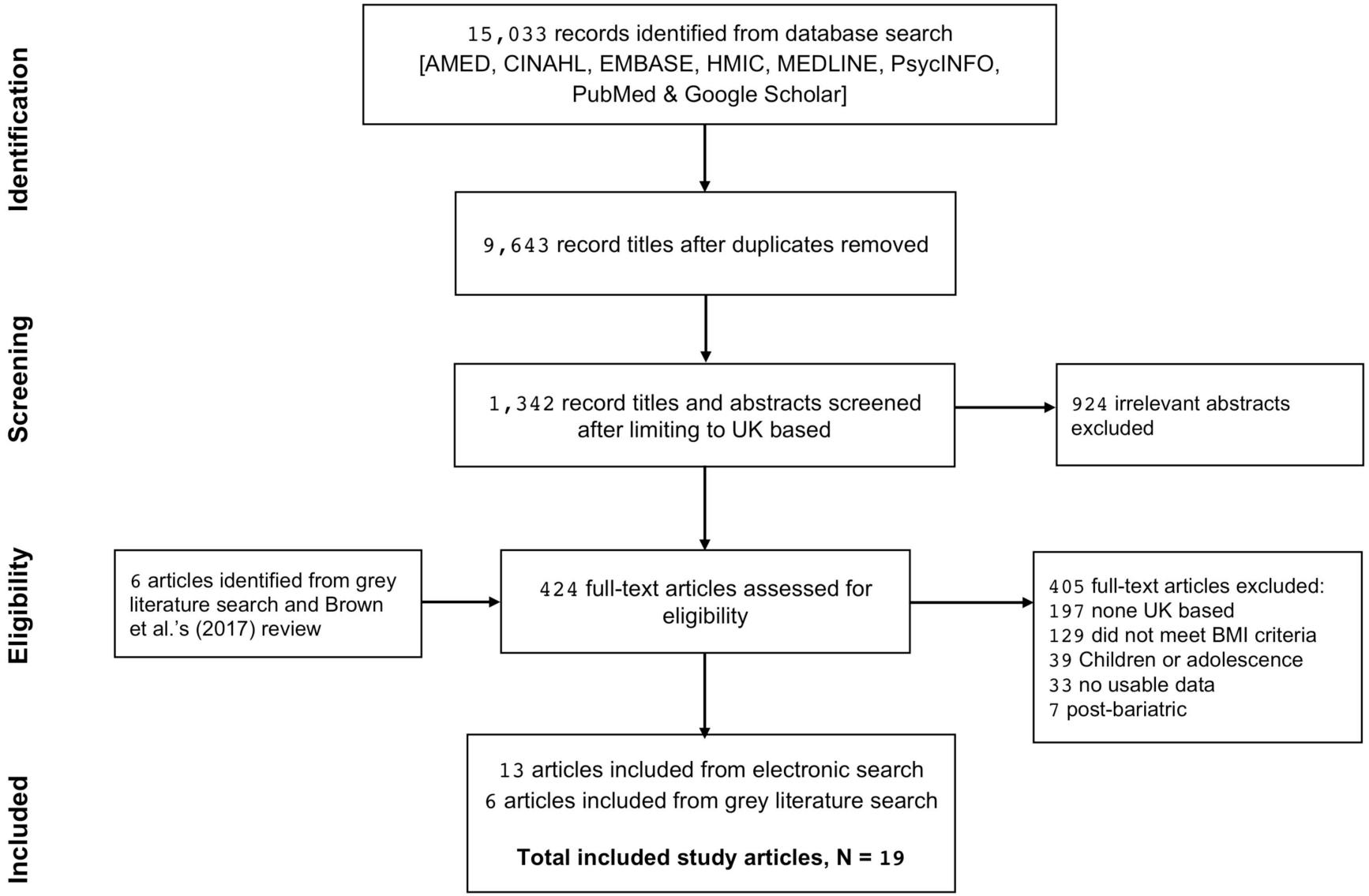

Figure 2.1 PRISMA flowchart.
Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart [73].

2.4.4 Risk of bias assessment

All included studies were assessed using the Cochrane Handbook for Systematic Reviews of Intervention tool [73]. The possibility of the following bias elements was carefully evaluated: allocation sequence, allocation concealment, blinding (of participants, personnel and outcome assessors), incomplete outcome data, and selective outcome for reporting or publication of data.

2.5 Results

1,342 article abstracts were identified as potentially relevant, and after reviewing 418 in full-text, 11 articles and 2 published study abstracts met the inclusion criteria and were included in the review. Grey literature search and reference lists check including Brown's et al (2017) systematic review yielded additional 6 study articles (see **Figure 2.1** Flow chart). In total, 19 studies were eligible for inclusion. The reasons for excluding 405 articles were: a) not being a UK based intervention; b) not Tier 3 or MWMP; c) did not meet BMI criteria; d) intervention intended for children or adolescents; e) no usable data (e.g. qualitative approach for satisfactory observations); and f) post-bariatric groups comparison. The 19 included studies were all published within the last 20 years in 15 different journals, all conducted within the UK.

Table 2.1 summarises details on study design, intervention type and descriptive summary, demographic characteristics of participants (N = 11,735), reported measurements and baseline characteristics and average reported health outcome results in three, six, twelve, eighteen, twenty-four-month intervals. The majority

of included studies (90%) did not reach 18 and 24 months, thus reporting MWMS true effect at these particular points of time was difficult. However, a decision was made to evaluate findings at the last endpoint possible as this may add value.

The majority of included studies (95%) reported our primary outcome of interest in weight and/or BMI from the baseline records up to their study endpoint. Turner et al (2015) was the study article that did not report weight in any form at baseline; however, this study reported rates of participants who achieved ≥5% and ≥10% weight reductions at their intervention endpoint of 12 months (i.e. 36% and 37%, respectively) [74].

Table 2.1 *List of included studies with summary characteristics and results.*

Author (year) Country	Sample size (N)	Intervention	Study design	Duration (months)	Age (yrs) Female (%)	Initial BMI & Weight (kg)	Endpoint BMI & Weight (kg)	Initial outcome variables	Endpoint outcome variables
Barratt (2008) [75] **England**	38	Dietetic led (Lifestyle)	Retrospective case-control analysis	6	42.9 ± 9.9 100.0	40.49 ± 8.36† 109.53 ± 23.92†	37.46† Weight NR	BP*: 124/80 HbA1c: 47.2 Cholesterol: 4.80 HDL: 1.30 ± 0.45 LDL: 2.87 ± 0.77 Triacylglycerol: 1.49 ± 0.79	119/79 40.2‡ 4.79 1.37 ± 0.32 2.81 ± 0.78 1.43 ± 0.97
Brown (2015) [76] **England**	828	SWM (SLiM)	Single group observational cohort (service evaluation)	6	48.2 ± 11.6 73.7	49.1 ± 9.2 135 ± 28.1	47.6† 131.4†	HbA1c: 63.9†	59.6†‡
Cheyette (2007) [77] **England**	49	SWM (Weight No More)	RCT	4	56.7 ± 9.7 47.0	34.1 ± 4.7 97.2 ± 15.1	BMI NR 93.4 ± 14.2	HbA1c: 68.3† Insulin usage: 72.0†	65.0† 62.0 ± 30.4
Hughes (2015) [78] **UK** **ABSTRACT**	272	Tier 3	Prospective cohort	12	NR	44.0 123.9	BMI NR 115.6	NR	NR
Jackson (2007) [79] **England**	89	Specialist health visitor with expertise in weight management	A prospective before-and-after study based in one primary healthcare centre	12	55.8 ± 13.8 80.9	37.4 ± 5.85 103.16 ± 16.9	33.11 ± 5.7‡ 91.64 ± 19.0‡	BP: 138.4/78.4 FBS: 5.44 ± 1.08 Cholesterol: 5.38 ± 1.19	124.4/69.6‡ 5.04 ± 0.60‡ 5.38 ± 1.33

Author (year) Country	Sample size (N)	Intervention	Study design	Duration (months)	Age (yrs) Female (%)	Initial BMI & Weight (kg)	Endpoint BMI & Weight (kg)	Initial outcome variables	Endpoint outcome variables
Jennings (2014) [46] **England**	230	Tier 3 SWMS	Single group observational cohort (service evaluation)	24	52.7 ± 13.6 70.0	44.1 ± 7.8 124.4 ± 27.3	41.0 ± 7.6‡ 115.8 ± 26.0	BP: 131/76 Waist: 128 ± 16.2 HbA1c: 57.8 ±15.3 PA Score: 3.4 ± 1.0	122/71‡ 118 ± 15.4‡ 53.7 ± 14.1‡ 2.8 ± 1.2‡
Kininmonth (2016) [80] **Huddersfield, UK** **ABSTRACT**	280	Tier 3 SWMS	Retrospective cohort	6	Age NR 67	49.4 ± 7.4 138.9 ± 27.2	48.5 ± 7.5 136.3 ± 27.5	NR	NR
Lean (2013) [81] **Scotland**	91	Low-energy Liquid diet LELD and Food Reintroduction	Feasibility study	12	45.7 ± 10.7 81.3	48.0 ± 7.6 131.1 ± 25.2	BMI NR 118.7†	NR	NR
Logue (2014) [82] **Scotland**	1,838	Structured educational lifestyle and GCWMS	Prospective observational study	12	49.1 ± 13.5 72.9	43.3 118.1	NR	NR	NR
MacLaughlin (2015) [83] **England**	338	Renal Weight Management Programme	Retrospective cohort study	12	52.3 ± 12.8 45.0	36.6 ± 5.3 Weight NR	BMI NR - 4.3 reduction‡	NR	NR
McLean (2016) [36] **Scotland**	1,838	GCWMS for anxiety and depression	Retrospective cohort study	12	48.1 ± 12.5† 72.2†	43.77 ± 7.23† 122.5 ± 24.2†	NR	NR	NR
Melville (2011) [84] **Scotland**	54	(TAKE 5) GCWMS	Before and after study (without control)	6	48.3 ± 12.0 59.3	40.0 ± 8.0 100.6 ± 26.8	39.1 ± 8.2‡ 96.1 ± 26.9‡	Waist: 122.1 ± 15.7	 115.8 ± 16.7‡
Morrison (2012) [85] **Scotland**	2,976	SWM GCWMS	Prospective uncontrolled cohort study	24	46.0 72.4	BMI stratified Weight NR	Stratified	NR	NR

Author (year) Country	Sample size (N)	Intervention	Study design	Duration (months)	Age (yrs) Female (%)	Initial BMI & Weight (kg)	Endpoint BMI & Weight (kg)	Initial outcome variables	Endpoint outcome variables
Nield (2016) [86] England	288	Specialist Community Weight Management Programme	Prospective cohort observational study	6	Age stratified 66.0	45.5 ± 6.6 126.9 ± 21.5	43.32†‡ 120.6†‡	PA min/week: 113.2 ± 233.2 Waist: 130.7 ± 14.6	107.4 ± 209.7‡ 125.0†‡
Ross (2008) [87] England	1906	Counterweight Programme SWM	Prospective uncontrolled cohort study	24	49.4 ± 13.5 77.0	37.1 ± 6.0 101.1	36.02† 98.04†	Stratified	Stratified
Rowe (2005) [88] England	100	Orlistat and behavioural interventions for diet and exercise	Prospective observational without control	24	54.6 ± 11.2† 55.0	39.5 ± 6.5 112.0 ± 20.9†	BMI NR 99.7 ± 32.4‡	HbA1c: 59.6† Insulin usage: 130 ± 135.4	52.8†‡ 90 ± 124.1‡
Ryan (2017) [89] England	141	SWMS multidisciplinary, biopsychosocial approach	Before and after study (without control).	12	52.2 ± 11.9 70.0	46.3 ± 7.2 127.2 ± 23.0	BMI NR Weight stratified	Pain: stratified	Stratified
Turner (2015) [74] Wales, UK	180	MDWMC - Tier 3	Service evaluation by semi-structured interviews and questionnaires	24	Age NR 72.7†	NR	NR	NR	NR
Wright (2012) [90] Scotland	199	SWMP	Cross-sectional	6	49.7 ± 12.6 76.4†	BMI NR 114.5 ± 23.4	BMI NR 109.4 ± 23.1‡	NR	NR

NR: Not Reported

† Observed, calculated or converted by reviewer.

‡ With statistical significance (i.e., P<0.05).

* Units: BMI (kg/m^2); Weight (kg); Blood Pressure (BP) (mmHg); HbA1c (mmol/mol^{-1}); Fasting Blood Sugars (mmol/L^{-1}); Insulin usage (Units); Cholesterol (mmol/L^{-1}); HDL& LDL (mmol/L^{-1}); Triacylglycerol (mmol/L^{-1}); Waist circumference (Centimetres); Physical Activity (PA) in a) score: where 4 being inactive & 1 active; and in b) minutes per week.

2.5.1 Study design

The study design ranged: one randomised controlled trial (RCT) [77], a semi-structured interview (service quality evaluation) study [74], a retrospective case-control [75], a feasibility study [81], a cross-sectional [90], two single-group observational cohort (service evaluation) studies [46,76], three retrospective (data analysis) cohort studies [36,80,83], and nine prospective cohort studies [78,79,82,84-89].

Five studies investigated the effect of Tier 3 services [46,74,78,80,90]. Three looked into the Glasgow and Clyde Weight Management Service (GCWMS) [36,82,85]. Whereas the remaining studies focused on further MWMPs including: 'TAKE-5' GCWMS [84], Dietetic led [75], 'SLiM' SWM [76], 'Weight No More' SWM [77], specialist health visitor programme [79], Low-Energy Liquid Diet (LELD) food reintroduction [81], Renal Weight Management Programme (RWMP) [83], specialist community weight reduction programme [86], 'CounterWeight' SWM [87], Orlistat weight reduction [88] and, biopsychological multidisciplinary programme [89]. Further details on study design and intervention description are in **Table 2.1**.

2.5.2 Risk of bias

All studies showed high risk in selection, performance, detection and attrition bias. This is because all included studies, except for the only RCT [77], were designed as evaluation (before and after), retrospective analysis or uncontrolled prospective

investigation. The risk of publication or reporting bias was low to unclear for all studies which may add to the overall reliability (see **Figure 2.2**). Attrition bias was evaluated high in consequence of the increased pattern of patients' drop-out. Drop-out rates were not fully investigated or discussed in all included studies.

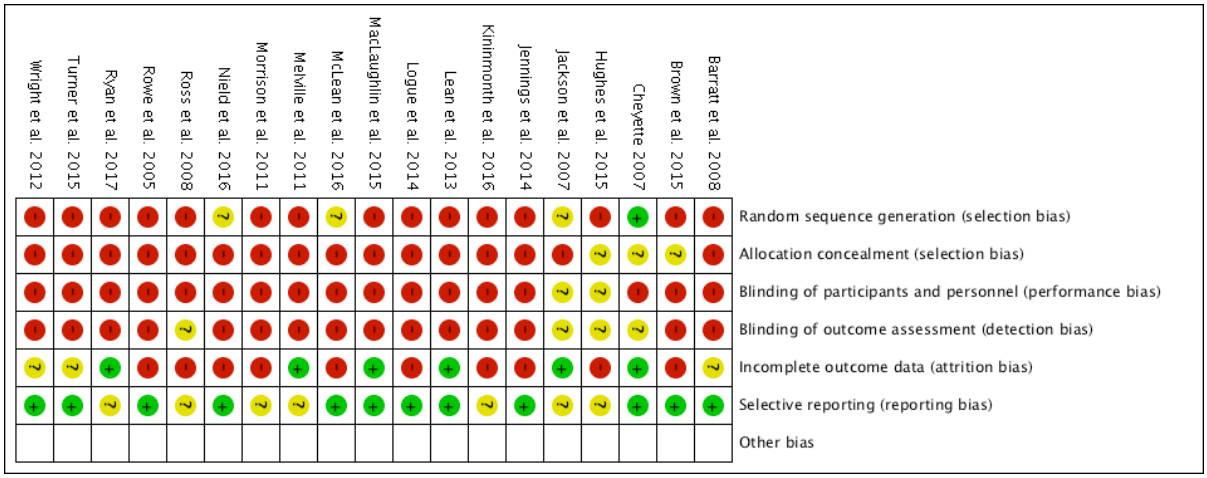

Figure 2.2 Risk of bias assessment.
Risk of bias assessment for each risk of bias element for all included studies.

2.5.3 Participants' characteristics

Women comprised the largest percentage of participants in all except two studies: Cheyette (2007): 47%; and MacLaughlin et al. (2015): 45% [77,83]. One study did not include men (Barratt et al., 2008) [75]. Age ranged from 18 to 75 years; mean age ranged between 40 and 60 years (mean: 49.2 years). Ethnicity was reported in groups by 5 (26%) studies with a clear majority being Caucasian (ranging from 47% to 96%); and with Black African or Asian descendants reported second [75,76,83,84,86].

2.5.4 Socioeconomic status

SES was reported in 7 (37%) studies in a five-level scoring classification [36,82,85-87,89,90]. In studies that included SES, the most deprived was reported with the highest rate compared to all other deprivation levels (ranging from 27% to 62%). Only Jennings et al. (2014) study reported education level, which included three layers (≤15 years: 30%, 15-19 years: 52%, and ≥19 years: 18%) [46]. In addition, Melville's et al. (2011) study reported participants' marital status (Married: 2%; Single: 98%) and their type of financial support (Live independently: 7.4%; Family carer: 31.5%; Paid carer: 61.1%) [84].

2.5.5 Primary outcomes of interest

Baseline BMI was reported by 90% of included studies except for Turner et al. (2015) and Wright et al. (2012) and ranged from 30.1 to 49.1 kg/m^2 [36,46,75-89]. Two studies reported BMI in stratified groupings which left the accumulative average BMI calculated from 16 studies at 42.54 kg/m^2. Baseline body weight in kilograms was also reported by 90% of included studies except for Morrison et al. (2011) and Turner et al. (2015) [36,46,75-84,86-90]. Turner et al. reported participants whom lost weight at 12 months, which was their intervention end-point [74]. Wright et al. (2012) reported weight at baseline and at six months (114.5 [±23.4] kg and 109.4 [±23.1] kg, P<0.001; respectively) [90]. The baseline accumulative average of weight is calculated at 117.88 kg (see **Table 2.2**).

At three months, the calculated average BMI from six studies is 42.40 kg/m^2 [46,76,79,80,86,87]; five of which reported statistical significance at (P<0.001)

[46,76,79,86,87]. Morrison et al. (2011), however, reported BMI in a stratification [85]. The mean reduction in weight ranged from 3.34 (±3.53) to 4.11 (±4.95) kg (P<0.001) in 6 studies [46,76,79,80,86,87]. An average of weight reduction with no BMI informed and with a reported statistical significance by Cheyette (2007) (2.2 [±2.7] kg; P<0.01) [77]. In total, eight studies (42%) reported change in BMI and/or body weight at three months from their baseline, and the majority reported statistically significance weight reduction with an accumulative average of 114.48 kg [46,76,77,79,80,85-87]. Six studies (31%) reported a percentage of participants who lost 5% or more of their initial weight (calculated mean: 22.95% of participants) [36,46,80,82,86,87]. Jennings et al. (2014) was the only study to report a 10% or more weight reduction rate among participants (3.6%) [46]. Details on rates are summarised in **Table 2.3**.

At six months, 11 studies (58%) reported changes in BMI or body weight or both [46,75-77,79,80,84,86-88,90]. The calculated average reduction in BMI is 1.89 kg/m^2 ranging from 0.8 to 3.3 kg/m^2 in eight studies with a cumulative average of 40.73 kg/m^2 [46,75,76,79,80,84,86,87]. The mean reduction in body weight was reported by ten studies (53%), with a calculated accumulative average of 112.17 kg [46,76,77,79,80,84,86-88,90]. Nine studies (47%) reported a 5% or more weight loss rate among participants with a calculated average of 39.2% [36,46,76,82,84,86-88,90]. Only two studies (11%) reported an average of 10.0% of participants whom lost 10% or more from their initial weight [46,76].

At one year, five studies (26%) reported change in BMI or weight or both [46,77-79,87]. BMI reduction was reported by three studies (16%) with a calculated average of 36.67 kg/m^2 [46,79,87]. Weight reduction was reported by five studies (26%), ranging from 2.8 to 11.6 kg reduction and with a calculated average of 102.89 kg [46,77-79,87]. An average of 43.4% of participants have achieved 5% or more weight loss; as reported by seven studies (37%) [36,46,74,78,82,87,89]. At this point, only two studies (11%) have reported 10% or more weight loss with a calculated average 29.4% of participants [46,74].

Table 2.2 *Summary of calculated average primary and secondary outcome results covered and reported by the included studies.*

		Baseline	***3 months***	***6 months***	***12 months***	***18 months***	***24 months***
BMI, kg/m²		42.5 ±14.1 (16)Δ	42.4 ±12.7 (6)	40.7 ±10.2 (8)	36.7 ±13.6 (3)		
Weight, kg		117.9 ±20.3 (16)	114.5 16.9 (7)	112.2 ±14.4 (10)	102.9 ±22.1 (5)	112.0 ±24.9 (1)	105.95 ±28.6 (2)
Waist circmf., cm		126.9 ±21.1 (3)	125.3 ±16.1 (2)	120.3 ±15.8 (3)	118.0 ±15.4 (1)		
HbA1c, mmol/mol		58.8 ±9.8 (5)	56.5 ±9.8 (2)	53.8 ±9.1 (5)	59.4 ±9.9 (2)		
FBS, mmol/L		5.4 ±1.1 (1)	5.1 ±0.7 (1)	5.1 ±0.9 (1)	5.0 0.6 (1)		
Insulin usage, Units		101.0 (2)	58.7 (1)	76.55 (2)	62.0 (1)		
Cholesterol, mmol/L		5.09 ±1.5 (2)	5.18 ±1.4 (1)	5.01 ±1.3 (2)	5.38 ±1.3 (1)		
BP mmHg	Systolic	134.7 (2)	129.5 (1)	124.5 (2)	123.2 (2)		
	Diastolic	77.2	72.6	75.9	70.5		
PA	Out of 4†	3.4	2.9	2.7	2.8		
	min/week‡	113.2	123.2	107.4			
Drop-out, %			9.1 (1)	33.4 (5)	44.1 (8)		74.1 (4)

± Calculated standard deviation.
Δ Superscript in-bracket numbers represent count of studies contributed in calculating the correlated average.
† Inverse score used by Jennings et al. (2014) to report physical activity where 4 being inactive and 1 is active.
‡ Physical activity reported by Nield et al. (2016) in minutes per week.

At eighteen months, Jennings et al. (2014) was the only study that reported change in kilograms [46]. The mean reduction in weight was 12.4 kg ($P < 0.001$) with 47.9% of the remaining participants who lost 5% or more and 26% lost 10% or more of their initial weight. At eighteen months, there were no additional outcome variables reported by any of the included studies.

At two years, three studies (16%) briefly reported weight change [46,85,88]. Jennings et al. (2014) and Rowe et al. (2005) reported weight change in kilograms from the remaining participants with an average reduction of 11.9 kg ($P < 0.01$) with a cumulated average of 105.95 kg [46,88]. Morrison et al. (2011) reported only the rate of participants whom lost 5 kg or more (13.6%) [85]. At this point, there were no additional outcome variables reported by any of the included studies. In addition, no prospective study went beyond two years of follow up. **Tables 2.*2*** and **2.3** and **Figure 2.5** represent calculated average results.

Table 2.3 *Calculated average rates of participants who have lost weight covered and reported by the included studies (%).*

	3 months	***6 months***	***12 months***	***18 months***	***24 months***
≥5% weight loss	23.98(7)Δ	39.20(9)	43.35(7)	47.90(1)	44.40(1)
≥10% weight loss	3.6(1)	10.0(2)	29.4(2)	26.0(1)	20.0(2)
≥5kg weight loss	27.20(2)	39.21(2)	40.90(2)		13.60(1)
≥10kg weight loss			36.0(1)		

Δ Superscript in-brackets numbers represent count of studies contributed in calculating the correlated average.

2.5.6 Secondary outcomes of interest

The included studies reported secondary outcome variables in a heterogeneity that made tracking a set of health outcome variables problematic. Eight studies

(42%) reported secondary health outcome variables at baseline: waist circumference, glycaemic control, lipids, BP and physical activity [46,75-77,79,84,86,88]. Details on baseline results are in **Table 2.2**.

At three months, Jennings et al. (2014) and Nield et al. (2016) reported significant reduction in waist circumference by an average of 4.02 cm ($P < 0.001$). The accumulative average of waist circumference was 125.3 cm. They also reported significant increase in physical activity levels, but with different measuring methodology[5] (Jennings: 17.2%; and Nield: 8.8% increase; $P < 0.001$) [46,86]. Cheyette (2007) and Jennings et al. (2014) reported improvements in glycaemic control. The reduction in insulin usage reported by Cheyette is 10.1 (±16.4) units ($P<0.01$); and an average of 56.5 mmol/mol in HbA1c[6] reported by two studies [46,77]. Jackson et al. (2007) reported a significant improvement in FBS by a reduction of 0.36 mmol/L from baseline. Jackson also reported improvement in BP with a significant mean reduction of 9.0 mmHg systolic and 5.8 mmHg diastolic ($P < 0.001$) and a mean reduction in cholesterol by 0.2 mmol/L ($P = 0.02$) [79]. **Table 2.2** and **Figure 2.3**.

[5] Jennings et al. (2014) reported physical activity through a 4-level scoring methodology with score number 4 being inactive and score number 1 being active. Nield et al. (2016) used minutes per week as the unit of measurement.
[6] Calculated average after conversion from percent to mmol/mol measurement units.

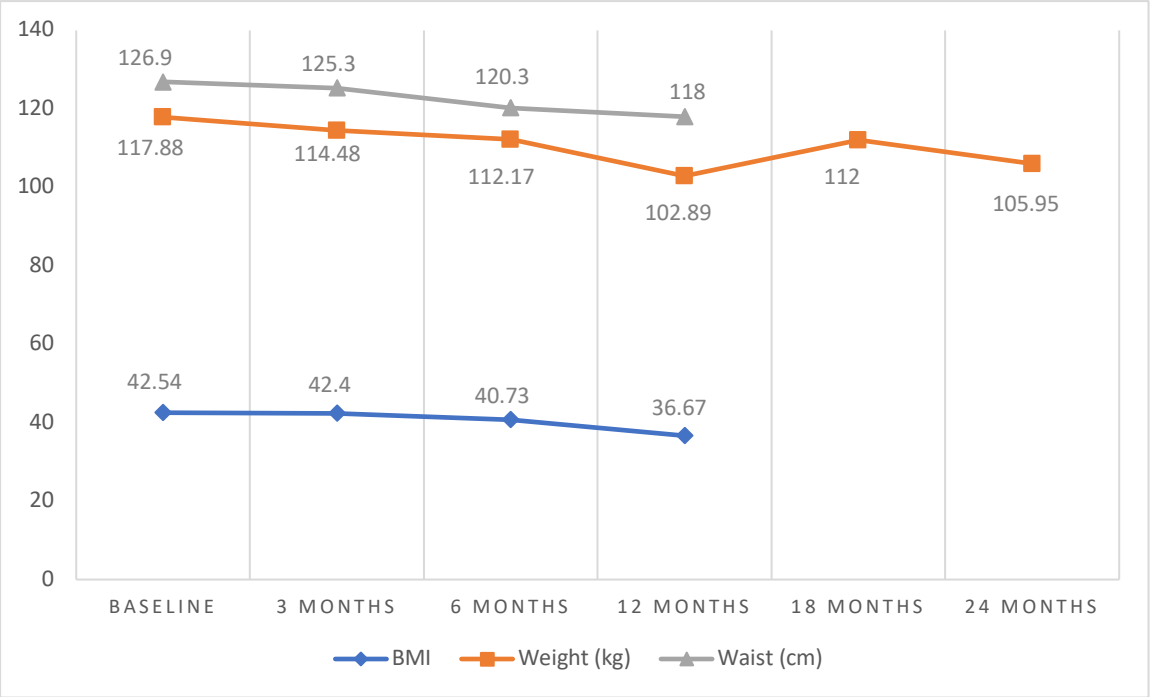

Figure 2.3 Metabolic outcomes of Tier 3 and MWMPs.
Average results for BMI (kg/m^2), weight (kg) and waist circumference (cm) at baseline and up to 24 months follow up from the included studies.

At six months, three studies (16%) reported further significant reduction in waist circumference with an average of 6.6 cm ($P < 0.001$) [46,84,86]. The waist circumference averaged at 120.3 cm. The average reduction in HbA1c from five studies (26%) is calculated at 4.86 mmol/mol ($P < 0.05$) [46,75-77,88]. Rowe et al. (2005) reported further significant reductions in insulin usage by a calculated mean of 40.0 units ($P < 0.001$) [88]. In addition, Jackson et al. (2007) indicated a significant constant decrease in FBS by 0.3 mmol/L from baseline ($P = 0.03$) [79]. Jackson, nonetheless, reported an insignificant reduction in cholesterol (by 0.15 mmol/L; $P = 0.6$). Jennings et al. (2014) reported a very significant increase in physical activity (by 26%; $P < 0.001$) from baseline; whereas Nield et al. (2016), reported a decline (from 123.2 min/week at 3 months to 107.4 min/week at 6 months) [46,86]. The calculated average reduction in BP was reported by two

studies (11%); with an average reduction in systolic BP by 10.2 mmHg and diastolic by 1.3 mmHg from baseline [46,86]. Five studies reported drop-out rate with an average of 33.4%, ranging from 18 to 60% [76,80,84,86,88] (**Table 2.2** and **Figure 2.4**).

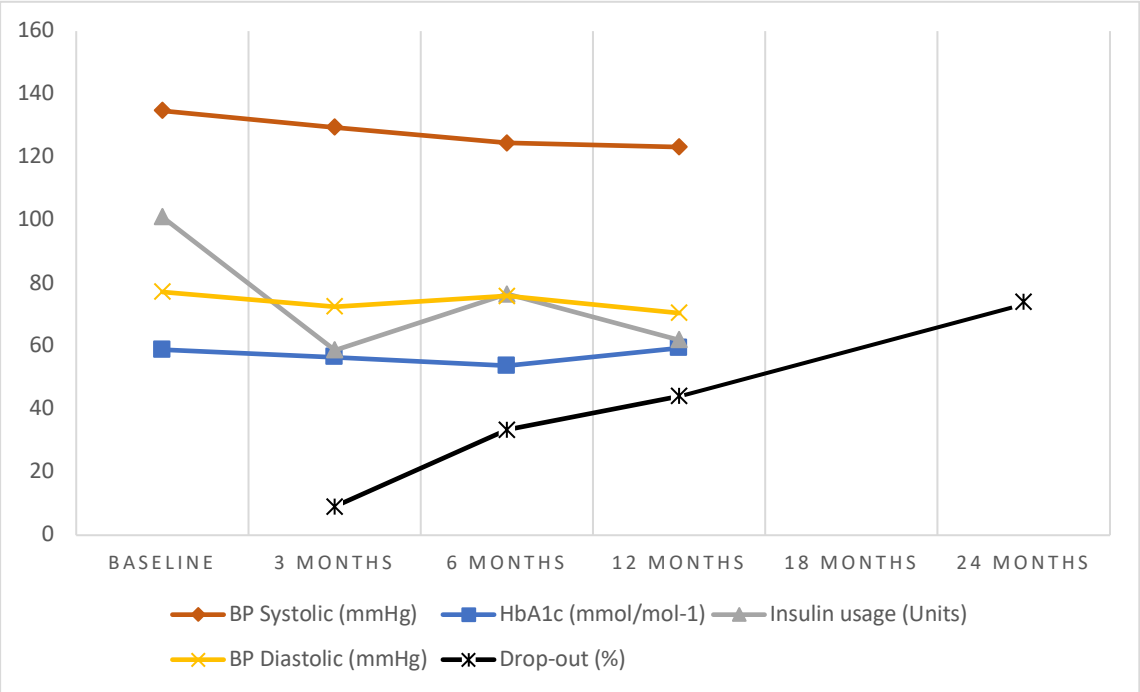

Figure 2.4 Additional outcome results from Tier 3 and MWMPs.
Calculated average results for systolic and diastolic blood pressure (mmHg), HbA1c (mmol/mol), insulin usage (units) as well as participants' drop-out rate (%) from the included studies.

At one year, HbA1c average results calculated from two studies (11%) was found to reclaim to the baseline calculated average (59.4 compared to 58.8 mmol/mol at baseline) [46,77]. Turner et al. (2015), however, noted that 36% of participants reported a reduction in insulin usage [74]. Cheyette's (2007) participants experienced a similar reduced level of mean insulin usage as they did at three months (62.0 [±30.4] units) [77]. Similarly, Jackson et al.'s (2007) participants had FBS tested as similar levels as three months of intervention (5.04 [±0.60] mmol/L).

Jackson also reported an insignificant change in cholesterol [79]. Both Jackson et al. (2007) and Jennings et al. (2014) reported a statistically significant decrease in BP with an average systolic reduction of 11.5 mmHg and in diastolic by 6.76 mmHg (P=0.001) [46,79]. Only one study reported physical activity with a similar level as the three months point of intervention (scored 2.8 at one year compared to 2.9 at three months) [46]. Waist circumference remained relatively constant compared to six months point; with a mean reported by one study 118.8 cm [46]. Eight studies reported increased drop-out rate with an average of 44.1% ranging from 15.6 to 78.3% [46,78,79,81-83,87,89]. **Table 2.2** and **Figure 2.3**.

At eighteen and twenty-four months, there were little or no secondary outcome variables reported by any of the included studies. Drop-out rate increased to an average of 74.13% at two years point; ranging from 62.0 to 80.5%, as reported by 4 studies [46,85,87,88]. **Table 2.2** and **Figure 2.4** summarise drop-out rates form included studies.

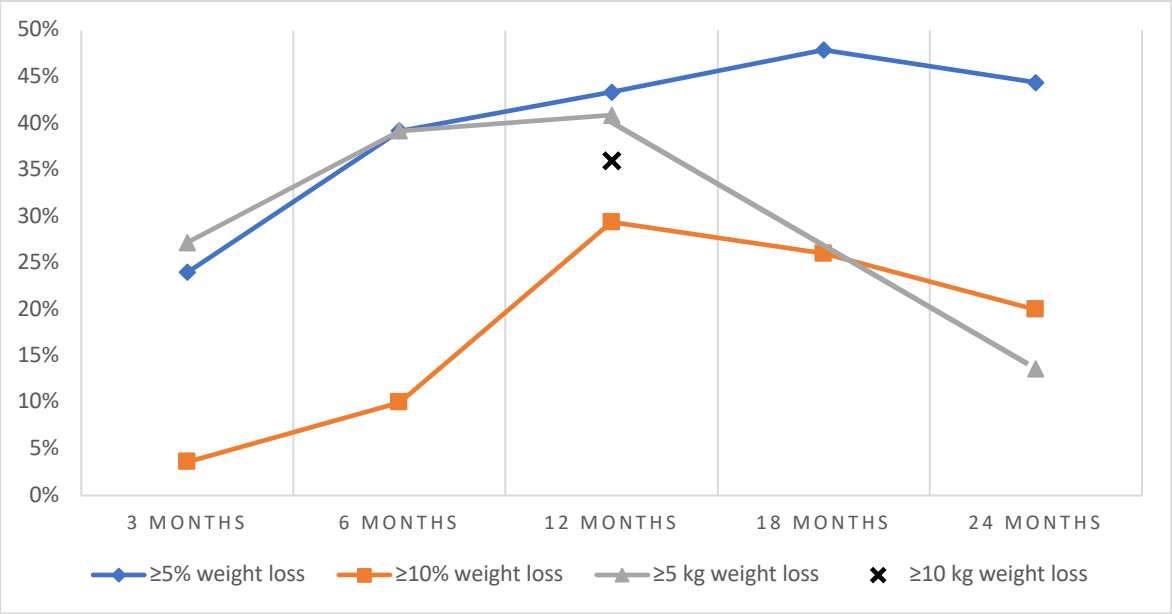

Figure 2.5 Rates of weight loss.
Calculated average rates for weight loss reported by the included studies.

2.6 Discussion

Although obesity has an increasing academic and clinical interest globally, the evidence on Tier 3 and all other MWMPs in the UK remains scarce [47]. The aim of the present review was to examine Tier 3 and MWMPs for adults with severe obesity. Our review fulfilled the PRISMA checklist for reporting systematic reviews (**Appendix 10.2**) [73], and it also supports the accumulating obtainable evidence that Tier 3 intervention reached positive influence on morbidly and among patients with severe obesity in the pre-bariatric stage. Evidence suggests that Tier 3 interventions are effective obesity treatment, especially during the early months of involvement.

In general, all MWMPs were found to reduce weight considerably and to improve other health outcomes measured from baseline on most reported health variables. The magnitude of the effect, however, seems to lose momentum after six months

of intervention. This later observation is crucial with regards to the appropriate timing for a bariatric surgical intervention. A small number of included studies discuss this phenomenon, perhaps due to the substantial proportion of participants who drop out at an accelerating rate beyond the three-month point of intervention. In addition, more recent studies have provided novel insights into the processes and mechanisms that underpin weight regain after weight loss. In addition to environmental and behavioural factors, physiological (or metabolic) adaptations to weight loss favour weight regain due to perturbations in the levels of circulating appetite-related hormones and energy homoeostasis, in addition to alterations in nutrient metabolism and subjective appetite. To maintain weight loss, individuals must adhere to behaviours that counteract physiological adaptations and other factors favouring weight regain [91,92]. It is difficult to overcome physiology with behaviour. Nonetheless, this, and variations in study duration, may contribute to preventing this review from comparing the true effect size between included studies. Though future research is required to examine secondary outcome variables such as glycaemic control and lipids (in stratifications) extensively, weight loss goals such as 5% weight loss (NICE guidelines) are reachable at early stages of interventions (see **Table 2.3**).

This review agrees with Brown's et al. (2017), which notes most available reviewed evidence comes from observational studies in which randomised selection and allocation into Tier 3 services would improve inference reliability [72]. The only RCT reviewed, for instance, lasted for a short intervention duration (four months) and

reported a modest mean reduction in weight (by 2.2 kg) [77]. At three months, the mean reduction in body weight from all studies that reported changes (including the RCT) reached 4.11 kg, thus almost doubling the reported RCT-measured effect.

Improvements in secondary health outcome variables were significant until the effect of the drop-out rate becomes apparent. This may be because all studies have excluded drop-out data from their analyses at each interval. At the three- and six-month points, however, we can appreciate achieved improvements in glycaemic control and BP. Most studies that reported secondary outcome variables related magnitude to a statistical significance. Physical activity, for instance, had an average increase reached 26% at three months ($P < 0.001$) then declined afterwards [46,86]. Despite the assessed high risk of bias, I have noticed no difference in magnitude between small and large sample size studies. Studies that reported demographic characteristics such as SES and/or education levels did not reveal distinct effects either. Thus, Tier 3 and MWMPs may have been preventive tools in the short- and mid-term, treating obesity regardless of sample size, demographical characteristics or comorbidities.

Studies invested in patients' emotional and motivational status, and which reported data for depression and anxiety, were just as likely to have a high rate of patient drop-outs as those that did not. This, in count, does not support the notion that weight reduction levels in those programmes were superior to other studies that did not target emotional health. McLean et al. (2016), for instance, concluded that patients with complex obesity who scored high for severe anxiety and/or

depression participating in an MWMP with integrated psychological support, achieved similar weight reduction outcomes compared to non-severe cases [36]. Thus, more research is needed regarding obese people's mental wellbeing, process and pathway for psychological intervention as well as robust outcomes from such interventions.

A majority of included studies were not as precise in discussing participants' reasons for dropping out. Extending efforts to assess and overcome drop-outs, appeared to contribute to a successful intervention (especially a multicomponent one) and the achievement of desired targets. This is because, as anticipated by commissioning parties, Tier 3's main goal is to help patients, at a minimum, to lose weight and improve most of their quality of life aspects, improve and induce remission of comorbidities or to optimise patients' preparation for a Tier 4 bariatric surgical intervention. The goal is, optimistically, helping patients to take control of their own lives and all other healthful elements; which is the drive for commissioning all tiered weight reduction interventions.

Brown et al. (2017) recently published a systematic review examining a set of criteria for interventions similar to the ones this review has covered [72]. This review has only excluded two studies from their selection, as one was of non-British origin and the other was comparing groups in post bariatric [71,93]. They reviewed 14 studies, and our conclusions were based on lines of theoretical analysis similar to theirs. Our review adds to the evidence base on a stratified basis with summaries for weight loss achieved and calculated average outcome results

and suggests further research regarding intervention's high drop-out rates as well as outcomes from psychological and physical activity interventions. More RCT-designed studies would greatly contribute to robust, real-life findings, as all possible confounding effects would ideally distribute evenly between study groups.

In summary, the reviewed evidence for the Tier 3 service and MWMPs suggests a short- to mid-ranged positive effect on patients with obesity living in the UK regarding accumulated reductions in body weight, glycaemic control, BP and subtle improvement in physical activity. The high drop-out rate may have contributed to limiting longer terms' progress in all positive results, especially those related to physical activity. More randomised trial investigations and drop-out explorations would improve overall reliability. Tier 3 service and MWMPs can assist adults with obesity living in the UK to lose weight and may slightly improve their overall health status.

2.7 Limitations

Studies published on Tier 3 and UK MWMPs are limited in number. Yet, most if not all of included studies are of high risk of bias in terms of allocation sequence, allocation concealment, blinding, incomplete outcome data. The only RCT reviewed has shown a modest change in weight compared to all included studies [77]. The high rate of drop-outs was present in most if not all included studies with inadequate reasoning. The majority have excluded non-completers' data from their final analysis.

Chapter Three: Prevalence of Comorbidities within Tier 3 Services

3.1 Summary

Objective: There is limited evidence regarding the prevalence of obesity-related comorbidities and the effectiveness of specialist multidisciplinary weight management (Tier 3) programmes prior to bariatric surgery. This paper aims to evaluate and report on the prevalence of comorbidities in patients attending Tier 3 services within a National Health Service setting.

Methods: The current study comprises an observational study of consecutive patients who attended the Tier 3 service at the East Midlands Bariatric Metabolic Institute during 2017.

Results: 430 patients attended the service over the study observation period. Twelve patients (2.8%) were excluded from our analysis due to incompleteness of data. 70.8% of patients were women, mean age at baseline was 46.4 years, mean and SD of body weight and BMI at baseline were 137.8 (±29.2) kg and 48.0 (±8.6) kg/m^2, respectively. The most common comorbidities recorded at baseline were T2D (31.1%), hypertension (31.1%), depression (26.1%), obstructive sleep apnoea (23.2%), and osteoarthritis (15.6%). Significant weight loss was observed at the three-month and six-month follow-up points, but not at the nine-month or twelve-month follow-up points. 22.5% of patients achieved weight loss of ≥ 5%.

Conclusion: The prevalence of comorbidities within this Tier 3 service was high. While specialised weight management services can achieve moderate weight loss as part of a multidisciplinary intervention, any future evaluation of clinical outcomes of specialist weight services should also include comorbidity outcomes.

3.2 Background and aims

Obesity is recognised as one of the leading healthcare challenges both in the UK and in the global context [94]. National Health Service (NHS) statistics have revealed that, in 2015, 27% of UK adults were obese, representing an increase of 12% from 1993 [95]. The percentage of adults classified as obese (i.e. BMI ≥30 kg/m^2) has since remained steady, but there has been an alarming 18% increase in hospital admissions for obesity-related comorbidities. Thus, whilst there were 525,000 admissions in 2015/16, this figure has risen to 617,000 in 2017/18.2 Worryingly, 20% of year 6 children (aged 10–11) and 10% of reception year children (aged 4–5) are now classed as obese [95]. Studies indicate that obesity increases the likelihood of developing serious comorbidities, including, but not limited to, diabetes, hypertension [96], gallstones [97], osteoarthritis [98], cardiovascular disease [99], sleep apnoea (among males) [100], and fatty liver disease [101]. A moderate sustained weight loss of 5–10% has been shown to be associated with significant clinical benefits in individuals with obesity and is therefore considered an important treatment objective [102].

The UK NHS has recommended the implementation of a tiered model for weight management [47]. Tier 1 interventions comprise general guidance and advice, as provided in widespread community-based environments. Tier 2 interventions encompass more complex measures, such as weight loss programmes, which are to be provided by either local public health bodies or commercial providers (e.g. Weight Watchers™ and Slimming World™). Tier 3 interventions are to be offered

by specialist MDT, charged with managing individuals with obesity either in a community or hospital setting. These teams consist of specialist dieticians, physicians, and clinical psychologist, as a bare minimum. The services are typically funded by local health clinical commissioning groups [7,47]. An important remit of a Tier 3 service is the preparation of appropriately selected patients for bariatric surgical intervention (Tier 4). However, while the prevalence of comorbidities in various community-based Tier 3 programmes has been reported (see **Chapter 2**), the prevalence of obesity-related comorbidities within hospital-based Tier 3 programmes remains unclear.

The proposed observational study aims both to examine the prevalence of obesity-related comorbidities and to obtain evidence of the effectiveness of Tier 3 interventions in patients admitted to the Tier 3 weight management service at East Midlands Bariatric Metabolic Institute (EMBMI). The service was evaluated with the aid of the Standard Evaluation Framework for Weight Management Interventions [103] and measured against the requirements stipulated in the *Clinical Commissioning Policy: Complex and Specialised Obesity Surgery* [7].

3.3 Methods

3.3.1 Setting

EMBMI is based in the Derby and Burton Teaching Hospitals NHS Foundation Trust. It comprises a regional tertiary referral centre for bariatric and metabolic surgery, which provides both Tier 3 and Tier 4 services. The Tier 3 service was developed in 2014 in response to the NHS England requirements formulated in 2013 which

required patients to access specialist Tier 3 interventions prior to undergoing bariatric surgery. This is a multicomponent specialist weight management service available to patients aged 18 years and over with complex obesity, defined by the NICE guidelines as BMI ≥ 35 kg/m^2 with obesity-related comorbidities or BMI ≥ 40 kg/m^2 without comorbidities. This equates to the obesity class II and class III threshold for 'severely obese' and 'very severely obese'. Patients are referred by their general practitioner or hospital doctor for consideration for bariatric surgery. The service is a time-limited multidisciplinary specialist weight intervention service with input from physicians, to aim of which is to screen and manage patient comorbidities. Specialist dieticians are provided to educate patients on mindful eating and to devise structured frameworks for caloric restriction and regulated eating behaviour, including portion control, slowing eating, and appropriate food choices. The service also includes a psychologist who can screen and manage relevant mental health disorders. The intensity and frequency of follow-up visits were determined by the clinical needs of patients and guided by regular MDT meetings. Suitability for surgery was assessed at a minimum of three months from the first visit.

3.3.2 Data collection

Patient data were obtained from electronic patient records. Inclusion criteria for this study required that all patients had attended a scheduled appointment at some point during 2017. Baseline data were derived from the first Tier 3 appointments in 2017, from correspondence sent to the patient's GP, and/or from

clinical notes made during the appointment. The following data were collected: age, gender, ethnicity, date of first visit, weight, height, BMI, blood pressure, previous bariatric surgery (if applicable), Epworth score if symptomatic of sleep apnoea, endoscopy results, full blood count, urea and electrolytes, liver function, calcium, lipid profile, HbA1c, thyroid, details of comorbidities present, and relevant medications received. The follow-up data, however, only included weight and BMI. Short-term weight outcomes were also reported as the mean weight change and 5% weight loss of those completing the programme, in order to generate a comparison with other programmes. Follow-up data were collected from a broad range of appointments, including dietician appointments and educational sessions. Follow-up periods were arranged into groups of three, six, nine and twelve months. Drop-outs comprised those patients who failed to attend follow-up appointments within Tier 3.

3.3.3 Statistical analysis

All referrals in 2017 were followed up until patients either completed or left the programme. Data were censured at 1 April 2018 to ensure full data were available. A visual inspection of the visual inspection of the histogram and an evaluation of the Shapiro–Wilk test revealed that the baseline weight data were found not to be normally distributed. Therefore, the Wilcoxon signed-rank test was used to statistically test differences in the data. For missing data, the method of last observation carried forward was used. The criteria for statistical significance was set at a P value of 0.05. SPSS version 24.0.2 (SPSS Inc, Chicago, IL, USA) was used

for the statistical analysis of the data. Descriptive patient characteristics were described as mean and standard deviations.

3.4 Results

3.4.1 Patient flow

Data were collected from 418 patients as part of the evaluation study. Ninety-eight patients provided follow-up data at the three-month stage, 94 supplied follow-up data after six months, and 41 were available for follow-up data after nine months. Following this, most patients were either discharged or referred for bariatric surgery. In total, 191 patients (45.69%) had at least one point of follow-up data. Ninety-three patients who did not have follow-up at the three-month stage did have a subsequent follow-up later in their treatment plan at the Tier 3 clinic. **Figure 3.1** illustrates the complete flow of patients through the Tier 3 service, from admission to the twelve-month point.

3.4.2 Patients' baseline characteristics and demographics

A total of 430 patients was recorded as presenting to the Tier 3 clinic in 2017. Of these, 418 met the inclusion criteria for the evaluation study. The remaining twelve were excluded because there were no recorded notes pertaining to their visit or because vital information, such as baseline body weight data, was unavailable. Of those who met the inclusion criteria, 296 (70.8%) were female. The mean and standard deviation baseline weight for the sample was 137.8 (±29.2) kg and the mean baseline BMI was 48.0 (±8.6) kg/m^2. The mean and standard deviation age, weight, and BMI for male patients was 47.0 (±12) years, 154.2 (±32.7) kg and 48.1

(±8.8) kg/m^2, respectively. The respective figures for female patients were 45.8 (±11.8) years, 131.1 (±32.7) kg, and 48.0 (±8.8) kg/m^2.

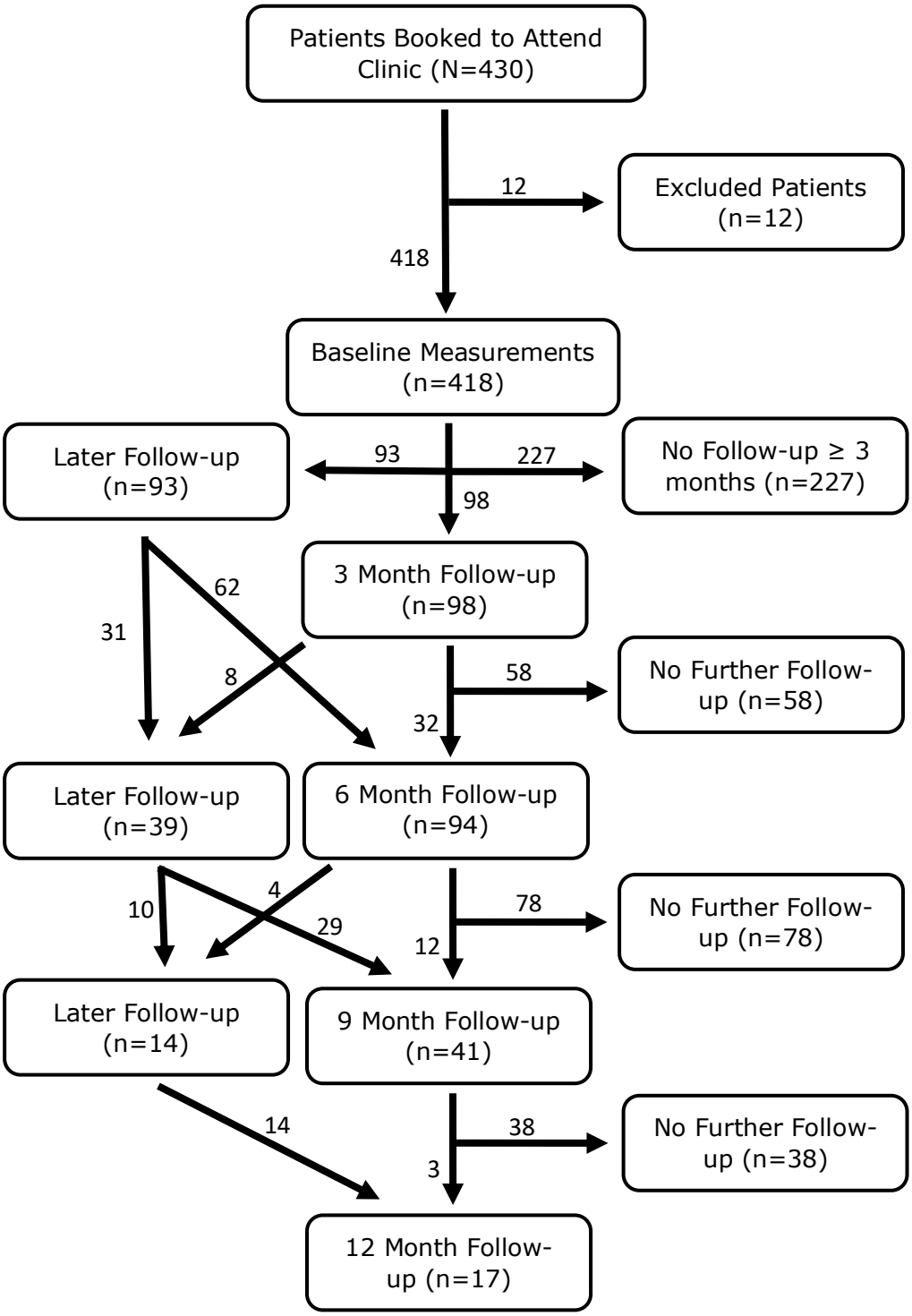

Figure 3.1 Flowchart diagram of Tier 3 service.
The progression of patients through the Tier 3 service from their first referral and up to the twelve-month of follow-up point.

Four patients (1.0%) were classified as overweight, 12 (2.9%) were class I obese, 48 (11.5%) were class II obese, and the remaining 354 (84.7%) were class III obese. In respect of ethnic identity, 267 (63.9%) patients were defined as White British whilst the ethnic identity of 115 (27.5%) patients was either not stated or not recorded. The remaining 36 (8.6%) patients were divided between a variety of ethnicities, including Bangladeshi, Black Caribbean, and Mixed ethnicity. **Table 3.1** summarises the baseline characteristics of the sample. Ninety-eight patients delivered follow-up data at the three-month point, 94 supplied follow-up data at the six-month point, 41 provided follow-up data at the nine-month point, and 17 furnished follow-up at the twelve-month point. In total, 191 (45.69%) patients had at least one point of follow-up data. A total of ninety-three patients, who did not have follow-up at the three-month point, were available to provide follow-up data at a further point in their treatment programme at the Tier 3 clinic.

Commonly occurring comorbidities included T2D (31.1%), hypertension (31.1%), depression (26.1%), obstructive sleep apnoea (23.2%), and osteoarthritis (15.6%). **Table 3.2** details the top thirty comorbidities which were observed. When assessing for comorbidity and weight clustering according to the age threshold, no significant differences were noted for the prevalence of comorbidities for the age thresholds <35 years, 35–49 years, 50–64 years, and over 65 years.

Table 3.1 *Baseline characteristics.*

Characteristics	***Number***	***Mean or %***	***SD***
Metabolic			
Body weight, kg	418	137.2	29.2
BMI, kg/m²	418	48.0	8.6
Demographic			
Age, years	418	47.1	12.2
Male	122	29.2%	
Female	296	70.8%	
Ethnicity			
White British	267	63.9%	
Unknown/not stated	115	27.5%	
White Other	13	3.1%	
Indian	3	0.7%	
Pakistani	3	0.7%	
Black Caribbean	3	0.7%	
Black African	2	0.5%	
White/Black Caribbean	2	0.5%	
Mixed Other	2	0.5%	
Other	2	0.5%	
White and Asian	2	0.5%	
Asian Other	1	0.2%	
Bangladeshi	1	0.2%	
White Irish	1	0.2%	
White/Black African	1	0.2%	
Obesity classification			
Overweight	4	1.0%	
Class I Obese	12	2.9%	
Class II Obese	48	11.5%	
Class III Obese	354	84.7%	

3.4.3 Baseline body weight by age

The median and interquartile range (IQR) weight and BMI for patients aged 35 years or lower were 135.9 (IQR: 121.6–149.1) kg and 42.2 (IQR: 36.2–44.6) kg/m^2, respectively. The respective data for those aged 35–49 years were 133.4 (IQR: 116.4–142.8) kg and 40.1 (IQR: 34.0–42.1) kg/m^2, for those aged 50–64 years were 130.2 (IQR: 115.2–139.7) kg and 39.1 (IQR: 33.5–41.8) kg/m^2, and for patients aged over 65 years the figures were 127.8 (IQR: 112.3–138.8) kg and 38.1 (IQR: 32.1–40.7) kg/m^2 respectively.

Table 3.2 *Prevalence of disease among Tier 3 patients.*

Disease	***Number***	***Per cent***
Type 2 diabetes	130	31.1
Hypertension	130	31.1
Depression	109	26.1
Obstructive sleep apnoea	97	23.2
Osteoarthritis	65	15.6
Asthma	62	14.8
Limited mobility	60	14.4
Gastroesophageal reflux disease	43	10.3
Chronic back pain	41	9.8
Polycystic ovarian syndrome	38	9.1
Anxiety	38	9.1
Fibromyalgia	32	7.7
Hypothyroidism	32	7.7
Non-alcoholic fatty liver disease	21	5.0
Lymphoedema	19	4.5
Arthritis (not specified)	18	4.3
Coronary heart disease	15	3.6
Hiatus hernia	15	3.6
Irritable bowel syndrome	15	3.6
High cholesterol	12	2.9
Chronic knee pain	12	2.9
Vitamin D deficiency	11	2.6
Heartburn	10	2.4
Atrial fibrillation	10	2.4
Chronic obstructive pulmonary disease	9	2.2
Migraine	9	2.2
Diabetic retinopathy	9	2.2
Previous myocardial infarction	9	2.2
Peripheral neuropathy	8	1.9
Previous cerebrovascular accident	7	1.7

3.4.4 Weight outcomes

As a surrogate marker of our patient population and the complex needs recorded at presentation, and in order to allow comparison with other evaluation studies, we undertook the assessment of short-term weight outcomes for our cohort. A significant reduction in median body weight was observed at three months when a comparison was made to the baseline (135.9 vs. 134.4 kg; $P < 0.001$), followed by a further reduction at six months (135.8 vs. 130.8 kg; $P < 0.001$). However, at

nine months the weight loss was non-significant, possibly due to the smaller number of patients remaining in the programme at this follow-up point since the majority of patients would have been transferred to a Tier 4 service at this stage (136.4 vs. 128 kg; P = 0.116). Overall, 43 patients out of the total 191 (22.5%) for whom follow-up data was provided were shown to have achieved weight loss equating to ≥5% of their baseline weight. This represents a success rate of 22.5%. Similar patterns of weight loss were observed in males and females. That is, these patients demonstrated significant weight loss at the three-month and six-months points, followed by non-significant weight loss at the nine-month point (**Table 3.3**).

Table 3.3 *Change in median baseline and follow-up weights at all of the follow-up stages with P-values from performing Wilcoxon signed rank test.*

	3 months	***6 months***	***9 months***
Patients with weight recoded	98	94	41
Median baseline weight, kg	135.9	135.8	136.4
Median follow-up weight, kg	134.2	130.8	128.0
P-value	< 0.001	< 0.001	0.116

3.5 Discussion

As this evaluation shows, addressing complex obesity and the comorbidities related to it is not straightforward. Significant comorbidities were evident in many patients at the time of their presentation to the hospital-based Tier 3 service. Before undergoing bariatric surgery, these patients required dietary, medical and psychological interventions. With a couple of exceptions, the baseline

characteristics of the patients in our study showed consistency with those reported in other studies. For example, the proportion of female patients in our study was 70.8%, which is comparable to the 70% recorded by Jennings et al. (2014) [46], and other studies [74,80,89]. It is widely recognised in the literature that the proportion of female patients who join specialist weight management programmes exceeds that of male patients. Also, there were strong similarities in the prevalence of major comorbidities between patients in our sample and those in Jennings et al.'s (2014) study, specifically depression (26.1% vs 31.3%), hypertension (31.1% vs 38.3%) and T2D (31.1% vs 31.7%). The noted exceptions were coronary heart disease (3.6% vs 11.7%) and sleep apnoea (23.2% vs 11.7%) [46]. We attribute these discrepancies to fundamental differences in the studies; our clinical service included detailed tests and questionnaire assessments at baseline, designed specifically to screen for comorbidities.

Notwithstanding the inherent difficulties associated with treating complex obesity, or that it was not the intention for this study to primarily be a comparative analysis, the format of this study that evaluated short-term weight outcomes permitted the differences in our patients' population and complex needs be compared with those in other studies. At the 3-month and 6-month points, significant weight losses had been recorded. Furthermore, from their baseline body weight, 22.5% of patients managed to lose ≥5% weight. This is significant as with 5% reduction in baseline weight, various metabolic improvements in beta cell function, and cardiometabolic parameters and systemic insulin sensitivity are reported [102,104]. Moreover, at

any length of follow-up, 22.5% of patients who lost ≥5% of their baseline weight is similar to the 23.7% of patients who lost ≥5% of their baseline weight during the six-to-twelve-month interval, excluding patients with either a three-month follow-up or no follow-up at all.

This study's weight outcomes were compared against those reported for a specialist weight management programme in Glasgow, which found that at the 12-month intervention point, 24% of patients had experienced ≥5% weight loss [82,85]. Despite this achievement, these results are less than the values reported in other similar studies, such as the 60% for all participants in Jennings et al. [46], and 47% at the 12-month period reported in a Canadian study [105]. However, at 48 kg/m^2, the mean baseline BMI for our cohort was greater than that of other reported cohorts (44.1 kg/m^2 [46], 43.3 kg/m^2 [82], and 44.7 kg/m^2 [105]). The implication is that level of obesity and obesity-related comorbidities of the patients in our study was severe than those of the other studies; therefore, our cohort would probably have a greater need for complex medical, dietetic and psychological interventions. There were also significant differences between our patient cohort and those individuals who take part in commercial weight loss programmes, such as WeightWatchers™. They report that the baseline mean BMI is 38 kg/m^2 and that 51% of participants lose 5% of body weight [106]. However, the outcome measure for the Lighten Up study was based upon final weights as reported by the patient [107]; yet the reliability of self-reporting measures is not robust due to possibility of weight being underreported [108].

The ethnicity of the sample group was broadly consistent with ethnicity demographic data for the East Midlands obtained from the 2011 census [109]. Whilst the ethnicity of 27.5% of the sample was either *Unknown* or *Not stated*, 63.9% were reported as *White British*. The census value for *White British* is 85.4%, so we assumed that some of the *Unknown* or *Not stated* were also *White British*. Similarly, the percentage of *White Other* in our sample was 3.1%, which is consistent with the census's 3.2%. Although the census figure for *South-East Asian* ethnicities is 5.6%, in our sample, it was only 1.8%. However, with more than a quarter of patients returning *Unknown* or *Not stated* responses, the actual percentage of *South-East Asian* participants may have been higher than 1.8%.

Compared to other studies with dropout rates of 14.3%, 62.5%, and 51%, our dropout rate at 12 months for 2017 was favourable, losing just 12.2% [46,78,85]. Given that our centre serves a geographic area of 4500 square miles with a population that exceeds 3 million inhabitants, this low rate of attrition is reassuring. Covering such a wide area, the ability to attend follow-up visits can be affected by travel or other practical issues rather than lacking motivation to attend the appointments. Other patients might have decided against surgery; therefore, they were discharged.

In summary, the Tier 3 service provided by EMBMI conforms with relevant commissioning guidelines. Rather than focusing on the effectiveness of specialist weight management service as determined by weight-centric assessments, the primary outcome measure for this study is the improvement of baseline

comorbidities. Indeed, ensuring comorbidities are optimally managed before surgery, as one of the key functions within EMBMI service; this can be delivered through referrals to relevant specialists or through the Tier 3 multidisciplinary management process. Unlike other studies, our study assesses the baseline weight and weight outcomes of patients presenting to our hospital-based Tier 3 programme as surrogate measures of their complex needs. Our study highlights the importance of developing a standardised Tier 3 assessment process that incorporate standardised outcome measures for comorbidities commonly associated with obesity. Explanatory research could be directed from the high prevalence of comorbidities revealed in this study.

3.6 Limitations

There are several limitations to our study. First, the baseline information collected was considerable but not comprehensive; including data of educational and socioeconomic status may have revealed additional insights. Also, where feasible, measuring each patient's waist circumference to gauge the proportion of central body fat, which has a recognised association of risk for coronary heart disease and T2D, would add a further dimension to the outcome measures; the importance of such measurements is recognised by NICE and Public Health England [8,21]. However, this is not practical with patients with severe obesity. Currently, no objective evaluations are made of cardiovascular, musculoskeletal, nephropathy or respiratory function as well as comorbid biochemical parameters, such as HbA1c, lipid and liver function profiles are not consistently retested at follow-up

sessions. Our patients' psychological state and progress could have been evaluated by administering quality of life and anxiety questionnaires (e.g. PHQ-9 and GAD-7) at follow-up. Other questionnaires that may have yielded useful information including ones that collect data on baseline levels of physical activity and healthy food consumption.

Chapter Four: Bariatric Intervention (Tier 4) on Metabolic Outcomes and Risk of Stratified Cardiovascular Disease

4.1 Summary

Aim: To compare non-fatal CV events and metabolic outcomes between cohorts of insulin-treated T2D patients with obesity, who underwent bariatric surgery, and of propensity-matched non-bariatric ones.

Methods: The Health Improvement Network (THIN) database was utilised to harvest data and details belonging to T2D patients. These data enabled the implementation of a retrospective cohort study that analysed 11,125 active (living) T2D patients. Propensity score matching (up to 1:6 ratio) was used to identify patients who underwent bariatric surgery (N = 131) and those who did not (non-bariatric cohort; N = 579). Follow-up analysis was conducted for 10 years (9,686 person-years), in order to compare differences in metabolic outcomes and CV risk events, including: acute myocardial infarction (AMI), stroke, coronary heart disease (CHD), heart failure (HF) and peripheral artery disease (PAD). Cox proportional regression was used to compute the outcomes between groups.

Results: The patients mean age was 52 (±13) years (60% female); the baseline weight and BMI were 116 (±25) kg and 41 (±9) kg/m^2, respectively. Significant reductions in weight and BMI were observed in bariatric group during the 10 years follow-up period. Furthermore, bariatric surgery had a significant cardio-protective effect, reducing the risk of non-fatal CHD (adjusted hazard ratio [aHR] 0.29, 95%CI: 0.16–0.52, P < 0.001) and PAD events (aHR 0.31, 95%CI: 0.11–0.89, P = 0.03). However, the surgery had no significant effect on AMI (aHR 0.98, P = 0.95), stroke (HR 0.87, P = 0.76) or HF (HR 0.89, P = 0.73) risks. Bariatric surgery had favourable effects on insulin independence, HbA1c and BP.

Conclusion: Bariatric surgery represents a significant contributor for improving health outcome of T2D patients. Specifically, among insulin-treated T2D patients with obesity, bariatric surgery is associated with significant reductions in non-fatal CHD and PAD events, lower body weight, HbA1c, BP and a greater likelihood of insulin independency during the 10 years follow-up period.

4.2 Background and aims

Obesity and T2D represent major global health problems, intrinsically linked with adverse cardiovascular outcomes [110,111]. At present, raised pro-inflammatory state, insulin resistance and endothelial impairments are widely recognised consequences derived from excess dysfunctional adipose tissue, which is directly responsible for the onset of obesity-associated coronary artery disease and of myocardial hypertrophy development [112]. Therefore, it has been demonstrated that CV outcome improvements are augmented by the implementation of a wide variety of weight loss programmes [113]. Although diet and exercise play a crucial role in obesity management, lifestyle alone may not achieve durable weight loss in the majority of patients [114]. Therefore, bariatric surgery has emerged as the most effective and durable strategy for long-term weight loss, in individuals with morbid obesity [115]. Previous studies have shown the beneficial effects of bariatric surgical procedures on cardiovascular outcomes [116-118].

Many patients with T2D will require insulin treatment to manage hyperglycaemia and to reduce the risk of long-term vascular complications [119]. However, insulin therapy is known to induce weight gain in the first year of treatment. Specifically, a significant increase in weight gain is induced following insulin treatment initiation, consequently giving rise to the cardiovascular risk [120]. Furthermore, a randomised controlled trial and observational studies revealed evidence implicating insulin therapy with increased CV risk and mortality in T2D patients [121-124], possibly due to weight gain, recurrent hypoglycaemia and iatrogenic

hyperinsulinemia [125,126]. Thus, a cohort of insulin-treated T2D patients represents a complex, heterogeneous and challenging group of individuals: many display significant comorbidities and high CV disease risk. At present, the bariatric surgery impact has yet to be elucidated on cardiovascular parameters and risks of insulin-treated T2D individuals, during routine clinical care. Therefore, we conducted a retrospective cohort study of PS-matched groups to compare stratified non-fatal CV events and metabolic outcomes among patients with severe obesity and with insulin-treated T2D who underwent bariatric surgery and a non-bariatric control cohort.

4.3 Methods

4.3.1 Study design and data sources

A retrospective cohort study was designed with the utilisation of anonymised and systematically computerised longitudinal primary care health records, extracted from The Health Improvement Network (THIN) database (**Appendix 10.3**). The database comprises details about individuals' demographics, lifestyle characteristics (e.g. alcohol use and smoking), major medical and surgical conditions, drug utilisation, and various health outcomes for over 17 million patients. Among these, 3.1 million individuals are registered as active (alive) patients. Patients' records were extracted from over 600 UK general practices [127]. We chose the dataset slice containing information for active insulin-treated T2D patients up to September 2017.

4.3.2 Ethics

Ethical approval was provided to THIN by the NHS South East Multi-centre Research Ethics Committee (MREC) (**Appendix 10.4**). The Scientific Review Committee (SRC) reviewed the study protocol for scientific merit and feasibility.

4.3.3 Study population

The dataset contained 11,125 adult patients (18 years and older, with no upper age limit) diagnosed with T2D, receiving any form of prescribed insulin therapy, up to September 2017. According to cohort type, the initial study time-point (patient index date) corresponded to bariatric surgery day (for the treated cohort) and to the first day of insulin therapy initiation (for the untreated, or control, cohort). The dataset was scanned to identify patients with no history of insulin use or those diagnosed with type 1 diabetes, for possible exclusion. The study, however, does not exclude patients based on Acceptable Mortality Reporting (AMR) because the exposed (treated) group found within THIN database is low in number.

4.3.4 Exposure and outcomes

This study interest was on bariatric surgical intervention (screened bariatric READ code list is available in **Appendix 4**, **Table 10.4.6**). The surgery represented patient exposure to remedial action. Its effectiveness was monitored during a 10-year long follow-up period, inclusive of the primary outcome and of the study concluding stage. Because of the time scale, this final stage corresponded to the actual end of study for most subjects, but also to unpredicted transfers or demise for some patients. Therefore, patients were censored throughout 10 years of follow-up,

following the development of primary outcome, transferred out, loss to follow-up or at the end of the study. The primary outcome represented patients' survivability against non-fatal CV events. Further stratification included CV events into time sections, as well as occurrence of Acute Myocardial Infarction (AMI), stroke, Coronary Heart Disease (CHD), Heart Failure (HF) and Peripheral Artery Disease (PAD). Specific READ codes from THIN database are available in **Appendix 10.5**.

Secondary outcomes included the likelihood of being off insulin during follow-up, as well as metabolic and health covariates, such as body weight, calculated BMI, HbA1c, total cholesterol and systolic/diastolic blood pressure (screened AHD code list is available in **Appendix 4**).

4.3.5 Covariates and follow-up strategy

We followed-up the treatment group, whom underwent bariatric surgery, comparing it with the PS-matched non-bariatric insulin-initiators group, from their first insulin prescription date up to the endpoint of 10-year of follow-up. Patients were excluded from the primary survival estimation on each stratified CV element, when CV events occurred prior to the designated baseline point.

Control (untreated, or non-bariatric) and bariatric surgery (treated) cohorts were subjected to the same baseline clinical parameters measurements conducted at similar time points. Specifically, bariatric surgery patients had their baseline parameters calculated[7] from 90 days up to one day before the surgery date.

[7] i.e. Average calculation will be taken from patients with more than one observation at a certain time window.

Similarly, non-bariatric patients had their baseline parameters calculated via the same time window, taking into account their first initiation of insulin therapy. Then, covariates were recalculated at 6-month and at each year time-point, for the duration of the 10 years follow-up period, with 90 days window on every concurring point of time[8].

4.3.6 Statistical analysis

The primary analysis was time to the risk (or survivability) of stratified non-fatal CV events (**Appendix 10.6**) on PS-matched groups. The PS model was estimated by using logistic regression model to adjust for baseline characteristics, thus, minimising allocation bias between groups. This PS procedure employed the user written coding (PSMATCH2) developed by Leuven and Sianesi (2003) and updated in February, 2018 [128]. The measurement of standardised differences, occurring before and after procedure, represented the basis for a balance assessment between bariatric (treated) and non-bariatric cohorts. The mean from continuous covariates and proportion of categorical variables were examined and summarised between groups. A maximum of 6 reference, control, individuals were paired to 1 treated patient, by means of implementing the closest match possible for all variables, including estimated PS and based on the likely treatment probabilities [129]. The reason for matching up to 1:6 ratio was made based on the maximum inclusion of control subjects to allow adequate power to compare the outcome of

[8] Patients' with partially missing observations will be included for multiple imputation procedure for feasible predictions.

interest of stratified cardio events. Furthermore, we employed a caliper of width equal to 0.05 of the standard deviation of the PS logit, to minimise distance within matched sets. This may improve match quality, but it would limit excessive number of matched subjects [130]. A caliper of width of 0.20, or lower, has been shown to result in optimal estimation compared to higher choices of caliper use [131]. PS was included in all Cox proportional hazards regression modelling, as it was considered a prognostic covariate.

The stratified log-rank test, with Kaplan-Meier survival curves, was used to compare the equality between the PS-matched groups. Thus, the absolute reduction in the probability of an event occurring within 10-year follow-up was calculated. Additionally, marginal hazard ratios were estimated, enabling the adjusted hazard quantification for an event occurring in the bariatric cohort, compared to the matched non-bariatric group. Proportional hazards assumptions were confirmed through the Schoenfeld residuals test. Point estimates with 95% Confidence Intervals (CIs), at the conventional statistical significance level of 0.05, were used in the regression models. The proportional hazards assumption was examined by comparing cumulative hazard plots grouped on exposure: no violations were observed.

Among covariates, missing data was managed through multiple imputations, using predictive means matching for continuous covariates [132], taking the division of exposure (i.e. bariatric), with accounting for age, gender, diabetes duration, Townsend deprivation status, marital status, smoking and alcohol use. Sensitivity

analysis was necessary to test and validate the multiple imputation approach suitability in resolving the missing data impact. To this end, the primary endpoints were compared with the dataset containing the missing values. These were found to be similar, thereby affirming the robustness of the imputation method employed, before PS-matching procedure was performed [133].

The student's *t* test was used to estimate the mean changes in continuous variables (e.g. body weight and HbA1c) in the PS-matched groups, throughout the 10-year follow-up period, compared to their baseline measurements. The Pearson X^2 was used to test on the likelihood of being off insulin at 5 and 10 years from the baseline. Statistical significance was considered at $P \leq 0.05$. To avoid the probability of type II error, the study was powered to 0.80. Additionally, the matched sample size of 710 was found to detect a true difference of less than 0.1, between the two groups at 5% significance level at baseline. The study fulfilled the STROBE criteria for reporting observational studies [134,135]. Throughout, SAS Software version 9.4 was used in the dataset management (SAS Institute, Cary, NC), the Stata Statistical Software version 15.1 was utilised in all carried analysis (StataCorp., College Station, TX), and the GraphPad/Prism version 8.0 was employed for results visualisation (La Jolla, CA).

4.4 Results

4.4.1 Patients characteristics and total follow-up

The inspection of the THIN databases enabled the identification of 155 patients that underwent bariatric surgery, among a total of 11,125 patients. The PS-

matching procedure allowed each of the 131 chosen bariatric patients[9] to be paired with up to 6 control subjects. This yielded a total number of 710 PS-matched participants. The median treatment duration was 10.07 years (interquartile range (IQR): 6.11–14.31 years). The median follow-up time was 8.42 years (IQR: 2.92–14.58 years), representing a total follow-up period of 9,686 person-years[10].

In the matched cohorts, the overall mean of age was 51.7 (±12.5) years, and 59.6% patients were females. The mean body weight, BMI and HbA1c level were 115.7 (±25.4) kg, 40.7 (±9.2) kg/m^2 and 71.2 (±18.1) mmol/mol, respectively. In both bariatric and non-bariatric groups, baseline characteristics were compared and their standardised differences shown in **Table 4.1**.

[9] The PS procedure has excluded 24 bariatric patients because there were no control individuals (or at least one individual) fit for the pre-established matching conditions.
[10] Person-years in this study was calculated based on CVD events and censoring duration (years).

Table 4.1 *Baseline characteristics.*

Baseline variables	Cohort					
	Full population [N = 11,125]			**Propensity matched [N = 710]**		
	Bariatric [n = 155]	**Non-bariatric** [n = 10,970]	**Std. diff***	**Bariatric** [n = 131]	**Non-bariatric** [n = 579]	**Std. diff†**
Demographics						
Age (years), mean (SD)	50.01 (11.1)	57.71 (13.3)	-0.694	50.74 (11.0)	51.96 (12.8)	-0.110
Gender, no (%)						
Female	89 (57.4)	5068 (46.2)	0.224	73 (55.4)	351 (60.6)	-0.107
Townsend deprivation, %						
Least deprived	14.0	21.7	-0.204	15.7	17.3	-0.044
Less	24.3	20.7	0.086	24.0	18.1	0.145
Average	17.6	21.4	-0.094	16.5	20.2	-0.094
More	20.6	20.9	-0.008	21.5	27.7	-0.144
Most deprived	23.5	15.3	0.209	22.3	16.8	0.14
Type 2 diabetes (yrs) , mean (SD)						
Diabetes duration	14.15 (7.7)	15.12 (8.4)	-0.125	13.97 (7.8)	14.89 (7.6)	-0.117
Insulin duration	7.36 (4.9)	8.01 (5.5)	-0.130	7.3 (4.8)	8.68 (5.5)	-0.287
Clinical parameters, mean (SD)						
Weight (kg)	127.3 (30.3)	90.79 (20.6)	1.204	123.22 (28.3)	114.88 (24.5)	0.294
Height (m)	1.7 (0.1)	1.68 (0.1)	0.201	1.7 (0.1)	1.69 (0.1)	0.102
BMI (kg/m²)	43.87 (10.0)	32.37 (7.5)	1.150	42.77 (9.6)	40.6 (9.0)	0.226
HbA1c (mmol/mol)	72.34 (19.3)	70.03 (17.2)	0.119	72.41 (18.6)	70.91 (17.9)	0.080
Fasting glucose (mmol/L)	9.83 (4.3)	9.93 (3.9)	-0.023	9.84 (4.3)	9.82 (3.9)	0.004
Blood glucose (mmol/L)	12.22 (8.8)	11.69 (5.3)	0.071	12.04 (9.1)	11.92 (5.3)	0.016
SBP (mmHg)	134.64 (14.6)	138.89 (16.5)	-0.271	135.06 (14.5)	136.4 (16.0)	-0.088
DBP (mmHg)	78.66 (8.4)	78.94 (9.6)	-0.031	79.3 (8.5)	78.77 (9.3)	0.058
Albumin (g/dL)	3.96 (0.4)	4.15 (0.5)	-0.368	3.96 (0.4)	3.96 (0.4)	-0.005
Alkaline Phosphatase (IU/L)	98.31 (47.1)	91.62 (43.0)	0.146	98.79 (48.8)	96.88 (51.5)	0.038
Serum creatinine (µmol/L)	91.74 (78.4)	92.68 (52.6)	-0.014	92.29 (84.0)	88.17 (57.7)	0.056
C-reactive protein (mg/L)	10.02 (11.4)	14.23 (25.9)	-0.208	10.15 (11.7)	10.07 (16.3)	0.006
Globulin serum (g/L)	30.98 (5.4)	29.93 (4.6)	0.206	30.87 (5.3)	30.73 (4.8)	0.027
Packed Cell Volume (L/L)	0.39 (0.04)	0.4 (0.05)	-0.142	0.39 (0.04)	0.39 (0.06)	0.003
Platelets count (10^9/L)	252.88 (99.4)	233.21 (101.2)	0.197	250.29 (100.3)	243.03 (111.5)	0.069
Triglyceride (mmol/L)	2.33 (1.5)	2.03 (1.3)	0.2	2.34 (1.6)	2.26 (1.4)	0.049
Total cholesterol (mmol/L)	4.47 (1.2)	4.49 (1.1)	-0.019	4.52 (1.2)	4.52 (1.2)	0.002
Low density lipoprotein (mmol/L)	2.39 (0.9)	2.39 (0.9)	0.001	2.39 (0.9)	2.44 (1.0)	-0.05
High density lipoprotein (mmol/L)	1.07 (0.3)	1.22 (0.4)	-0.439	1.07 (0.3)	1.1 (0.3)	-0.091
Alcohol status, %						
Unknown	3.7	3.1	0.03	3.3	3.0	0.017
Ex-drinker	11.8	7.0	0.162	11.6	11.5	0.003

Never	33.1	31.3	0.039	33.1	33.1	-0.002
Current	51.5	58.5	-0.143	52.1	52.4	-0.006
Smoking status, %						
Ex-smoker	33.1	37.1	-0.085	31.4	36.9	-0.116
Never	52.9	49.7	0.064	52.9	52.2	0.015
Current	14.0	13.1	0.025	15.7	10.9	0.141

Diabetes duration is time from first diagnosis of diabetes to date of initiation with insulin drug (index date).
*** Standardised differences are the absolute difference in means or percentages divided by the SD of the treated group. Resulting standardised difference after 1:6 matching based on average treatment effect on treated propensity score technique and robust variance estimation.**
† Mean of standardised difference after matching (0.081), i.e. at 8% difference measured between the matched groups.

4.4.2 Cardiovascular event rates

For non-fatal CHD, the survival probability was significantly different between matched bariatric and non-bariatric groups at 1-year (98.0% vs 89.6%), 5-year (92.2% vs 67.6%) and 10-year (88.2% vs 51.6%) follow-up time-points (log-rank test P < 0.001) (**Figure 4.1c**). A total of 277 (18 vs 259) events were observed, with a crude event rate of 52.4 (21.4 vs 58.2) per 1000 person-years (95%CI: 46.6–58.9). In addition, for non-fatal PAD, the survival probability was significantly different at 5-year (90.5% vs 78.8%) and 10-year (84.0% vs 53.1%) follow-up time-points (log-rank test P = 0.007) (**Figure 4.1e**). A total of 59 (6 vs 53) events were observed, with a crude event rate of 62.1 (25.9 vs 73.8) per 1000 person-year (95%CI: 48.1–80.2). For non-fatal AMI, stroke and HF, the survival probabilities displayed little or no statistical significance of a difference, after comparison between the matched groups throughout the 10 years follow-up period (log-rank test P > 0.5) (**Figure 4.1a**, **4.1b and 4.1d**). **Table 4.2** shows a summary of the events for each of the stratified CV components, with absolute event rates.

Table 4.2 *Non-fatal cardiovascular events, crude incidence rates and hazard ratios of events in the matched groups.*

	Bariatric (N = 131)	***Non-bariatric (N = 579)***
AMI		
No of events/person-years	13/153	95/1084
Absolute rates[a] (95% CI)	84.9 (49.0–146.2)	87.6 (71.6–107.1)
HR[b] (95% CI)	1.03 (0.57–1.86)	1 (reference)
aHR[c] (95% CI)	0.98 (0.54–1.77)	1 (reference)
Stroke		
No of events/person-years	8/137	40/547
Absolute rates (95% CI)	58.2 (29.1–116.4)	73.0 (53.5–99.6)
HR (95% CI)	0.77 (0.34–1.72)	1 (reference)
aHR (95% CI)	0.87 (0.36–2.10)	1 (reference)
CHD		
No of events/person-years	18/840	259/4446
Absolute rates (95% CI)	21.4 (13.5–34.0)	58.2 (51.6–65.8)
HR (95% CI)	0.31 (0.19–0.52)	1 (reference)
aHR (95% CI)	0.29 (0.16–0.52)	1 (reference)
HF		
No of events/person-years	13/205	91/1327
Absolute rates (95% CI)	63 (36.9–109.5)	68.6 (55.8–84.2)
HR (95% CI)	0.81 (0.44–1.49)	1 (reference)
aHR (95% CI)	0.89 (0.47–1.70)	1 (reference)
PAD		
No of events/person-years	6/231	53/718
Absolute rates (95% CI)	25.9 (11.6–57.6)	73.9 (56.4–96.7)
HR (95% CI)	0.27 (0.09–0.74)	1 (reference)
aHR (95% CI)	0.31 (0.11–0.89)	1 (reference)

[a] *Absolute rate at 1000 person-years.*
[b] *HR (unadjusted hazard ratio)*
[c] *aHR (adjusted hazard ration). Adjusted for age, diabetes duration, oral antidiabetic drug use, diuretics use, antihypertensive drug use, Townsend deprivation status, alcohol & smoking status and HbA1c level.*

4.4.3 Risk of cardiovascular disease

By comparing the matched cohorts, analysis of CV stratification elements illustrated how bariatric surgery may exercise a protective effect. In particular, in the bariatric group, the risk of non-fatal CHD and PAD was significantly lower (by 71% and 69%, respectively), compared to the matched non-bariatric group (CHD

aHR: 0.29, 95%CI: 0.16–0.52, P < 0.001; PAD aHR: 0.31, 95%CI: 0.11–0.89, P = 0.03). These findings were adjusted for age, HbA1c level, diabetes duration, oral antidiabetic drug use, diuretics use, antihypertensive drug use, Townsend deprivation status, alcohol use and smoking status. Despite protective tendency of bariatric intervention against non-fatal AMI, stroke and HF, none of which was found with statistical significance (AMI aHR: 0.98, 95%CI: 0.54–1.77, P = 0.94; stroke aHR: 0.87, 95%CI: 0.36–2.10, P = 0.75; HF aHR: 0.89, 95%CI: 0.47–1.70, P = 0.73) (**Table 4.2**).

4.4.4 Changes in metabolic outcomes

During the 10-year follow-up period, it became apparent that the bariatric group experienced significant benefits including the reduction of body weight and BMI, when compared to baseline. This advantage was not observed in non-bariatric patients (see **Table 4.1** for baseline measurements). In particular, for bariatric vs non-bariatric patients, body weight and BMI observations were: at 1-year follow-up time-point 97.5±24.2 vs 109.8±18.6 kg, 34.2±9.0 vs 38.8±7.4 kg/m^2, respectively; at 5-year follow-up time-point 98.9±23.3 vs 107.1±18.2 kg, 34.8±9.2 vs 37.8±7.3 kg/m^2, respectively; and at 10-year follow-up time-point 94.1±20.1 vs 107.6±17.3 kg, 32.9±7.7 vs 38.0±7.1 kg/m^2, respectively (**Figure 4.2a and 4.2b**).

Furthermore, HbA1c reduction was statistically significant (i.e. P < 0.01), up to 6 years of follow-up. In the bariatric vs non-bariatric groups, HbA1c levels were: at 1-year time-point 60.3±18.2 vs 72.0±17.9 mmol/mol, at 3-year time-point 66.1±16.8 vs 71.3±17.8 mmol/mol, and at 6-year time-point 68.1±16.9 vs

72.8±18.8 mmol/mol. Interestingly, analysed HbA1c levels were not significantly different between control and treated groups after the 7-year follow-up time-point (**Figure 4.2c**). Total cholesterol was found to be significantly reduced during the first six months of follow-up (4.12±0.99 vs 4.50±1.14 mmol/L, P = 0.008) (**Figure 4.2d**).

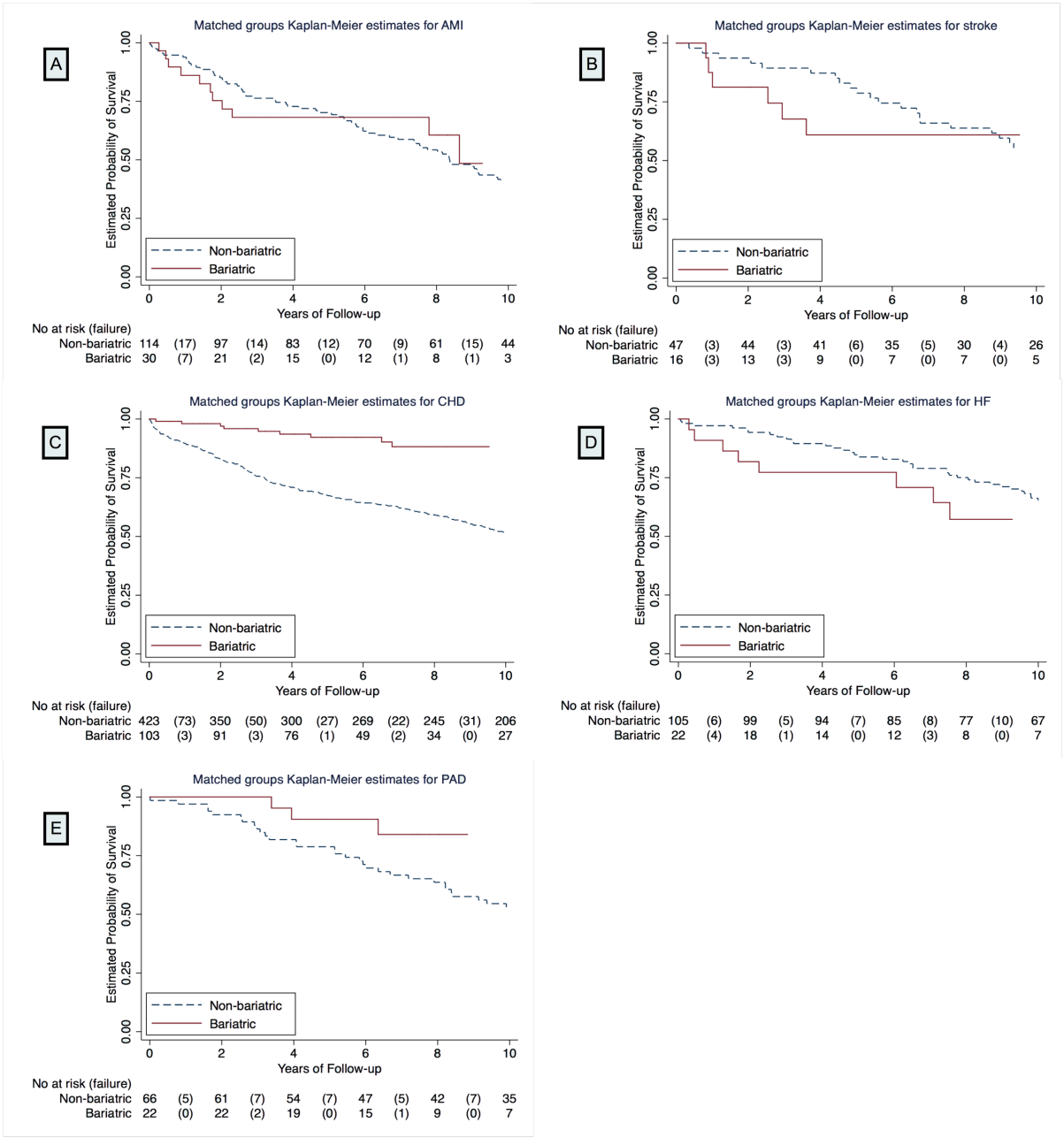

Figure 4.1 Cardiovascular survival plots.
Cardiovascular Kaplan-Meier survival plots for the matched cohort throughout 10 years of follow-up.

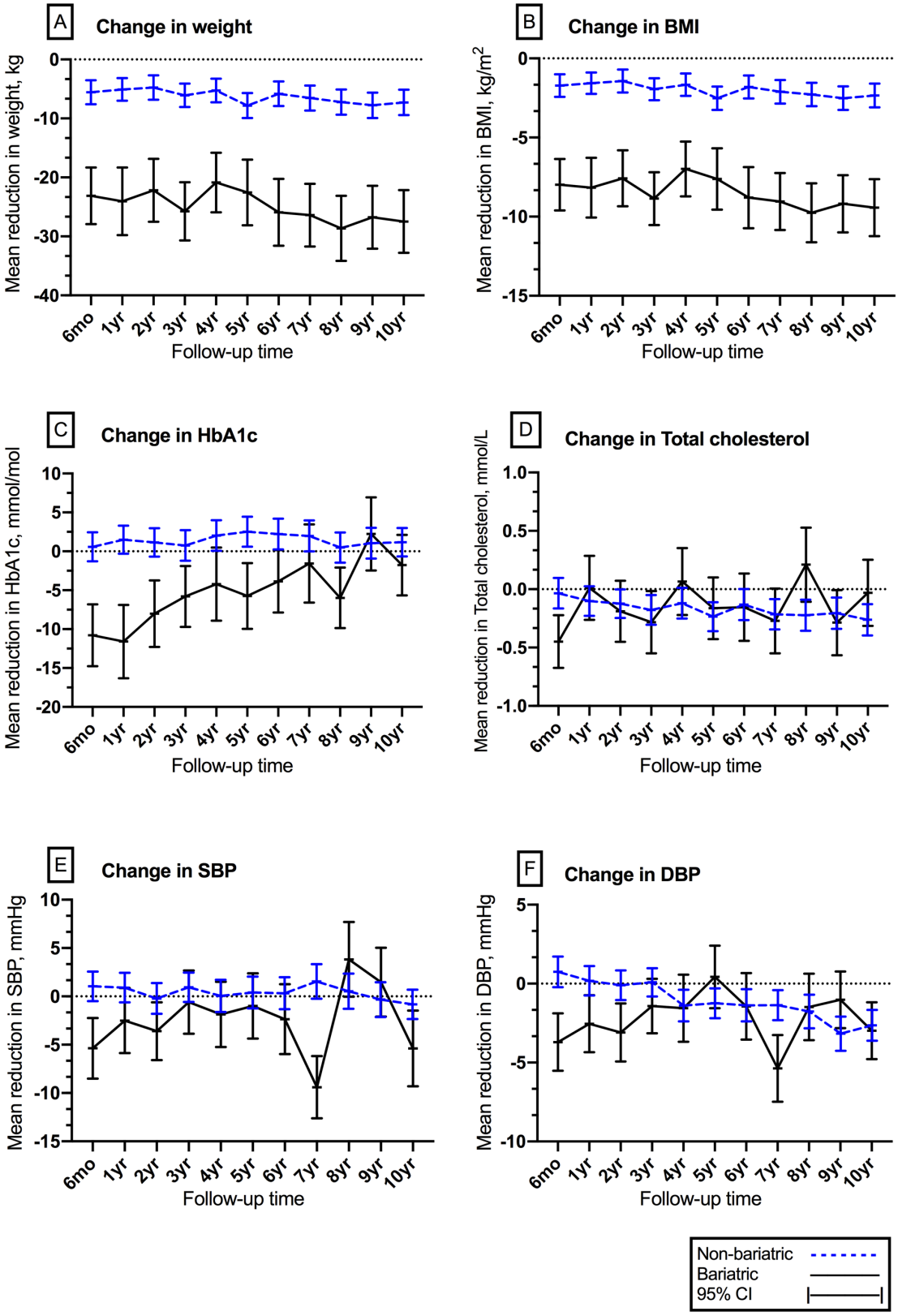

Figure 4.2 Metabolic outcomes from the matched groups.
Mean difference in reduction in weight and health outcome variables between the matched groups throughout 10 years of follow-up compared to baseline.

In addition, bariatric surgery exercised a positive impact on the patients' blood pressure, from the very early stages post-intervention. Specifically, the systolic blood pressure was: at 6-month time-point 130±18 vs 137±16 mmHg, P < 0.001; and at 1-year time-point 133±17 vs 137±15 mmHg, P = 0.07 (**Figure 4.2e**). The diastolic blood pressure displayed a statistically significant reduction in the bariatric vs non-bariatric groups (P < 0.05) up to 2 years of follow-up (6-month: 76±10 vs 79±9; 1-year: 77±9 vs 79±9; 2-year: 76±10 vs 79±10 mmHg) (**Figure 4.2f**). **Figure 4.2** illustrates the analysed outcome variables reduction in the matched cohort, during the 10 years follow-up period, when compared to their baseline measurements, with respective 95% confidence intervals.

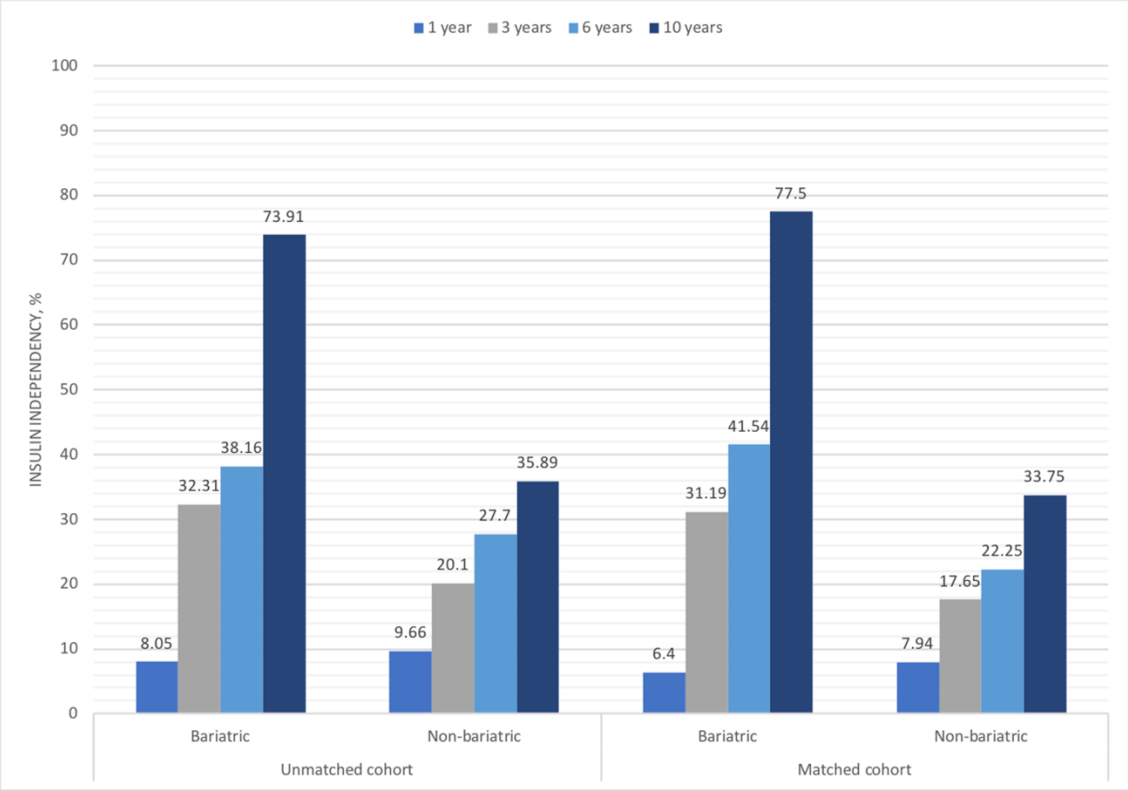

Figure 4.3 Insulin independency.
Proportions (%) of insulin independency in bariatric vs. non-bariatric in both matched and full cohorts.

Analysis of insulin dependency revealed that, following bariatric intervention, 6.4% patients became insulin independent at 1-year follow-up time-point, compared to 7.9% non-bariatric individuals. However, this difference was of little or no statistical significance (X^2=0.35, P = 0.55). Nevertheless, this effect became significant at the 3-year time-point: now, 31.2% bariatric patients became independent from insulin use, compared to 17.6% non-bariatric (X^2=10.59, P = 0.001). At 6-year time-point, 41.5% bariatric patients became independent from insulin use, compared to 22.2% non-bariatric (X^2=11.47, P = 0.001). Finally, at 10-year time-point, 77.5% bariatric patients were independent from using insulin, compared to 33.7% non-bariatric (X^2=28.71, P < 0.0001) (**Figure 4.3**).

4.5 Discussion

Analysing patients' long-term health records can reveal practices that improve both the patient's own health outcomes and the healthcare system. By studying the records of patients stored in the THIN database, this study found an association between bariatric surgery and the reduction in risk of non-fatal CHD and PAD events by 71% and 69% respectively. These same patients with obesity and T2D also demonstrated significant improvements in their body weight, blood pressure, HbA1c level and insulin dependency. However, risk of AMI, stroke and heart failure showed little or no reduction.

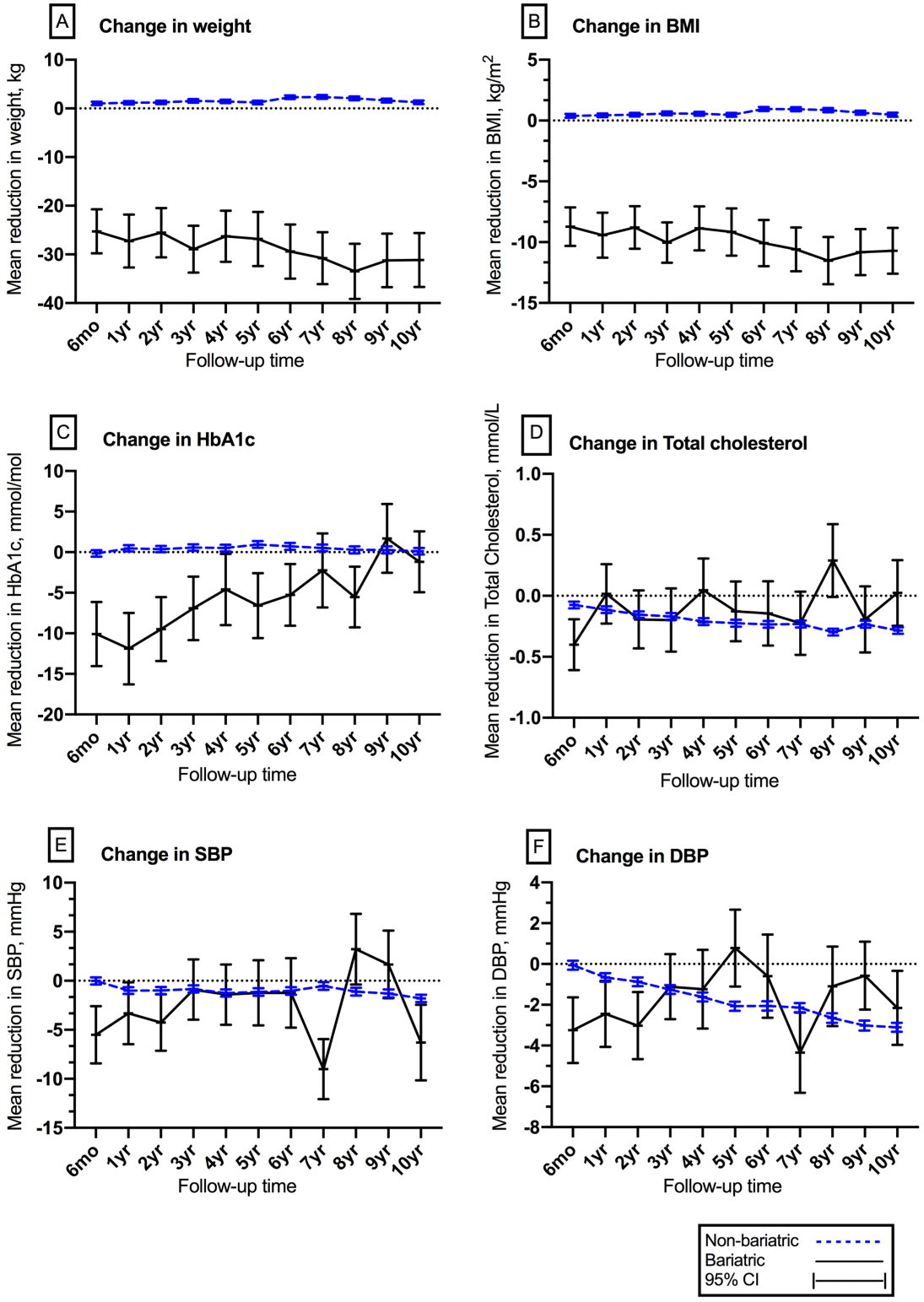

Figure 4.4 Metabolic outcomes from the full cohort.
Mean difference in reduction in weight health outcome variables between the unmatched groups (full cohort) throughout 10 years of follow-up compared to baseline.

Our findings are consistent with published research into the cardiovascular and metabolic benefits of bariatric surgery [116-118]. However, our study differed by focusing on T2D patients who receive insulin treatment, as the risks of cardiovascular events are recognised as being increased in these patients [119,121,122,124]. Even though cardiovascular events and mortality is reduced by bariatric surgery, the post-bariatric surgery risk of death in T2D patients is still 35% greater than the general population [136]. Thus, this study contributes evidence to the cardiovascular benefits of bariatric surgery for this cohort of patients who are likely to have an ongoing elevated risk of CV.

One study notes that although T2D patients had reduced myocardial infarction, the incidence of stroke was unaffected [117]. Yet an analysis of the interactions between factor and treatment indicate that the effect of bariatric surgery upon AMI was greater in those patients with elevated total cholesterol and triglyceride levels, suggesting that the greatest benefits were likely to be achieved by patients with dyslipidaemia. The mean LDL-cholesterol and triglyceride levels of our PS-matched cohort were respectively optimised at 2.4 and 2.3 mmol/L after statin therapy. This highlights the value of statin therapy for this cohort of patients with dyslipidaemia, as well as potentially accounting for the inadequate reduction in AMI. Regardless, PAD events within this patient cohort were significantly reduced. The clinical significance of this novel finding should not be underestimated. After controlling for potential confounders like dyslipidaemia, hyperglycaemia and

hypertension, the conclusion of one recent study is there is a casual association between obesity and PAD [137].

It is well recognised that insulin therapy promotes weight gain [120]. Our study revealed that following bariatric surgery, patients experienced significant reductions in body weight. The study also predicted that patients who had bariatric surgery would lose significantly more weight than control patients do. Interestingly, these reductions were enduring, and still in effect 10 years later. Weight loss was observed in our PS-matched control cohort, which can probably be attributed to the concurrent use of a GLP-1 analogue, an adjunct to insulin treatment; randomised controlled trials support the use of GLP-1 for weight loss [138,139]. Furthermore, our non-PS-matched control cohort did not demonstrate weight loss, indicating the PS-matching protocol used in this study was robust (**Figure 4.4**). Compared to patients who underwent bariatric surgery, fewer patients who received GLP-1 therapy in combination with other weight-loss antidiabetic interventions such as sodium glucose co-tranporter-2 (SGLT-2) inhibitor and restricted calorie intake, became insulin independent in the PS-matched control cohort.

It is noteworthy that unlike the reduction in weight that endured over the 10-year follow-up duration, the statistically significant reduction in HbA1c only persisted for 6 years following surgery. HbA1c levels rose in the intervening follow-up assessments. Other studies that have compared medical/lifestyle interventions and bariatric surgery outcomes found that regardless of the treatment regimen,

T2D patients experienced a decrease in HbA1c for up to 5 years after surgery [140-142]. The conflict between HbA1c and long-term weight outcomes imply that the subsequent increases in HbA1c are not associated with body weight [140]. However enduring the benefits that bariatric surgery confers upon HbA1c and insulin independence and weight might be, they significantly reduce the long-term risk of vascular complications associated with diabetes. This almost certainly translates as long-term financial savings for the NHS.

The relatively large sample size of T2D insulin-treated patients from a real-world population is a major strength of this study, and the results can be generalised to the entire UK or other comparable populations. That is, the results of our study have application in other populations that share a similar demographic profile. The study's statistical power is adequate and the data for other time-varying covariates is sufficient to adjust for possible confounders. Using a robust PS-matching protocol, we adjusted for a large set of factors that may have varied at baseline. This adjustment is important, because the complex decision-making process that underpins the success of bariatric surgery often exceeds NICE guidelines.

In conclusion, this study indicates that the risk of non-fatal CHD and PAD events in insulin-treated T2D patients and with severe obesity is significantly reduced by bariatric surgery. Also, compared to matched controls, bariatric-surgery patients experience significant reductions in BP, HbA1c, insulin dependency and body weight.

4.6 Limitations

Being retrospective, one significant shortcoming of this study is identified with our inability in measuring and adjusting the insulin therapy dosage. This could give rise to some lingering perplexities in the significance of this study. In addition, the reliability of diabetes duration constitutes a confusing factor, due to the ongoing issue of identifying incident versus prevalent diabetes. Furthermore, the classification of exposure into broad bariatric surgery types may have masked the effects of individual bariatric surgery types, potentially driving our study away or closer to the null hypothesis.

Chapter Five: Bariatric Intervention (Tier 4) on Renal Outcomes for Patients with and without Microalbuminuria

5.1 Summary

Aim: To compare the effect of bariatric surgery on renal, cardiovascular and chronic kidney disease (CKD) outcomes among insulin-treated T2D patients with obesity, with or without microalbuminuria.

Methods: A retrospective cohort study was conducted among 11,125 active T2D patients, whose details were extracted from the THIN database. Propensity score matching (up to 1:6 ratio) was used to identify patients who underwent bariatric surgery (N = 131), paired with non-bariatric cohort of individuals (N = 579). In order to measure potentially existing differences in cardiovascular events and renal outcomes risks, a 10-year follow-up period was analysed (6,487 person-years).

Results: For PS-matched cohorts, baseline mean values were as follow: age was 52 (±13) years (60% female), body weight was 116 (±25) kg, BMI was 41 (±9) kg/m^2, estimated glomerular filtration rate (eGFR) was 70.4 (±20) mL/min/1.73m^2, and median albumin-creatinine ratio (uACR) was 2.0 mg/mmol (interquartile range (IQR): 0.9–5.2 mg/mmol). Bariatric surgery was significantly associated with a 54% reduction in developing crude CKD. A protective effect from CKD was induced by bariatric surgery in patients displaying microalbuminuria at baseline (aHR: 0.42, 95%CI: 0.18–0.99, P = 0.050). After comparison with baseline values, eGFR was significantly increased, favouring the bariatric group during 75% of the follow-up time (i.e. $P < 0.05$). However, no significant improvements were observed when analysing composite non-fatal CVD episodes (aHR: 0.36, 95%CI: 0.11–1.13, P = 0.079). Albumin levels were significantly reduced throughout two years following surgery (3.9 vs 4.1 g/dL, $P < 0.001$). Little or no statistical association to the intervention could be found for uACR as well as total protein levels.

Conclusion: Bariatric surgery may protect patients with insulin-treated T2D, with or without microalbuminuria, against CKD risk. Interestingly, composite non-fatal CVD risk was reduced after the procedure, which appeared to exercise a mild protective effect on these individuals. Additionally, bariatric surgery is associated with improvements in overall renal outcomes, including eGFR.

5.2 Background and aims

Glomerular hyperfiltration, followed by microalbuminuria, is an obesity-associated renal function that begins with declining eGFR, and with progressive increases in urinary albumin excretion [143-145]. In obesity, dysfunctional adipose tissue is associated with increased pro-inflammatory state, insulin resistance, hyperglycaemia, endothelial dysfunction and hypertension. These represent known risk factors for the development and progression of cardiovascular disease and chronic kidney disease [112,146]. Furthermore, many T2D patients require insulin treatment to control hyperglycaemia. This is relevant within the context of diabetic kidney disease, since insulin therapy is known to induce 4–9 kg weight gain during the first year of treatment [120]. Obesity per se represents a significant risk factor for the appearance of proteinuria and end-stage renal disease (ESRD) [146].

Moreover, a direct link exists between insulin therapy and an increased cardiovascular risk and mortality in T2D patients, as recently reported following randomised controlled trials, and epidemiological and observational studies [121,122,124,126]. Thus, a cohort of insulin-treated T2D patients represents a complex heterogeneous, challenging group of patients, presenting significant comorbidities and high CKD risk. CKD is defined by an estimated GFR of less than 60 mL/min/1.73m^2, or by the presence of increased urinary albumin excretion (microalbuminuria indicated by urine ACR of 3.0–30.0 mg/mmol), or overt proteinuria (uACR > 30.0 mg/mmol). These are independent risk factors for CV and kidney disorders in the general population and in patients with diabetes [147].

Therefore, the significant cardiorenal outcomes amelioration justifies the implementation of an effective weight loss programme, able to achieve significant and lasting results [113]. Although diet and exercise play a crucial role in obesity management, lifestyle alone may not achieve durable weight loss in the majority of patients [114]. Therefore, bariatric surgery has emerged as the most effective and durable strategy for long-term weight loss in individuals with morbid obesity [115].

Despite its clear benefits on body weight and glycaemic outcomes in T2D individuals, bariatric surgery impact is less clear when considering the development and progression of CKD or microalbuminuria. Previous studies have reported improvements in uACR [148-151], which can be observed not long after surgery [149,150]. This is thought to be driven by multi-factorial improvements in blood pressure, HbA1c and BMI [149]. A further study concluded that bariatric surgery should be offered as early treatment to patients with microalbuminuria, or with overt proteinuria, to prevent CKD from progressing to an end-stage kidney disease [152]. However, many of these studies were small case series, not specific to individuals with insulin-treated diabetes, had variable albuminuric state at baseline, or did not adjust for important confounders. Likewise, a systematic review illustrated incosistent results, when assessing renal outcomes following bariatric surgery [153]. Additionally, a number of studies noted harmful effects on kidneys on patients with obesity who received bariatric intervention. For example, there may be an increased risk of kidney stone formation after malabsorptive

bariatric surgery, which is considered to be linked with surgery-induced fat malabsorption [34]. Furthermore, despite weight loss benefits, there are negative metabolic outcomes related to bariatric intervention, such as nutritional deficiencies, reduction in lean body mass and bone density loss. These are highly relevant in patients with CKD risk [154].

A retrospective exploration of bariatric surgery outcomes represents the core method of this study, which objective is to ascertain the procedure potential contribution in preventing CKD, in improving renal-cardiovascular performance, and in influencing health and renal outcomes in patients with and without microalbuminuria (i.e. uACR > 3.0 mg/mmol).

5.3 Methods

5.3.1 Study Design and Data Sources

This is a retrospective cohort study, conducted on the same data source slice selected for the cardio-metabolic study in **Chapter 4** (see **Subsection 4.3.1**).

5.3.2 Ethics

Ethical approval was provided to THIN by the NHS South East Multi-centre Research Ethics Committee (MREC). The Scientific Review Committee (SRC) reviewed this study's protocol for scientific merit and feasibility.

5.3.3 Study population

This study was conducted analysing the same population selected from the THIN database, as described in the **Chapter 4** (see **Subsection 4.3.3**).

5.3.4 Exposure and outcomes

Our exposure of interest is bariatric surgical intervention for insulin-treated T2D patients and with severe obesity. The surgery represented patient exposure to remedial action. Its effectiveness was monitored during a 10-year long follow-up period, inclusive of the primary outcome and of the study concluding stage. Because of the time scale, this final stage corresponded to the actual end of study for most subjects, but also to unpredicted transfers or demise for some patients.

Primary outcomes represented patients' survivability against diagnosed CKD events, with further stratification to include CKD and composite CVD events, from a selected population with microalbuminuria (uACR > 3 mg/mmol) at baseline. The risk of CKD was measured according to observed CKD data, reported with specific dates in the main THIN database (screened READ code list is available in **Table 10.4.7**, **Appendix 4**). Additionally, the THIN database contained information on CKD events, assessed and reported by healthcare professionals following specific NHS good medical practice guidelines related to the illness (eGFR < 60 or ACR > 3.5), implemented across all primary care establishments.

The composite CVD events included the first occurrence of either acute myocardial infarction, stroke, coronary heart disease, heart failure or peripheral artery

disease. Observations of CVD events were obtained in a similar manner as with events of CKD reporting system, prearranged and precisely coded by THIN.

Secondary outcomes included likelihood of improvement in eGFR, as well as in health covariates, including levels of uACR, total protein, and albumin and serum creatinine.

5.3.5 Covariates and Follow-up Strategy

The treatment group comprised individuals undergoing bariatric surgery and being insulin-treated T2D from the date of surgery. They were followed up and compared with their PS-matched insulin initiators, from their first insulin prescription date up to the endpoint of the 10-year follow-up period.

Patients with diagnosed CKD, or with CVD events occurred prior to the designated baseline point, were excluded from the primary survival estimation on each stratified element. Depending on the treatment category, all clinical parameters measurements were harvested at similar time-point analysis for creating the study baseline reference. For instance, patients who underwent bariatric surgery will have their baseline parameters calculated for 90 days, up to 1 day before the surgery date. Similarly, the non-bariatric patients will have their baseline parameters calculated during the same time window, prior to their first initiation of insulin therapy. Covariates were recalculated at 6 months and at each year time-point during follow-up, with a 90-day window on every concurring point of time.

5.3.6 Statistical Analysis

Similar to the analysis procedure used in **Chapter 4**, the primary investigation considered time-dependent occurrence linked to the risk of crude CKD events and of stratified (according to microalbuminuria basis) CKD and CVD events in the PS-matched groups. The PS model was estimated by using a logistic regression approach, in order to adjust for baseline characteristics, thus, minimising allocation bias between groups. The balance assessment was made between bariatric (treated) and non-bariatric (untreated) groups by measuring standardised differences before and after the matching procedures. The mean from continuous covariates and proportion of categorical variables between groups were examined and summarised. A maximum of 6 reference, control, individuals were paired to 1 treated patient, by means of implementing the closest match possible for all variables, including estimated PS and based on the estimated treatment probabilities [129].

The technicality of PS matching, managing missing data and related analyses, utilised in this study, are fully outlined in **Chapter 4** (see **Subsection 4.3.5**). A sensitivity analysis was included in this study. Its necessity stemmed from the need to fill gaps from missing data, to assess their impact and to validate our multiple inputting adequacy. To this end, in the inputted (or predicted) renal outcomes within the dataset, the primary endpoints were compared with the dataset with missing values. These were found to be similar up to two years of follow-up. Hence,

a decision was made to limit the renal outcome covariates to this point of reliable predictions.

Student's *t* test was used to estimate the mean changes in continuous variables (e.g. uACR and total protein) in the PS-matched group for 2 years of follow-up, compared to their baseline measurements. We limited these variables to 2 years because of the significant amount of missing data beyond this point. This shortcoming restricted multiple imputation from producing reliable predictions. Nonetheless, eGFR was at a predictable level up to 5 years, enabling the employment of Pearson X2 to test the likelihood of improvement occurrence throughout 5 years, when compared to the baseline. Wilcoxon rank-sum test was used to check differences in medians for nonparametric variables (i.e. uACR). Statistical significance was considered at $P \leq 0.05$. To avoid the probability of type II error, the study was powered to 0.86. The matched sample size of 710 was found to detect a true difference of less than 0.1, between the two groups at 5% significance level. The study fulfilled the STROBE criteria for reporting observational studies [134,135].

Throughout, SAS Software version 9.4 was used in the initial dataset management (SAS Institute, Cary, NC), Stata/SE Statistical Software version 15.1 was utilised in all carried analysis (StataCorp., College Station, TX), and GraphPad/Prism version 8.1.0 was employed for results visualisation (La Jolla, CA).

5.4 Results

5.4.1 Patients' Characteristics and Total Follow-up

From a total population of 11,125 patients with insulin-treated T2D in THIN database, we identified 155 patients who have had bariatric surgical operations. The PS matching procedure has allowed 131 bariatric patients to be matched with up to six control subjects 579. This yielded a total number of (N = 710) PS-matched participants. The median treatment duration was 10.07 years (interquartile range (IQR): 6.11–14.31 years). The median follow-up was 12.8 years (IQR: 5.1–14.5 years) for the matched cohort, representing a total follow-up period of 6,487 person-years[11]. The mean age for the matched groups at baseline was 51.7 (±12.5) years; 59.6% were females. The mean body weight, BMI and HbA1c level were 115.7 (±25.4) kg, 40.7 (±9.2) kg/m^2 and 71.2 (±18.1) mmol/mol, respectively. The mean eGFR was 70.4 (±20.5) mL/min/1.73m^2, with a median uACR of 2.0 (IQR: 0.9–5.2) mg/mmol. The baseline characteristics in both bariatric and non-bariatric groups were compared between the full and matched cohort with respective standardised differences and are shown in **Table 4.1**.

5.4.2 Probability of survival and event rates

The probability of survival for CKD in the full cohort was significantly different between bariatric and non-bariatric groups: at 1 year (99.2% vs 97.7%), 5 years (96.9% vs 89.9%) and 10 years (94.9% vs 80.2%) of follow-up (log-rank test P value: 0.028). However, the estimates of CKD event rate in the unadjusted PS matched

[11] Person-years in this study was calculated based on CKD events and censoring duration (years).

cohort showed little or no statistical significance of a difference throughout 10 years of follow-up (log-rank test P value: 0.19). A total of 119 CKD events were observed (16 vs 103) with a crude event rate of 18.3 (14.5 vs 19.1) per 1000 person-years (95%CI: 15.3–21.9).

The difference in probability of survival for CKD in patients with microalbuminuria was statistically insignificant in both full and matched cohorts (log-rank test P values: 0.14; and 0.24, respectively). In the matched group, a total of 51 CKD events were observed (8 vs 43) with a crude event rate of 22.2 (14.3 vs 25.4) per 1000 person-years (95%CI: 17.2–29.8).

The difference in probability of survival for composite CVD in patients with microalbuminuria was statistically insignificant in both full and matched cohorts (log-rank test P values: 0.28; and 0.54, respectively). In the matched group, a total of 43 CVD events were observed (10 vs 33) with a crude event rate of 55.0 (49.5 vs 56.9) per 1000 person-years (95%CI: 40.8–74.2). **Figure 5.1** and **Table 5.1** summarise the observed events, event rates and differences in the probability of survival.

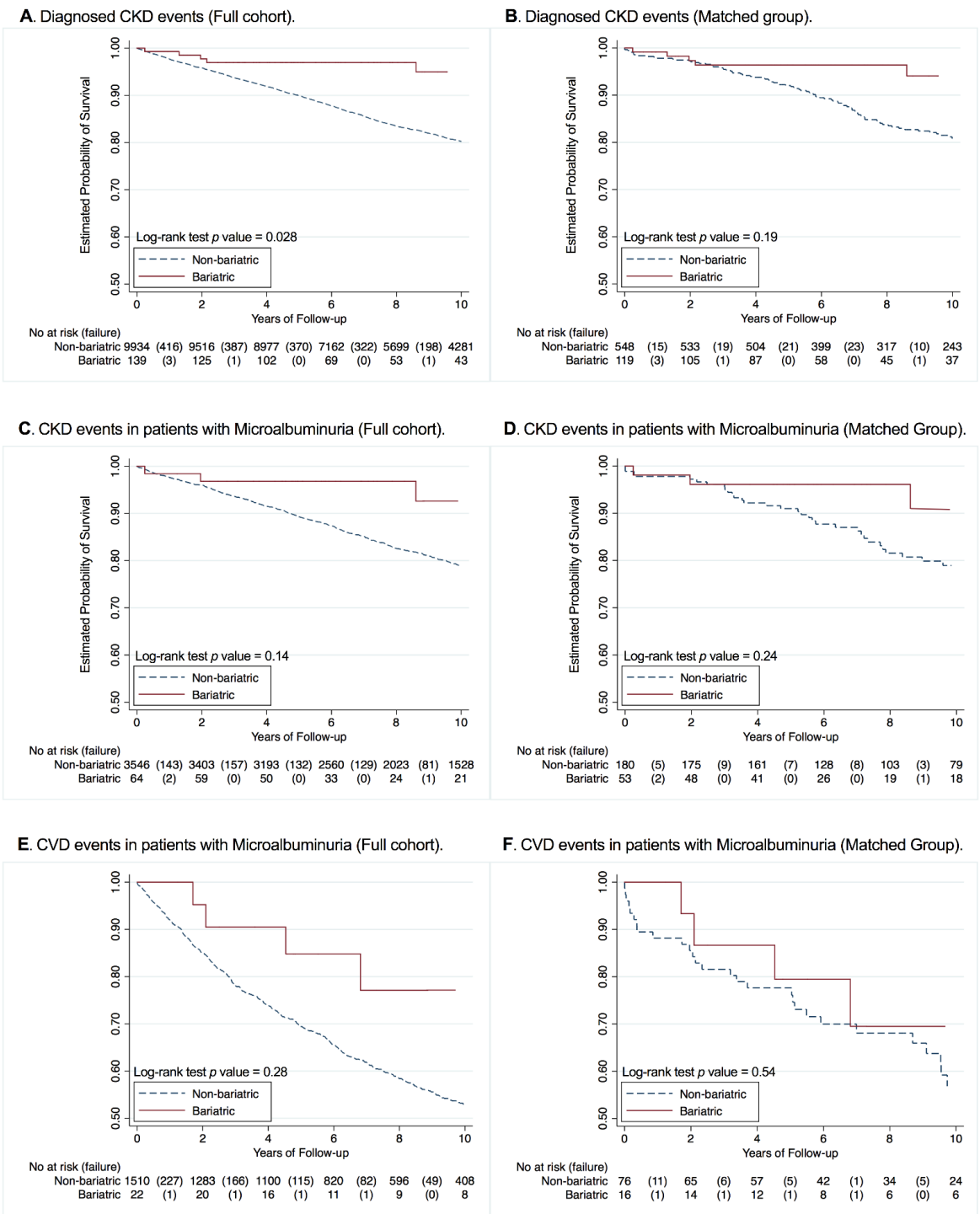

Figure 5.1 CKD survival plots.

Bariatric vs. non-bariatric Kaplan-Meier survival plots for diagnosed CKD events in (A) Full and (B) matched cohorts, diagnosed CKD events in patients with microalbuminuria (i.e. uACR > 3 mg/mmol) at baseline in (C) full and (D) matched cohorts, and composite CVD events in patients with microalbuminuria at baseline in both (E) full and (F) matched cohorts throughout 10 years of follow-up.

5.4.3 Risk of CKD

Bariatric surgery showed remarkable protective effect against crude CKD in the full cohort and in the adjusted matched group. In the full cohort, patients whom had been treated with bariatric surgery had 47% lower risk to develop CKD compared to non-bariatric patients (aHR: 0.53, 95%CI: 0.30–0.91, P = 0.021). Similarly, the matched cohort showed a statistical significance of a magnitude favouring the bariatric group with a protective effect of 54% against crude CKD risk (aHR: 0.46, 95%CI: 0.24–0.85, P = 0.013). **Table 5.1a** shows a summary of adjusted and unadjusted hazard ratios in the crude CKD risk for matched and unmatched patient groups.

5.4.4 Risk of CKD in Patients with Microalbuminuria

Despite a protective tendency against CKD, patients with microalbuminuria at baseline have little or no statistical evidence of a similar protective effect in the full cohort (aHR: 0.71, 95%CI: 0.33–1.5, P = 0.38). However, the estimates imply a protective influence against CKD favouring the bariatric group in the matched cohort (aHR: 0.42, 95%CI: 0.18–0.99, P = 0.050). The adjustments made for this model have only omitted 13.2% of observed events. **Table 5.1b** shows a summary of adjusted and unadjusted hazard ratios in CKD risk for patients with microalbuminuria at baseline.

Table 5.1 *Survival results against CKD and CVD events.*
Survivability of patients against (A) crude CKD events, (B) CKD events in patients with microalbuminuria at baseline as well as (C) composite CVD events and their respective crude incidence rates and hazard ratios of events in the full cohort and in the matched group.

Survival Analysis	*Bariatric*	*Non-bariatric*
A. Crude CKD events		
Full cohort, n	139	9,934
Events/person-years, n	16/1,283	2,032/96,843
Absolute rates[a] (95% CI)	12.5 (7.6–20.3)	20.9 (20.1–21.9)
HR[b] (95% CI)	0.56 (0.33–0.95)[†]	1 (reference)
aHR[c] (95% CI)	0.53 (0.30–0.91)[†]	1 (reference)
Matched cohort, n	119	548
Events/person-years, n	16/1,102	103/5,385
Absolute rates (95% CI)	14.5 (8.9–23.7)	19.1 (15.8–23.2)
HR (95% CI)	0.67 (0.37–1.22)	1 (reference)
aHR[d] (95% CI)	0.46 (0.24–0.85)[†]	1 (reference)
B. CKD in patients with microalbuminuria		
Full cohort, n	64	3,546
Events/person-years, n	8/650	775/34,517
Absolute rates (95% CI)	12.3 (6.1–24.6)	22.4 (20.9–24.1)
HR (95% CI)	0.59 (0.29–1.20)	1 (reference)
aHR (95% CI)	0.71 (0.33–1.5)	1 (reference)
Matched cohort, n	53	180
Events/person-years, n	8/558	43/1,694
Absolute rates (95% CI)	14.3 (7.2–28.7)	25.4 (18.8–34.2)
HR (95% CI)	0.62 (0.28–1.39)	1 (reference)
aHR (95% CI)	0.42 (0.18–0.99)[†]	1 (reference)
C. CVD in patients with microalbuminuria		
Full cohort, n	22	1,510
Events/person-years, n	10/258	710/11,304
Absolute rates (95% CI)	38.7 (20.8–72.0)	62.8 (58.3–67.6)
HR (95% CI)	0.70 (0.37–1.34)	1 (reference)
aHR (95% CI)	0.30 (0.09–0.96)[†]	1 (reference)
Matched cohort, n	16	76
Events/person-years, n	10/202	33/580
Absolute rates (95% CI)	49.6 (26.7–92.2)	56.9 (40.5–80.0)
HR (95% CI)	0.77 (0.34–1.75)	1 (reference)
aHR (95% CI)	0.36 (0.11–1.13)	1 (reference)

[a] Absolute rate at 1000 person-years.
[b] HR (unadjusted hazard ratio).
[c] aHR (adjusted hazard ration). Adjusted for age, diabetes duration, duration of antihypertensive drug use, diuretics use, antidiabetic drug use (i.e. Premix) and deprivation (Townsend) status.
[d] Adjusted for age, diabetes duration and insulin drug use.
[†] P < 0.05 (probability reference).

5.4.5 Risk of CVD in Patients with Microalbuminuria

In the full cohort, patients with microalbuminuria, who had been treated with bariatric surgery, had a 70% lower risk in developing CVD (aHR: 0.30, 95%CI: 0.18–0.96, P = 0.043). The added adjustments for this model have omitted 37.1% out from the unadjusted model. However, the same adjustments helped to reveal evidence of little or no statistical effect of such protection against composite CVD in the matched cohort (aHR: 0.36, 95%CI: 0.11–1.13, P = 0.079). **Table 5.1c** shows a summary of adjusted and unadjusted hazard ratios in composite CVD risk for patients with microalbuminuria.

5.4.6 Change in Secondary Outcome Variables

Significant reductions in the matched cohort (i.e. P < 0.001) favouring the bariatric group vs non-bariatric were observed in terms of body weight and BMI throughout 5 years of follow-up time compared to baseline. Body weight and BMI for bariatric vs non-bariatric were at 1-year point (97.5 [±24.2] vs 109.8 [±18.6] kg; 34.2 [±9.0] vs 38.8 [±7.4] kg/m^2, respectively), at 3-year point (95.7 [±19.4] vs 108.8 [±18.4] kg; 33.5 [±7.4] vs 38.3 [±7.2] kg/m^2, respectively) and at 5-year point (98.9 [±23.3] vs 107.1 [±18.2] kg; 34.8 [±9.2] vs 37.8 [±7.3] kg/m^2, respectively).

The nonparametric analysis for the uACR medians revealed little or no statistical significance of a difference between bariatric and non-bariatric groups in both matched and full cohorts. In the full cohort, the median uACR in bariatric group at baseline was 2.0 vs 1.91 mg/mmol in non-bariatric (Z = −1.28, P = 0.19), at 1-year point 2.33 vs 1.90 mg/mmol (Z = −1.86, P = 0.06), and at 2-year point 2.42 vs 2.06

mg/mmol (Z = −0.87, P = 0.38), respectively. In the matched cohort, the median uACR in the bariatric group at baseline was 2.03 vs 1.90 mg/mmol in the non-bariatric group (Z = −1.75, P = 0.08), at 1-year point 2.31 vs 1.95 mg/mmol (Z = −1.36, P = 0.17) and at 2-year point 2.42 vs 2.02 mg/mmol (Z = −0.67, P = 0.50), respectively.

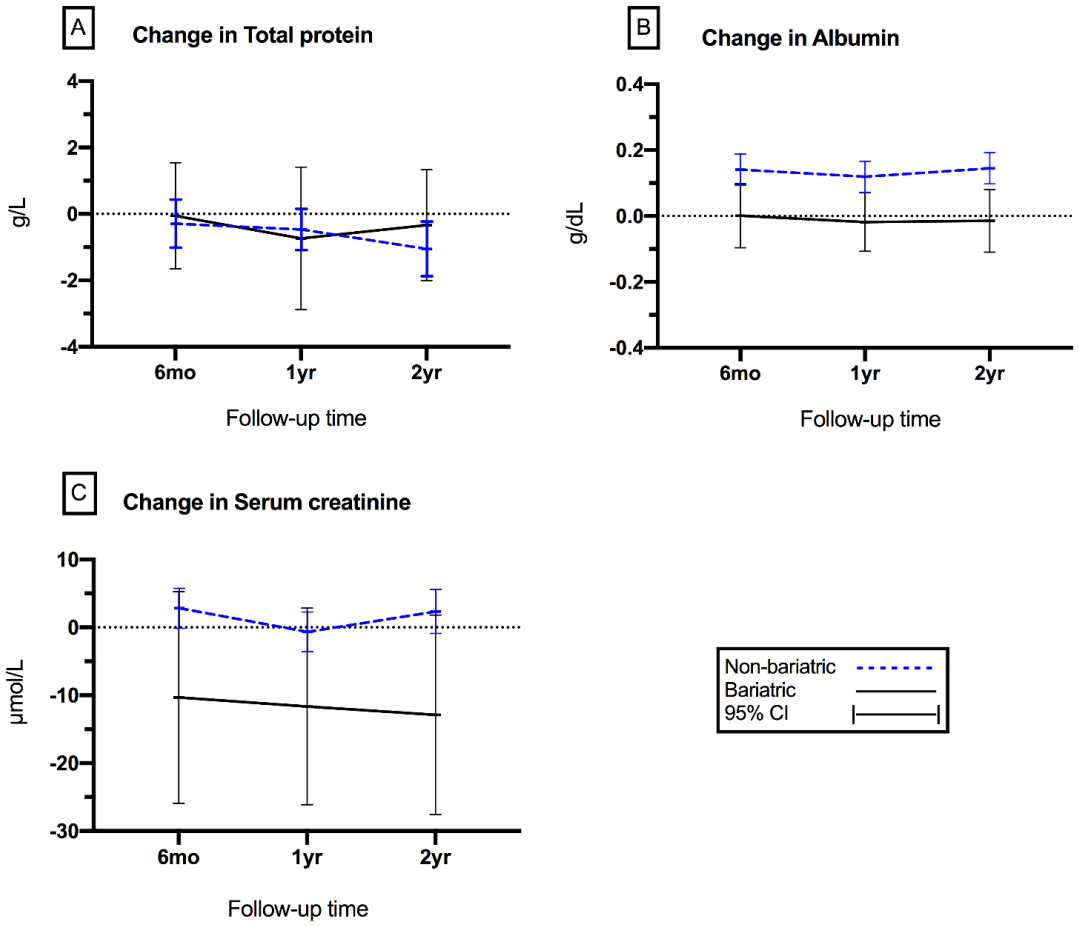

Figure 5.2 Renal outcomes.
Mean change in (A) Total protein (g/L), (B) Albumin (g/dL), and (C) Serum creatinine (µmol/L) in the matched groups, bariatric vs non-bariatric, compared to baseline.

There have been significant improvements in eGFR throughout 5 years of follow-up favouring the bariatric group in both full and matched cohorts. In the matched cohort, the eGFR was at similar levels at baseline with a mean of 68.7 in bariatric

patients vs 70.8 mL/min/1.73m^2 in non-bariatric (t_{708} = 1.05, P = 0.29). Mean eGFR for the bariatric compared with non-bariatric group were 72.4 vs 68.4 mL/min/1.73m^2 (t_{708} = −2.07, P = 0.038) at 1 year and 71.4 vs 68.4 mL/min/1.73m^2 (t_{708} = −1.48, P = 0.13) at 3 years. However, during the fourth and fifth years of follow-up, the analysis of mean differences reported statistical significance favouring the bariatric group versus non-bariatric with 72.9 vs 66.8 mL/min/1.73m^2 at 4 years point (t_{708} = −3.14, P = 0.001) and with 74.2 vs 67.8 mL/min/1.73m^2 at 5 years point, respectively. **Figure 5.3** illustrates proportions of both bariatric and non-bariatric patients with eGFR ≥ 60 mL/min/1.73m^2 throughout 5 years of follow-up.

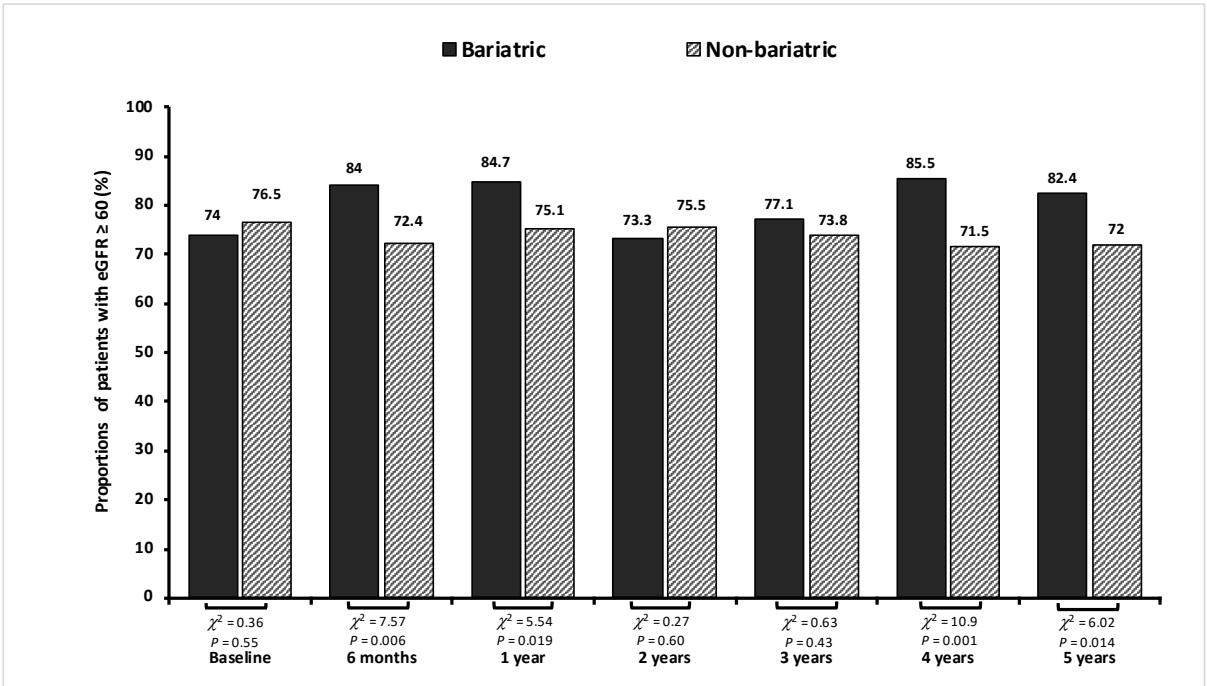

Figure 5.3 eGFR proportions.
Proportions of patients (%) in the matched cohort with eGFR ≥ 60 (mL/min/1.73 m^2) throughout 5 years of follow-up.

The serum creatinine was also significantly reduced in the bariatric group compared to their PS-matched non-bariatric counterparts during the 2 years of follow-up—following the baseline point. Both groups were at similar levels of serum creatinine at baseline with a mean of 90.1 (±84.1) µmol/L in bariatric vs 88.4 (±57.7) µmol/L non-bariatric (t_{708} = −0.27, P = 0.78). Mean creatinine for the bariatric group vs non bariatric was 79.7 vs 91.2 µmol/L (t_{708} = 2.59, P = 0.009) at 6 months, 78.4 vs 86.1 µmol/L (t_{708} = 2.11, P = 0.03) at 1-year point, and 77.2 vs 90.5 µmol/L at 2-year point (t_{708} = 2.65, P = 0.008) (**Figure 5.2c** shows differences in serum creatinine compared to baseline observations).

In the matched cohort, the bariatric group had significantly lower albumin levels compared to non-bariatric throughout 2 years of follow-up. The total protein level showed a slight clinical change with a statistical significance of a difference at 1-year point, but with no difference detected in the remaining points of follow-up time. **Figure 5.2** shows mean differences between the matched groups while reflecting back to baseline observations for (a) total protein and (b) blood albumin.

5.5 Discussion

This study analysed insulin-treated T2D patients with severe obesity. The obtained results established a direct contribution exercised by bariatric surgery intervention in promoting a CKD protection effect in these patients. In addition, it observed improvements occurring in overall patients' renal outcomes, benefitting individuals with or without microalbuminuria at baseline. Despite the matched cohort showing little or no statistically significant difference in the protective

action against the risk of composite non-fatal CVD, following surgery, estimates suggest a positive influence with lower event rates favouring the bariatric group. Furthermore, full cohort survival analysis indicated a profound effect protecting those microalbuminuria patients, who had received bariatric intervention treatment, when investigating composite non-fatal CVD events. Additionally, an overall eGFR levels improvement was noted within the bariatric matched group throughout 5 years of follow-up (**Figure 5.3**).

This study took advantage of a novel procedure, which has not been previously employed, as demonstrated by reviewing published research [155,156]. This novel approach included an indirect assessment of time-to-event according to the baseline patients' renal status. This timely phase involved the allocation of full and the PS-matched cohorts into further stratifications, leading to proper follow-up for survival investigation. With this approach, bariatric surgical intervention provided additional evidence for a protective effect benefiting T2D patients, with or without detected microalbuminuria at baseline.

Obesity is associated with glomerular hyperfiltration. Therefore, increased risk of microalbuminuria and/or proteinuria exists in patients with obesity, with or without renal disease [144,157]. A direct connection had been previously shown to exist between bariatric surgery and glomerular hyperfiltration decrease. In these studies, this effect appeared within the first year post-surgery and was linked with the most significant weight loss outcome [158,159]. The link between fat mass and glomerular hyperfiltration is multifactorial. However, it is in part due to

increase in angiotensin II levels, which enhances tubular sodium reabsorption and activates tubulo-glomerular feedback [160]. These occurrences lead to vasodilation of the afferent arterioles, with a consequent increase in renal blood flow, intraglomerular pressure and eGFR [159]. However, while a decreased glomerular hyperfiltration may induce reductions in microalbuminuria and proteinuria levels, eGFR is expected to diminish [161]. At present, limited knowledge is available, concerning the longer-term effect of bariatric surgery on eGFR and CKD outcomes in insulin-treated T2D patients. Therefore, this patient cohort became the natural protagonist for the present study analysis, particularly, after taking into account their significant adverse cardiorenal outcome risks [121,122,126] and the insulin treatment negative impact on weight gain, which is an established predictor of renal problems occurrence [120]. In addition, patients with diabetes are associated with accelerated loss of lean muscle mass [162]. Interestingly, bariatric surgery is associated with further loss of skeletal muscle mass and function [163]. Since markers of both muscle mass and strength represent important outcomes predictors in CKD patients [164], this study findings contribute to reassure on the protective effects of bariatric surgery against CKD progression. In a recent study, for instance, less than 10% progressed to CKD within seven years of post-bariatric intervention and five (out of 2,144) patients developed ESRD during the follow-up period as they were included in a very high-risk category [165].

The main strength of this study lays in the inclusion of a relatively large cohort of T2D patients, receiving insulin therapy, who underwent bariatric surgery in a real-world population. In addition, our database is largely representative of the UK population. Therefore, this chapter findings can be transposed to a variety of populations that share similar demographics with the UK. The relatively large patients' cohort provides adequate statistical power and contains information on other time-varying covariates, useful to adjust for potential confounders. We adjusted for a set of factors that would likely to differ at baseline.

Lastly, we should mention that this study discovered that bariatric surgery induced a limited, but detectable, protection on composite non-fatal CVD risk, notwithstanding its main significant advantageous effect against risk of developing CKD on patients with severe obesity and with T2D, with or without microalbuminuria. Therefore, bariatric surgery helps overall improvement in renal outcomes, such as eGFR.

5.6 Limitations

Similarly to the explanation given in **Chapter 4** (**Subsections 4.6**), some residual shortcomings may persist in our study. For example, our classification of albuminuria was based on a single measurement. This is in contrast to current recommendations, requiring at least two measurements for its definition. Nevertheless, we believe that a significant amount of predictive information can be ascertained from using a single urinary albumin measurement within a large patient cohort, such as the one analysed in this study. In addition, the effect of

competing hazards may bias estimates of risk, as it is the case with all studies assessing CV or ESRD risks associated with eGFR and albuminuria. The reason for this is identified in the elevated uACR and low eGFR being risk factors for non-renal diseases, and in the associated differential mortality in high-risk individuals, which may confound hazard ratio estimates for CV events. Finally, this study did not include an assessment of potential baseline alterations induced by the effect of medications on glycaemic and blood pressure symptoms. Therefore, this study cannot account for any differences that may influence the association between uACR and outcomes. However, a necessity exists for prospective investigation and appropriate investment to verify or examine real-world effects of bariatric surgical intervention on renal function and stability of patients with severe obesity, who are dependent on insulin treatment. It is also important to note that the rapid decline in body weight usually cause a substantial reduction in patients' muscle mass. This reduction influence almost all blood biochemical elements in which such alteration may become a sensible source of bias for CKD evaluation made in this chapter.

Chapter Six: Metabolic and Liver-related Outcomes of Bariatric Surgery (Tier 4) in Patients with High Risk of Liver Disease

6.1 Summary

Aim: To investigate the metabolic and liver-related outcomes of bariatric surgery among patients with insulin-treated T2D and non-alcoholic fatty liver disease (NAFLD) who are at high risk of liver fibrosis.

Methods: The study comprises a retrospective cohort comparison of patients with NAFLD and Fib score > 1.45, who received bariatric intervention vs comparable patients who received no bariatric intervention. Metabolic (HbA1c, body weight, BMI and Fib-4 score) and composite liver-related outcomes (cirrhosis, portal hypertension, liver failure and hepatoma) were compared between groups over a period of five years. The outcomes were adjusted for baseline and time-varying co-variates.

Results: 4,108 patients were included in the study sample, 45 of whom underwent bariatric surgery. The mean age at baseline was 62.4±12.4, 43.8% female, and the mean body weight, BMI, and HbA1c were 89.5 (±20.8) kg, 31.7 (±7.6) kg/m^2 and 68.4 (±16.7) mmol/mol respectively. In addition, the median Fib-4 score was 2.3 (IQR:1.7–4.2). During the five years during which follow-up outcomes were recorded, the body weight and BMI reductions were significantly lowered compared to baseline in the bariatric group. Similarly, the HbA1c levels were lower in the bariatric group, with a statistical significance observed in the first and second post intervention years (bariatric vs non-bariatric at 1-year: 63.1 vs 68.1; P=0.042; and at 2-year: 62.7 vs 68.1, P=0.028). No significant difference (bariatric group 8.9% vs non-bariatric 4.7%) was observed in the Fib-4 scores or the likelihood of developing composite liver disease during the follow-ups between the groups (X^2=1.75, P = 0.18).

Conclusion: Bariatric surgery amongst patients with insulin-treated T2D and who had at high risk of liver fibrosis was associated with significant improvements in metabolic outcomes. No significant adverse effect was observed with regards to liver related outcomes.

6.2 Background and aims

As the obesity epidemic continues to grow, non-alcoholic fatty liver disease (NAFLD) has become the most common cause of chronic liver disease, [166,167] with a prevalence estimated to equate to between 20% and 30% of the general population. NAFLD is a disease spectrum, which starts with fatty liver and steatosis, after which it and progress to steatohepatitis, hepatic inflammation, and cirrhosis, where cumulative liver injury results in liver fibrogenesis associated with portal hypertension, hepatic synthesis dysfunction, liver failure, and the need for liver transplantation [33,168,169].

NAFLD is also considered to be a metabolic disorder that results from complex interactions between genetic, hormonal, and nutritional factors [170]. Up to 85% of patients with NAFLD are with obesity and have been diagnosed with type 2 diabetes (T2D) [166]. Although there are well-recognised associations between NAFLD, insulin resistance, and hyperinsulinemia [166,170], little is known about liver-related outcomes among T2D patients and with obesity who are receiving exogenous insulin treatment [121,171,172].

The implementation of lifestyle and nutritional management, as a means of inducing sustained weight loss, forms the cornerstone of NAFLD treatment. However, the extent to which patients with morbid obesity comply with lifestyle and nutritional guidelines is variable. There is mounting evidence that bariatric surgical intervention is associated with significant improvements in liver histology and the resolution of NAFLD [173,174]. However, there are ongoing concerns and

uncertainties regarding the safety and efficacy of bariatric surgery when performed in patients with more advanced liver disease. This ambiguity is associated with reported incidences of sepsis, portal vein thrombosis, anastomotic leak, bleeding varices, fulminant hepatic failure, and peri- and post-operative mortality following bariatric surgery [175-178]. Furthermore, while findings reveal that liver histology was stable in the first year after surgery, progressive fibrosis has been reported after 5 years and has been independently associated with high body mass index (BMI) and hyperinsulinaemia [179].

This study, therefore, aims to investigate the safety and metabolic results of bariatric surgery in patients with insulin-treated T2D who are at an increased risk of liver fibrosis (Fib-4 score > 1.45) during five years of retrospective follow-up.

6.3 Methods

6.3.1 Study design and data sources

The current study comprises a brief retrospective cohort comparison of bariatric intervention (exposure) on patients experiencing NAFLD (i.e. Fib-4 score > 1.45) at baseline and are with insulin-treated T2D. The sample was grouped according to exposure and retrieved from THIN. This study was conducted on the same data source slice employed in the cardiometabolic study in **Chapter 4** (see **Subsection 4.3.1**).

6.3.2 Ethics

Ethical approval was provided to THIN by the NHS South East Multi-centre Research Ethics Committee (MREC). The Scientific Review Committee (SRC) reviewed this study's protocol for scientific merit and feasibility.

6.3.2 Study population

The dataset contains 11,125 adult patients, aged 18 years and over, who have been diagnosed with T2D and prescribed with some form of insulin therapy. The index date for patients was based on either the day of bariatric surgery or, in the event that they had not received bariatric intervention, the first initiation of insulin therapy. The dataset was scanned to identify and potentially exclude patients with no history of insulin use, with a Fib-4 score less than 1.45, or with a diagnosis of type 1 diabetes.

6.3.3 Exposure and outcomes

Our exposure of interest is bariatric surgical intervention for NAFLD patients with insulin-treated T2D. The metabolic outcomes of interest included in this study comprise body weight, BMI, Fib-4 scores, and HbA1c levels during the five-year retrospective follow-up period. In addition, we examined the variables influencing the likely development of composite liver disease, including encephalopathy, liver failure, bleeding varices, cirrhosis, and hepatoma (screened READ code list is available in **Table 10.4.8**, **Appendix 4**).

6.3.4 Covariates and follow-up strategy

The baseline clinical parameters were measured at a similar point in time according to the treatment categories of patients. For example, patients who underwent bariatric surgery will have their baseline parameters calculated[12] from 90 days up to one day prior to their scheduled surgery. Similarly, non-bariatric patients will have their baseline parameters calculated using the same time window in accordance with their first initiation of insulin therapy. Thus, covariates were recalculated at the six-month stage, and at each year point during follow-up, with a ninety-day window on every concurring point of time up to the five-year follow-up stage.

6.3.5 Statistical analysis

Student's *t* test was used to estimate the mean changes in continuous variables in the treatment group for a five-year follow-up period. The Wilcoxon rank-sum test was employed to test the magnitude of difference between the medians of non-parametric continuous variables (i.e. Fib-4 scores). Pearson's X^2 test was used in proportions between groups regarding liver disease events within the complete follow-up period. The statistical significance was set at a p level of 0.05. Missing data among covariates were managed through multiple imputations using predictive means matching for continuous covariates, taking into account variables such as exposure (i.e. bariatric), age, gender, diabetes duration, Townsend

[12]Average value is calculated for multiple entry records that were found during the 90 days window for the same variable.

deprivation status, marital status, smoking, and alcohol consumption. To test the adequacy of our multiple imputation approach in addressing the impact of any missing data, we conducted a sensitivity analysis wherein the primary endpoints in the imputed dataset were compared with the dataset with missing values. The results were comparable at the follow-up stages. Throughout this process, we used Stata/SE Statistical Software version 16.1 for all carried analysis (StataCorp., College Station, TX) and GraphPad/Prism version 8.4.2 for visualisation (La Jolla, CA).

6.4 Results

6.4.1 Patient characteristics

From a total population of 11,125 patients in the THIN database, we identified and included 4,108 NAFLD patients (i.e. with Fib-4 score >1.45) and with insulin-treated T2D, 45 of whom underwent bariatric surgical intervention. Of the NAFLD patients, 43.8% were female. The mean age at baseline of these patients was 62.4 (±12.4), with their mean body weight, BMI, and HbA1c being 89.5 (±20.8) kg, 31.7 (±7.6) kg/m^2, and 68.4 (±16.7) mmol/mol respectively. The median Fib-4 score at baseline was 2.3 (IQR: 1.7–4.2). Of this NAFLD sample, 14.2% were defined as most deprived, 23.5% as least deprived, and 20.5% towards second, third and fourth quintiles on the deprivation scale.

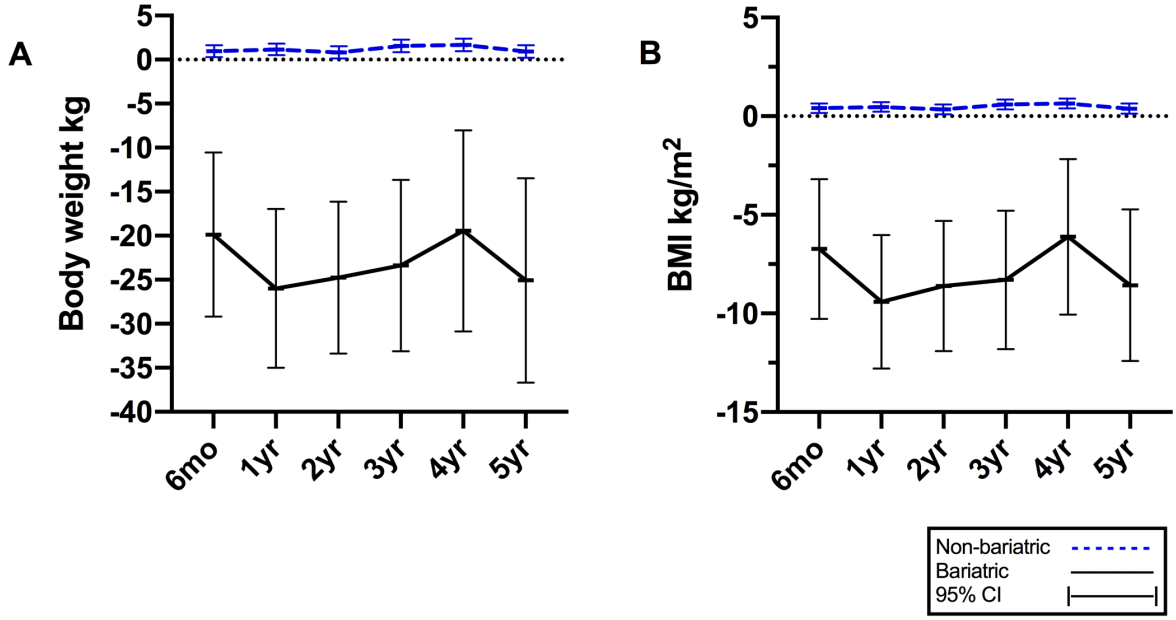

Figure 6.1 Change in weight and BMI.
Mean change in (A) body weight and (B) BMI (95%CI) comparing bariatric vs non-bariatric during five years of follow-up compared to baseline.

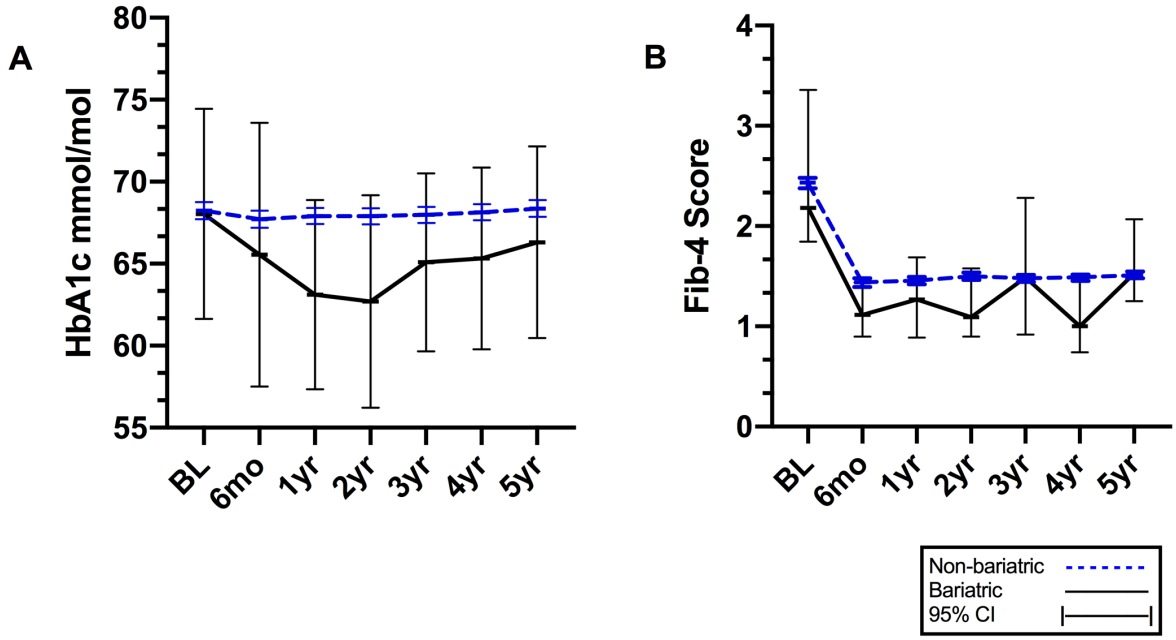

Figure 6.2 Mean HbA1c and median Fib-4 scores.
Bariatric vs non-bariatric in (A) mean HbA1c and in (B) median Fib-4 score (95%CI) during five years of follow-up.

6.4.2 Changes in metabolic and liver related outcomes

During the five years of follow-up period, body weight and BMI were significantly lower amongst patients in the bariatric group when compared to their baseline measurements. No significant weight change was noted amongst patients in the non-bariatric group during this period. (**Figures 6.1a** & **6.1b, Table 6.1**). Similarly, HbA1c levels were lower within the NAFLD bariatric group throughout the study period. However, this finding only had statistical significance during the first and second years of the study period (bariatric vs non-bariatric at 1-year: 63.1 vs 68.1, P = 0.042; and at 2-year: 62.7 vs 68.1, P = 0.028) (**Figure 6.2a**). The Fib-4 scores were maintained at lower levels due to the benefits associated with bariatric intervention, albeit with little or no statistical significance throughout the entire follow-up period (**Figure 6.2b**). The likelihood of developing composite liver disease throughout the study period was higher amongst patients in the bariatric group (8.9%) compared to those non-bariatric group (4.7%), again with little or no statistical significance of this difference (X^2=1.75, P = 0.18) **(Table 6.1).**

Table 6.1 *Metabolic outcomes for patients with NAFLD at baseline* (i.e. Fib-4 score > 1.45).

Metabolic outcomes	***Bariatric*** *(N=45)*	***Non-bariatric*** *(N=4,063)*	**P-*value*†**
Body weight kg, mean(SD)			
Baseline	119.2 (30.7)	89.2 (20.4)	< 0.0001
6 months	99.9 (21.6)	90.6 (19.9)	0.002
1st year	93.6 (20.4)	90.8 (19.8)	0.35
2nd year	94.9 (23.1)	90.4 (19.7)	0.13
3rd year	96.2 (19.8)	91.2 (20.0)	0.12
4th year	100.9 (21.9)	91.3 (20.1)	0.003
5th year	95.4 (21.0)	90.5 (19.9)	0.13
BMI kg/m², mean(SD)			
Baseline	42.5 (11.4)	31.6 (7.5)	< 0.0001
6 months	35.7 (7.6)	32.1 (7.4)	0.002
1st year	33.0 (7.6)	32.2 (7.3)	0.45
2nd year	33.7 (9.2)	32.0 (7.3)	0.16
3rd year	34.0 (7.1)	32.3 (7.3)	0.15
4th year	36.2 (10.3)	32.4 (7.3)	0.001
5th year	33.7 (9.2)	32.1 (7.3)	0.16
HbA1c mmol/mol, mean(SD)			
Baseline	68.0 (20.8)	68.4 (16.7)	0.88
6 months	65.5 (25.5)	67.9 (16.6)	0.37
1st year	63.1 (18.5)	68.1 (15.7)	0.042
2nd year	62.7 (20.5)	68.1 (15.6)	0.028
3rd year	65.0 (16.7)	68.2 (15.5)	0.22
4th year	65.3 (17.1)	68.3 (15.7)	0.23
5th year	66.3 (18.0)	68.6 (16.1)	0.38
Fib-4 scores, median(IQR)			
Baseline	2.18 (1.79)	2.31 (2.53)	0.59
6 months	1.11 (0.74)	1.32 (1.36)	0.31
1st year	1.27 (1.10)	1.34 (1.33)	0.52
2nd year	1.09 (0.89)	1.38 (1.43)	0.15
3rd year	1.48 (1.80)	1.36 (1.39)	0.81
4th year	1.00 (0.96)	1.37 (1.43)	0.030
5th year	1.52 (1.69)	1.39 (1.41)	0.44
Composite Liver disease events, (%)			
During 5 years	8.9%	4.7%	0.18

† *P < 0.05 (probability reference).*

6.5 Discussion

This increasing prevalence of obesity and NAFLD has caused bariatric surgery to be increasingly utilised as a proven means of either halting or reversing the progression of liver disease in patients with NAFLD [173,174]. In a large meta-

analysis involving 766 patients, significant improvement in liver histology was reported following different bariatric surgical interventions [180]. Amongst patients with cirrhosis, no major complications were reported in six patients who underwent laparoscopic sleeve gastrectomy. However, two patients developed transient ascites and hepatic encephalopathy [178]. Three further studies have been conducted which review laparoscopic sleeve gastrectomy or gastric bypass operation in a total of 39 patients with cirrhosis. These studies have reported no postoperative mortality or liver-related complications [181-183]. Conversely, several studies have reported complications following bariatric surgery in patients with cirrhosis. In an early survey of non-laparoscopic bariatric surgeries, 125 cases of cirrhosis were identified, of which, 11 patients died peri- or post-operatively from fulminant hepatic failure [184]. Whilst laparoscopic procedures have been shown to significantly improve clinical outcomes, Dallal's et al. [185] research revealed multiple potential postoperative complications in 9 out of 30 patients with cirrhosis, including anastomotic leaks, acute tubular necrosis, prolonged intubation, ileus, and the need for blood transfusions. A subsequent case study involving 23 patients with cirrhosis who had undergone various laparoscopic bariatric procedures reported complications in 8 patients. The complications included anastomotic leak, infection, and bleeding requiring blood transfusion. However, no liver decompensation or perioperative mortality was reported [186]. Therefore, there are ongoing concerns about the safety and efficacy of bariatric surgery among patients who already have liver fibrosis at the time of surgery.

T2D is independently associated with increased risk of complications from bariatric surgery [187] and is intrinsically connected to the pathogenesis associated with NAFLD via hyperinsulinaemia and insulin resistance [166,170]. Despite this, many of the aforementioned studies have not investigated the risk of adverse liver outcomes following bariatric surgery with specific reference to patients with T2D. Crucially, earlier research has indicated that bariatric surgery is associated with an increased risk of liver fibrosis progression after five years. Furthermore, this research also highlights an independent association with hyperinsulinaemia [179]. Our study, which was undertaken in patients with insulin-treated T2D at high risk of liver fibrosis (defined as Fib 4 score of > 1.45), demonstrated significant improvements over the five-year study period in weight and HbA1c outcomes, with no significant worsening of liver fibrosis score nor any significant increased incidence of composite liver disease outcomes, such as encephalopathy, liver failure, bleeding varices, cirrhosis, and hepatoma. Specifically, these findings were deduced in comparison with patients who did not have bariatric surgery. Whilst this data provided some reassurance regarding the safety and efficacy of bariatric surgery in this high-risk group, the non-significant trend towards a higher risk of liver-related complications amongst patients who had bariatric surgery suggests the need for caution. Scrupulous pre- and post-operative screening needs to be implemented in order to identify and manage individuals with more advanced liver disease prior to bariatric surgery. Unfortunately, this approach may not be consistently applied across all bariatric centres with many patients with significant liver disease not being identified or medically optimised prior to bariatric surgery

[188]. A large scale study of patients who underwent bariatric surgery reported that the presence of compensated cirrhosis was associated with an increased length of hospital stay and involved a two-fold increased risk of mortality [176,189]. Patients with decompensated cirrhosis had even worse outcomes with a combined in-hospital mortality rate for both compensated and decompensated cirrhosis of 1.2%, with mortality rates lower at high volume centres (> 100 procedures per year) compared to lower volume centres [176].

In summary, this study supports the role of bariatric surgery in improving metabolic parameters amongst those high-risk patients with T2D who are also at increased risk of liver fibrosis. However, comprehensive pre- and post-operative screening needs to be implemented to identify and manage individuals with more advanced liver disease prior to bariatric surgery. In this way, it becomes possible to reduce the risks of immediate, short- and long-term complications associated with bariatric surgery.

6.6 Limitations

Several limitations to this study must be addressed. For example, this research seeks to investigate a specific patient group at high risk of adverse outcomes, i.e. insulin-treated T2D, and Fib-4 > 1.45 and to compare outcomes in the presence or absence of bariatric surgery. Consequently, the number of patients in the bariatric surgery group is too small to permit a robust proper propensity-matched analysis to be performed. Nonetheless, the number of patients analysed in this study who have liver disease is comparable or in excess of the numbers previously reported

in a general patient cohort of bariatric surgery patients. The sources of our data have allowed us, where possible, to adjust for confounders. In addition, the number of patients with diagnosed cirrhosis at baseline and during follow-up is too small. Nevertheless, we consider it possible that patients with cirrhosis are often missed prior to surgery and, therefore, under-reporting may have influenced the information in our database. Utilising a Fib-4 threshold of 1.45 would therefore identify all patients (with or without cirrhosis) who are at high risk of liver fibrosis at baseline.

Chapter Seven: Health Utilisation of Post Bariatric Surgery and Effect on Composite Obesity-related Comorbidities

7.1 Summary

Aim: To assess the bariatric surgical intervention associated healthcare costs and the risk of developing obesity-related comorbidities, in insulin-treated T2D patients with obesity.

Methods: A retrospective cohort study was conducted among 11,125 insulin-treated T2D patients, whose details were stored within the THIN electronic primary care database, in the UK. Propensity score matching was performed for bariatric surgery with non-bariatric cohort (N=160) in a 1:1 ratio. In order to ascertain the existence of potential significant variations between the control and the bariatric surgery cohorts, drug prescriptions costs were compared with expenses for GP visits, hospitalisation and laboratory tests, during a 5-year follow-up period. Cox proportional regression was used to compute differences in the composite risk of obesity-related comorbidities. Chi-square analysis was employed to explore differences in insulin independency and diabetes remission proportions during follow-up.

Results: The baseline mean values were as follow: age was 48.3 years (±12.9) (61% female), and BMI was 39.3 kg/m^2 (±9.3). During the follow-up period, anti-diabetic drug cost was significantly lower in the bariatric group, than in the non-bariatric (median cost/person (£): 527.77 (IQR: 1,196.11) vs. 1,564.13 (IQR: 1,576.01); $P < 0.001$). Overall, aggregate cost analysis showed a significant total healthcare cost reduction in the bariatric group (median cost/person (£): 1,597.96 (IQR: 2,631.84) vs. 2,440.12 (IQR: 2,242.95); $P = 0.050$). A significant 44% degree of protection, from obesity-related comorbidities, was afforded by bariatric surgery, following comparison with non-bariatric patients (aHR: 0.56; 95%CI: 0.32–0.96; $P = 0.036$). Additionally, insulin independency rate was significantly higher in the bariatric group, than in the non-bariatric, throughout all follow-up points, with the ration being 48.1% vs. 28.9% at year five; $P = 0.044$.

Conclusion: Cost efficiency evidence could be detected for bariatric surgery. However, this study failed to establish significant cost savings for the procedure. This surgical intervention has a protective effect against obesity-related comorbidities and it promotes increased likelihood of insulin independency during the 5-year follow-up period.

7.2 Background and aims

Obesity and T2D are major global health problems that are intrinsically linked with adverse health outcomes [110,111], the risk of which can be reduced by significant weight loss [113]. While diet and exercise play a crucial role in obesity management, lifestyle or pharmacotherapy may not achieve durable weight loss in the majority of patients [114,190,191]. Therefore, bariatric surgery has emerged as the most effective and durable strategy for long-term weight loss maintenance in individuals with morbid obesity [115]. Previous studies have shown that bariatric surgical procedures may offer important health benefits to people with severe and morbid obesity. These benefits include reductions in body weight [192], remission of established T2D [50] and other long-term conditions [193], as well as reduction in mortality [194,195].

It is noteworthy that the significant costs, attached to bariatric surgery and to the associated follow-up care, represent an element that may explain its variable accessibility across the UK. Some studies suggest that bariatric surgery may represent a cost-saving initiative for health systems [196]. However, health care utilisation studies have not supported this theory, after analysis of the effect of bariatric surgery. A clear demonstration of cost-effectiveness appears to have been discovered, but cost savings could not be detected, particularly when comparing bariatric procedures with routine medical care or intensive lifestyle interventions, due to post-surgical costs after 3 years of surgery [197-199]. Therefore, short-term focus on cost saving should shift towards an attention on

patients beneficial effects of surgery: further analysis is required for ascertaining individuals' long-term health and well-being improvements following bariatric procedure. Importantly, a previous study has reported that the long-term health care cost of bariatric surgery varies depending on the patient glucose status at baseline [200]. However, at present, no cost studies and only few cost-effectiveness analyses have examined the impact exercised by specific patient subgroups on the health care system, following bariatric surgery. This question is critical to establish an economic case for bariatric surgery.

To this end, many T2D patients will require insulin treatment to manage hyperglycaemia and to reduce long-term vascular complications risks. It is an established fact that a significant 4 to 9 Kg weight gain is triggered by the initiation of insulin therapy within the first year. This side effect is exacerbated by insulin dosage increases [120], simultaneously raising CV risks [201]. Thus, a cohort of insulin-treated T2D patients represent a complex, heterogeneous and challenging group of individuals. Many of them present significant comorbidities, high CV disease risk and, therefore, high health care costs. The study aim is to assess a number of associated healthcare costs elements from bariatric surgical intervention, and the risk of developing composite obesity-related comorbidities in insulin-treated T2D patients with severe obesity.

7.3 Methods

7.3.1 Study design and data sources

This retrospective cohort study was conducted analysing patients data selected from the THIN database. THIN is a UK primary health care database that systematically computerised longitudinal and anonymised patients health records from primary care physicians. Further details on the data source is available in **Chapter 4** (**Subsection 4.3.1**).

7.3.2 Ethics

Ethical approval was provided to THIN by the NHS South East Multi-centre Research Ethics Committee (MREC). The Scientific Review Committee (SRC) reviewed the study protocol for scientific merit and feasibility.

7.3.3 Study population

The collected THIN dataset contains 11,125 adult patients, aged 18 years and over. There was no upper age limit for patients diagnosed with T2D and who had been prescribed with a form of insulin therapy, up to September 2017. According to cohort type, the initial study time-point (patient index date) corresponded with the bariatric surgery day (treated cohort) or with the insulin therapy initiation first day, for those not undergoing surgery (untreated, or control, cohort). The dataset was scanned to identify patients with baseline date prior to 1 January 2000, with no history of insulin use or diagnosed with type 1 diabetes, for possible exclusion.

7.3.4 Exposure and outcomes

Our exposure of interest is bariatric surgical intervention for insulin-treated T2D patients with severe obesity. The surgery represented patient exposure to remedial action. Its effectiveness was monitored during a 5-year long follow-up period, inclusive of the primary outcome and of the study concluding stage. Because of the time scale, this final stage corresponded to the actual end of study for most subjects, but also to unpredicted transfers or demise for some patients. Primary outcomes were defined within the survival rate of patients against diagnosed obesity-related comorbidity events. The risk of obesity-related comorbidities was estimated during the first occurrence of one of the following observed (or diagnosed) episodes:

i. coronary heart disease or stroke,
ii. cancers, including breast, bowel or womb cancer,
iii. hypertension,
iv. gallbladder disease or gallstones,
v. osteoarthritis,
vi. gout,
vii. sleep apnoea or asthma,
viii. high blood cholesterol or atherosclerosis,
ix. liver diseases, including alcohol and non-alcohol fatty liver disease,
x. chronic kidney disease or nephropathy,
xi. gastro-oesophageal reflux disease (GORD),
xii. reported episodes of severe depression or dementia.

For our analysis, it was possible to mine the data records within the THIN database for specific dates associated with recorded reports of the listed events. Events of obesity-related comorbidities were assessed and reported by health professionals, following good medical practice standards applied across the NHS primary health provision and covered by the THIN database collective systems.

GBP drug cost distribution was retrieved from specific prescription dates, reported within the THIN main database. The cost for each prescribed drug was added through the use of current BNF filing systems [202]. Drugs were grouped into the following seven main categories:

i. insulin,
ii. oral anti-diabetic,
iii. GLP-1 analogues,
iv. anti-hypertensive,
v. lipids lowering,
vi. diuretics,
vii. Aspirin.

A screened drug list, with genericnames, is provided in **Appendix 10.7**.

Additionally, it was possible to retrieve from the THIN database details regarding GP visits, hospitalisation and requests for laboratory tests, even though different forms were used for documenting these factors, requiring some investigative exercise. Specifically, GP visits frequency was calculated considering the number of blood pressure readings reported in the database. Hospitalisation had several

codes, to indicate specific admission procedures, such as 'Hospital inpatient' and 'Emergency hospital admission'. Each was associated to a specific cost. Finally, the THIN database medical records included a specific section for lab tests requests. All service costs were added by reflecting each specific service procedure made to the National Schedule of Reference Costs (NHS Reference Costs: 2015 to 2016) [203]. If provided prior to the specified index-points, prescriptions and health services were excluded from this analysis.

A number of secondary outcomes of interest revealed the following:

i. likelihood of being off insulin during the follow-up time, due to absence of insulin prescriptions,

ii. being within defined diabetes remission parameters: patients were categorised as being in diabetes remission if their estimated HbA1c levels were at 48mmol/mol or less, in addition to being off any form of anti-diabetic prescriptions throughout.

7.3.5 Covariates and follow-up strategy

Patients, that received bariatric surgery interventions, represented the treatment group and were the subject of this study follow-up focus. Their propensity-score was matched to insulin-initiators from their first insulin prescription date. Patients with diagnosed obesity-related comorbidity events, which occurred prior to the designated baseline point, were excluded from the primary survival estimation. In line with patient's treatment category, the baseline clinical parameters were measured at a similar point of time. Specifically, a period, comprising 90 days to

one day prior to procedure date, constituted the time when baseline parameters were calculated within bariatric surgery patients. Likewise, non-bariatric patients had their baseline parameters calculated within the same period, according to their first initiation of insulin therapy. Covariates were, recalculated at each year time-point during follow-up, with a 90-day window on every concurring point of time.

7.3.6 Statistical analysis

In the form of PS-matched groups, primary analysis allowed the timeframe to incorporate the risks of composite obesity-related comorbidity events. The PS model was estimated by using a logistic regression model, in order to adjust baseline characteristics, minimising allocation bias between groups. The measurement of standardised differences, occurring before and after procedure, represented the basis for a balance assessment between bariatric (treated) and non-bariatric cohorts. The mean from continuous covariates and proportion of categorical variables were examined and summarised between groups. Each treatment subject was matched to one reference subject (1:1 ratio) at the nearest distance, measured by the estimated PS. This was based on the estimated treatment probabilities [129]. In order to minimise distance within matched sets, we employed caliper of width equal to 0.1 of the standard deviation of the PS logit. The aim was to improve match quality and to limit possibility of excessive numbers of matched subjects. A caliper of width of 0.2 or lower resulted in optimal estimation, compared to higher choices of caliper use [131]. In consideration of a

prognostic covariate, PS was included in all Cox proportional hazards regression modelling.

The stratified log-rank test, with Kaplan-Meier failure-function curves, respectively, were used to compare the equality between the PS matched groups. The absolute probability reduction of an event occurring within 5-year follow-up period was calculated. Additionally, the comparison of the adjusted event occurrence hazard quantification, between the bariatric and the matched non-bariatric groups, was enabled by the estimation of marginal hazard ratios. Proportional hazard assumptions were confirmed through Schoenfeld residuals test. Point estimates with 95% Confidence Intervals (CIs) were accepted at the conventional statistical significance level of $P \leq 0.05$, in the regression models. The proportional hazards assumption was examined by comparing the cumulative hazard plots, grouped on exposure. No violations were observed.

Missing data among covariates were managed through multiple imputations using the predictive means matching for continuous covariates with accounting to exposure (i.e. bariatric), age, gender, diabetes duration, Townsend deprivation status, marital status, smoking and alcohol use [132]. sensitivity analysis was conducted to fill gaps from missing data, to assess their impact and to validate our multiple inputting adequacy [133].

The student's *t* test was employed to measure differences between means in parametric continuous variables, such as service cost distribution. Wilcoxon's rank-sum test was used to test the magnitude of differences between medians of non-

parametric continuous variables, including drug cost distribution. Finally, Pearson's Chi-square test was used to compare proportions of insulin independency, as well as diabetes remission rates between groups. Statistical significance was considered at $P \leq 0.05$, as standard. To avoid the probability of type II error, the study was powered to 0.88 and the matched sample size of 160 subjects with detected true difference of less than 0.13 between the two groups at 5% significance level. The study fulfilled the STROBE criteria for reporting observational studies [134,135]. The SAS Software version 9.4 was used throughout the initial dataset management (SAS Institute, Cary, NC), Stata/SE Statistical Software version 15.1 was employed in all carried analyses and visual illustrations (StataCorp., College Station, TX).

7.4 Results

7.4.1 Patient characteristics and total follow-up

From a total population of 11,125 patients, we identified 9,875 patients within the inclusion criteria and fit for PS-matching procedure, 133 patients of which were identified to have undergone bariatric surgical operations. The PS-matching procedure has allowed 80 control subjects to be matched with 80 treatment (bariatric) patients. This yielded a total number of 160 PS-matched participants. The median treatment duration was 6.06 years (interquartile range [IQR]: 4.67–8.69 years). The median follow-up was 4.26 years (IQR: 1.61–6.13 years), representing a total follow-up time of 693.5 person-years.

The mean age for the matched cohort at baseline was 48.3 (±12.9) years; 60.6% were females. The mean body weight, BMI and HbA1c level were 111.0 (±26.4) kg, 39.3 (±9.3) kg/m^2 and 72.2 (±18.7) mmol/mol, respectively. The baseline characteristics in both bariatric and non-bariatric groups were compared in full and matched cohorts with respective standardised differences are illustrated in **Table 7.1**.

7.4.2 Probability of survival against comorbidities

The unadjusted probability of survival in the PS-matched cohort showed tendency towards a protective effect against composite obesity-related comorbidity events with little or no statistical significance of a difference from proportions between bariatric and non-bariatric groups: at 1-year (81.3% vs 78.8%), 3-year (67.2% vs 61.2%) and 5-year (60.0% vs 51.9%) of follow-up (log-rank test P = 0.34). A total of 69 events were observed (31 bariatric vs 38 non-bariatric) with a crude event rate of 99.5 (83.9 vs 117.2) per 1000 person-years (95%CI: 78.6–125.9).

Table 7.1 *Baseline characteristics.*

	Cohort					
	Full population [N = 9,875]			**PS matched cohort [N = 160]**		
Baseline variable	**Non-bariatric** [n = 9,742]	**Bariatric** [n = 133]	**Std. diff***	**Non-bariatric** [n = 80]	**Bariatric** [n = 80]	**Std. diff†**
Demographics						
Age (yrs), mean (SD)	58.4 (13.3)	48.2 (10.2)	0.862	48.4 (15.2)	50.2 (10.2)	-0.140
Gender, no (%)						
Female	6,284 (64.5)	61 (45.7)	0.386	44 (54.7)	51 (63.6)	-0.183
Townsend deprivation, %						
Least deprived	12.9	21.6	-0.233	14.7	13	0.049
Less	25	20.5	0.106	26.7	16.9	0.239
Average	15.3	21.1	-0.151	17.3	19.5	-0.055
More	22.6	21	0.039	17.3	22.1	-0.119
Most deprived	24.2	15.7	0.213	24	28.6	-0.104
Type 2 diabetes (yrs), mean (SD)						
Diabetes duration$^{\Delta}$	14.1 (7.61)	13.7 (7.75)	0.052	11.7 (6.39)	13.7 (8.26)	-0.273
Insulin dependency	6.8 (4.4)	6.9(5.0)	-0.016	4.6 (3.3)	6.8 (5.1)	-0.522
Drug use duration (yrs), mean (SD)						
Oral antidiabetics	10.5 (5.8)	11.6 (5.8)	-0.182	10.2 (5.3)	11.1 (5.8)	-0.161
Antihypertensive	11.9 (6.6)	12.4 (6.7)	-0.075	12.0 (5.4)	12.2 (6.7)	-0.043
Lipids lowering	9.9 (4.8)	10.2 (5.3)	-0.062	9.6 (4.3)	9.8 (5.4)	-0.045
Diuretics	8.9 (6.9)	8.2 (7.3)	0.089	6.9 (6.3)	7.8 (6.8)	-0.133
Aspirin	8.5 (5.4)	8.0 (5.6)	0.084	7.6 (5.8)	7.4 (5.6)	0.031
Clinical parameters, mean (SD)						
Weight (kg)	90.6 (20.8)	123.8 (30.4)	-1.274	108.1 (27.3)	113.9 (25.3)	-0.220
Height (m)	1.68 (0.10)	1.69 (0.11)	-0.024	1.68 (0.10)	1.69 (0.12)	-0.186
BMI (kg/m^2)	32.2 (7.7)	43.9 (10.7)	-1.260	38.7 (10.2)	39.8 (8.3)	-0.120
HbA1c (mmol/mol)	69.7 (17.3)	73.3 (19.7)	-0.194	72.2 (18.7)	72.2 (18.8)	-0.0014
Fasting glucose (mmol/L)	9.90 (3.9)	9.83 (4.4)	0.019	9.87 (4.1)	10.04 (4.9)	-0.037
Blood glucose (mmol/L)	11.66 (5.3)	12.34 (9.3)	-0.089	12.33 (5.5)	11.11 (5.4)	0.223
SBP (mmHg)	138.5 (16.4)	134.9 (14.1)	0.236	135.8 (16.3)	135.7 (14.2)	0.011
DBP (mmHg)	78.9 (9.6)	78.5 (8.3)	0.050	77.9 (9.1)	79.3 (8.6)	-0.151
Triglyceride (mmol/L)	2.04 (1.31)	2.29 (1.59)	-0.179	2.53 (1.85)	2.31 (1.54)	0.131
Total cholesterol (mmol/L)	4.49 (1.16)	4.595 (1.25)	-0.087	4.47 (1.36)	4.62 (1.36)	-0.107
Low density lipoprotein (mmol/L)	2.40 (0.98)	2.48 (0.89)	-0.082	2.56 (1.01)	2.45 (0.98)	0.1095
High density lipoprotein (mmol/L)	1.22 (0.39)	1.09 (0.29)	0.358	1.08 (0.26)	1.11 (0.29)	-0.113
Alcohol status, %						
Unknown	3.2	3.4	-0.011	2.7	7.8	-0.232

Ex-drinker	13.7	7	0.221	14.7	3.9	0.378
Never	31.5	30.9	0.013	30.7	46.8	-0.335
Current	51.6	58.7	-0.143	52	41.6	0.21
Smoking status, %						
Ex-smoker	31.5	36.7	-0.112	26.7	33.8	-0.155
Never	54.8	49.6	0.105	54.7	58.4	-0.076
Current	13.7	13.7	0.001	18.7	7.8	0.325

[Δ] Diabetes duration is time from first diagnosis of diabetes to date of initiation with insulin drug.
*** Standardised differences are the absolute difference in means or percentages divided by the SD of the treated group. Resulting standardised difference after 1:1 matching ratio based on average treatment effect on treated propensity score technique and robust variance of estimation.**
† Mean of standardised difference in post PS matching (0.054), i.e. at less than 6% difference level measured.

Throughout, however, bariatric surgery showed a significant protective effect against composite obesity-related comorbidities in the adjusted[13] matched cohort. Patients underwent bariatric surgery had 44.3% lower risk to be diagnosed with obesity-related comorbidities compared to patients who have not had bariatric surgery (aHR: 0.56, 95%CI: 0.32–0.96, P = 0.036). **Figure 7.1** and **Table 7.2** summarise the observed events, event rates and differences in the probability of survival in the adjusted and unadjusted analyses.

The exact count with READ codes of obesity-related comorbidity events are available in **Appendix 10.8**.

[13] *Adjusted for treatment duration, fasting glucose, blood lipids, drug use (i.e. antihypertensive, diuretics and aspirin), smoking status and deprivation (Townsend) scale. Number of subjects in post adjustment was N=151, with 65 events observed.*

Table 7.2 *Survivability against obesity-related comorbidity events.*
Survivability of patients against observed obesity-related comorbidity events, crude incidence rates and hazard ratios of events in the matched Bariatric and Non-bariatric groups.

Survival analysis	***Non-bariatric***	***Bariatric***
Obesity-related comorbidity events		
Cohort, n	80	80
Events/person-years	38/324	31/369
Absolute rates[a] (95% CI)	117.2 (85.3–161.1)	83.9 (59.0–119.3)
HR[b] (95% CI)	1 (reference)	0.79 (0.49–1.28)
aHR[c] (95% CI)	1 (reference)	0.56 (0.32–0.96)[†]

[a] *Absolute rate at 1000 person-years.*
[b] *HR (unadjusted hazard ratio).*
[c] *aHR (adjusted hazard ration). Adjusted for treatment duration, fasting glucose, blood lipids, drug use (i.e. antihypertensive, diuretics and aspirin), smoking status and deprivation (Townsend) scale.*
[†] *P < 0.05 (probability reference).*

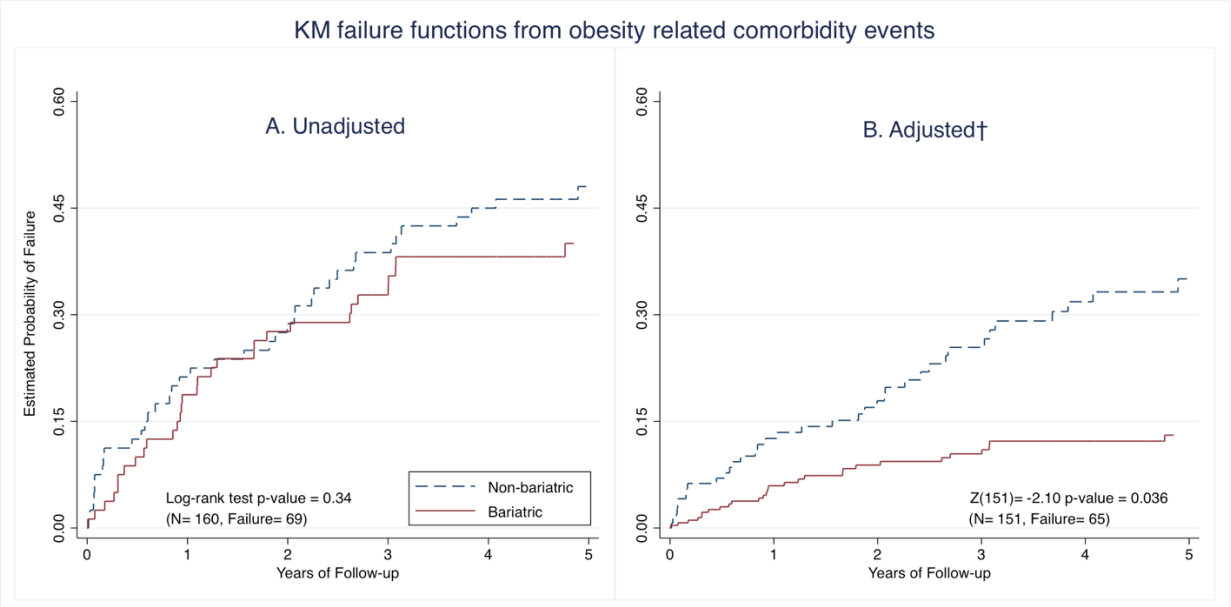

Figure 7.1 Failure function plots of obesity-related comorbidities.
Bariatric vs matched non-bariatric Failure Function plots of obesity-related comorbidity events. († Adjusted for treatment duration, fasting glucose, blood lipids, drug use (i.e. antihypertensive, diuretics and aspirin), smoking status and deprivation (Townsend) scale).

7.4.3 Drug and services frequency and cost distribution

The database was thoroughly screened for all included drug and service categories that had been provided to each individual subject in the matched cohort. The total frequency of drug and services utilised during follow-up were 24,564 and 3,028 respectively. Drug use frequency in more details is provided in **Appendix 10.9**. During the five years, bariatric patients cost significantly lower than non-bariatric in antidiabetic drug prescriptions (median: £627.60 vs £1,564.11; $P < 0.001$). The additional drug category (included: antihypertensive, lipids lowering, diuretics and aspirin) was statistically insignificant for the difference between medians despite the higher expenses coming from bariatric patients (£108.02 vs £90.72; $P = 0.97$). Similarly, bariatric group was with higher cost in the service utilisation category (included: GP visits, hospitalisation and laboratory test requests) with little or no statistical significance of this difference between cost means (bariatric £1,505.32 vs non-bariatric £1,058.54; $P = 0.056$).

The reduction in antidiabetic drug costs was found to be overwhelmingly leading this comparison towards a reduction in the aggregated cost favouring the bariatric group. This included all analysed categories with a statistical significance favoring the bariatric group (median: £1597.96 vs £2440.12; $P=0.050$). Cost and frequency distribution details are displayed fully for each analysed subcategory in **Table 7.3**.

Table 7.3 *Drug and service cost (in British Pounds) and frequency comparison between matched bariatric and non-bariatric groups throughout five years of follow-up.*

Cost elements	Non-bariatric (N = 80)		Bariatric (N = 80)		
Drug cost distribution†	**Frequency**	**Median cost (IQR)**	**Frequency**	**Median cost (IQR)**	**Probability of a difference**
Drug utilisation overall	13,352	1,685.5 (1,860.9)	11,212	727.8 (1,554.1)	$Z_{(157)}$= 4.02; *P*< 0.001
Total spent		151,898.20		103,926.60	–
Antidiabetic drug use	6,428	1,564.1 (1,576.0)	3,536	627.6 (1,205.7)	$Z_{(153)}$= 4.38; *P*< 0.001
Total spent		135,219.70		75,095.51	–
Insulin	3,022	1,161.9 (1,191.4)	1,271	604.3 (1,159.1)	$Z_{(133)}$= 2.83; *P*= 0.004
1st year	854	289.3 (252.3)	252	171.7 (240.9)	$Z_{(123)}$= 3.42; *P*< 0.001
2nd year	636	287.1 (179.4)	252	205.8 (233.9)	$Z_{(100)}$= 2.23; *P*= 0.023
3rd year	601	286.2 (168.5)	273	228.5 (233.4)	$Z_{(91)}$= 1.16; *P*= 0.25
4th year	524	302.2 (203.2)	232	221.7 (219.0)	$Z_{(79)}$= 2.22; *P*= 0.026
5th year	407	260.4 (280.6)	262	294.6 (275.6)	$Z_{(70)}$= -0.57; *P*= 0.57
Total spent		95,464.50		45,240.32	–
Oral antidiabetic drugs	3,226	140.1 (366.1)	2,102	85.0 (119.1)	$Z_{(134)}$= 1.49; *P*= 0.13
1st year	793	34.6 (42.2)	446	23.1 (32.7)	$Z_{(123)}$= 2.51; *P*= 0.012
2nd year	679	32.6 (46.3)	451	28.8 (40.9)	$Z_{(109)}$= 0.89; *P*= 0.37
3rd year	608	28.8 (74.1)	457	22.4 (30.4)	$Z_{(99)}$= 1.01; *P*= 0.32
4th year	697	34.6 (93.3)	394	33.3 (37.8)	$Z_{(86)}$= 0.62; *P*= 0.54
5th year	449	28.5 (118.9)	354	22.1 (64.1)	$Z_{(78)}$= 0.61; *P*= 0.55
Total spent		25,801.76		16,616.09	–
GLP-1 analogues	180	863.3 (1,230.1)	166	863.2 (1,955.2)	$Z_{(23)}$= 0.12; *P*= 0.90
1st year	66	549.4 (266.1)	26	163.8 (163.7)	$Z_{(15)}$= 1.25; *P*= 0.21
2nd year	44	561.3 (235.4)	49	667.1 (245.7)	$Z_{(12)}$= -0.96; *P*= 0.33
3rd year	19	359.9 (104.1)	34	559.6 (313.9)	$Z_{(9)}$= -1.11; *P*= 0.26
4th year	26	392.4 (174.0)	32	470.9 (235.4)	$Z_{(10)}$= -0.63; *P*= 0.53
5th year	25	313.9 (156.9)	25	235.4 (255.9)	$Z_{(11)}$= 0.28; *P*= 0.78
Total spent		13,953.45		13,239.10	–
Additional drug use	2,629	90.7 (282.4)	3,831	108.0 (236.3)	$Z_{(139)}$= 0.042; *P*= 0.97
Total spent		16,678.45		28,831.12	–
Antihypertensive drug	3,513	72.3 (156.1)	3,876	67.2 (143.0)	$Z_{(111)}$= 0.31; *P*= 0.76
1st year	996	18.8 (38.3)	854	15.2 (45.9)	$Z_{(101)}$= 0.99; *P*= 0.32
2nd year	792	19.2 (30.1)	874	20.1 (40.6)	$Z_{(95)}$= -0.05; *P*= 0.95
3rd year	623	14.4 (29.8)	771	20.6 (41.6)	$Z_{(86)}$= -1.29; *P*= 0.19
4th year	612	17.0 (34.0)	709	18.1 (44.9)	$Z_{(77)}$= -0.35; *P*= 0.73

5th year	490	21.8 (28.8)	668	16.6 (48.4)	$Z_{(68)}$= -0.18; *P*= 0.86
Total spent		10,113.76		14,152.48	–
Lipids lowering drugs	1,755	20.1 (29.8)	2,034	24.0 (39.8)	$Z_{(124)}$= 0.21; *P*= 0.84
1st year	432	6.0 (5.9)	441	6.1 (7.5)	$Z_{(108)}$= 0.24; *P*= 0.81
2nd year	358	6.1 (4.8)	445	6.2 (8.1)	$Z_{(104)}$= -0.04; *P*= 0.97
3rd year	346	5.2 (6.0)	438	8.1 (7.1)	$Z_{(94)}$= -1.35; *P*= 0.18
4th year	349	5.3 (8.3)	377	7.9 (6.5)	$Z_{(81)}$= -1.02; *P*= 0.31
5th year	270	5.9 (7.4)	333	8.4 (7.8)	$Z_{(70)}$= -1.26; *P*= 0.21
Total spent		3,782.35		3,366.74	–
Diuretics	873	32.3 (69.8)	933	23.1 (73.8)	$Z_{(63)}$= 0.68; *P*= 0.50
1st year	259	13.7 (15.2)	203	9.1 (12.6)	$Z_{(48)}$= 1.21; *P*= 0.22
2nd year	214	12.6 (19.9)	208	9.8 (18.8)	$Z_{(43)}$= 0.41; *P*= 0.68
3rd year	156	16.8 (22.7)	208	13.2 (22.1)	$Z_{(37)}$= -0.17; *P*= 0.87
4th year	132	12.6 (20.3)	163	7.4 (23.1)	$Z_{(31)}$= 0.09; *P*= 0.92
5th year	112	14.7 (18.3)	151	18.9 (28.9)	$Z_{(25)}$= -0.57; *P*= 0.56
Total spent		1,637.18		9,816.07	–
Aspirin	784	21.3 (51.1)	836	27.0 (39.8)	$Z_{(68)}$= 0.71; *P*= 0.48
1st year	262	9.9 (9.9)	198	7.1 (12.8)	$Z_{(57)}$= 1.74; *P*= 0.080
2nd year	170	9.2 (7.4)	164	8.8 (5.7)	$Z_{(47)}$= -0.12; *P*= 0.90
3rd year	121	7.8 (12.8)	190	7.9 (9.9)	$Z_{(41)}$= -0.21; *P*= 0.83
4th year	119	12.8 (9.9)	146	7.5 (5.7)	$Z_{(32)}$= 1.49; *P*= 0.14
5th year	112	12.9 (8.2)	138	8.5 (8.5)	$Z_{(29)}$= 2.26; *P*= 0.024
Total spent		1,145.16		1,495.83	–
Service cost distribution [Δ]	Frequency	Mean cost (SD)	Frequency	Mean cost (SD)	Probability of a difference
Clinical utilisation overall	1,571	1,058.5 (1,059.5)	1,457	1,505.3 (1,752.4)	$t_{(155)}$= -1.92; *P*= 0.056
Total spent		81,508.13		120,445.00	–
GP visits	876	679.1 (452.4)	953	719.3 (531.6)	$t_{(154)}$= -0.51; *P*= 0.61
1st year	252	208.9 (139.2)	257	207.3 (130.4)	$t_{(144)}$= 0.07; *P*= 0.94
2nd year	198	176.4 (163.4)	203	189.3 (149.9)	$t_{(129)}$= -0.47; *P*= 0.64
3rd year	163	159.5 (134.7)	185	184.0 (168.6)	$t_{(119)}$= -0.89; *P*= 0.38
4th year	150	175.6 (112.3)	175	193.4 (137.7)	$t_{(103)}$= -0.73; *P*= 0.47
5th year	113	172.9 (126.1)	133	198.5 (147.7)	$t_{(77)}$= -0.83; *P*= 0.41
Total spent		52,288.44		56,824.88	–
Laboratory tests use	636	103.3 (81.4)	390	65.8 (47.3)	$t_{(96)}$= 2.77; *P*= 0.0067
1st year	142	32.9 (27.1)	66	25.5 (13.4)	$t_{(54)}$= 1.16; *P*= 0.25
2nd year	120	25.0 (16.7)	74	22.2 (16.9)	$t_{(64)}$= 0.65; *P*= 0.52

3rd year	156	35.2 (32.5)	72	24.3 (13.7)	$t_{(58)}$= 1.54; *P*= 0.13
4th year	122	31.0 (27.6)	89	24.1 (17.6)	$t_{(60)}$= 1.16; *P*= 0.25
5th year	96	30.1 (24.4)	89	31.4 (22.3)	$t_{(47)}$= -0.21; *P*= 0.83
Total spent		5,164.32		3,158.68	–
Total Health Utilisation	Frequency	Median cost (IQR)	Frequency	Median cost (IQR)	Probability of a difference
Aggregate distribution	14,923	2,440.1 (2,242.2)	12,669	1,597.9 (2,631.8)	$Z_{(160)}$= 1.95; *P*= 0.050

† *Non-parametric probability test used for reported drug users only.*
Δ *parametric probability test used for reported service users only.*

7.4.4 Change in BMI

There have been reductions in BMI favoring the bariatric group vs non-bariatric throughout all follow-up time points and with established statistical significance except for the fifth year. The mean BMI for bariatric vs non-bariatric was at 1-year (34.1 [±8.3] vs 38.2 [±9.7] kg/m^2, P = 0.005), at 3-year (33.5 [±7.2] vs 37.3 [±7.8] kg/m^2, P = 0.001), and with little or no statistical significance of a difference at 5-year point (34.0 [±8.4] vs 36.1 [±8.5] kg/m^2, P = 0.13), respectively.

7.4.5 Proportions of insulin independency and diabetes remission

During follow-up, patients underwent bariatric surgery have had a significantly higher likelihood of being off insulin compared to their matched controls. Throughout, the average proportion of insulin independency from the bariatric group was 41.5% compared to 19.7% non-bariatric (**Figure 7.2**). Diabetes remission proportions were at higher levels during follow-up, favoring the bariatric group with statistical significance at 5-year point (11.5% vs 2.0%, P=0.050). Throughout, the bariatric group was twofold higher in overall remission proportion, compared to non-bariatric; 12.9% vs 5.2%, respectively (**Figure 7.3**).

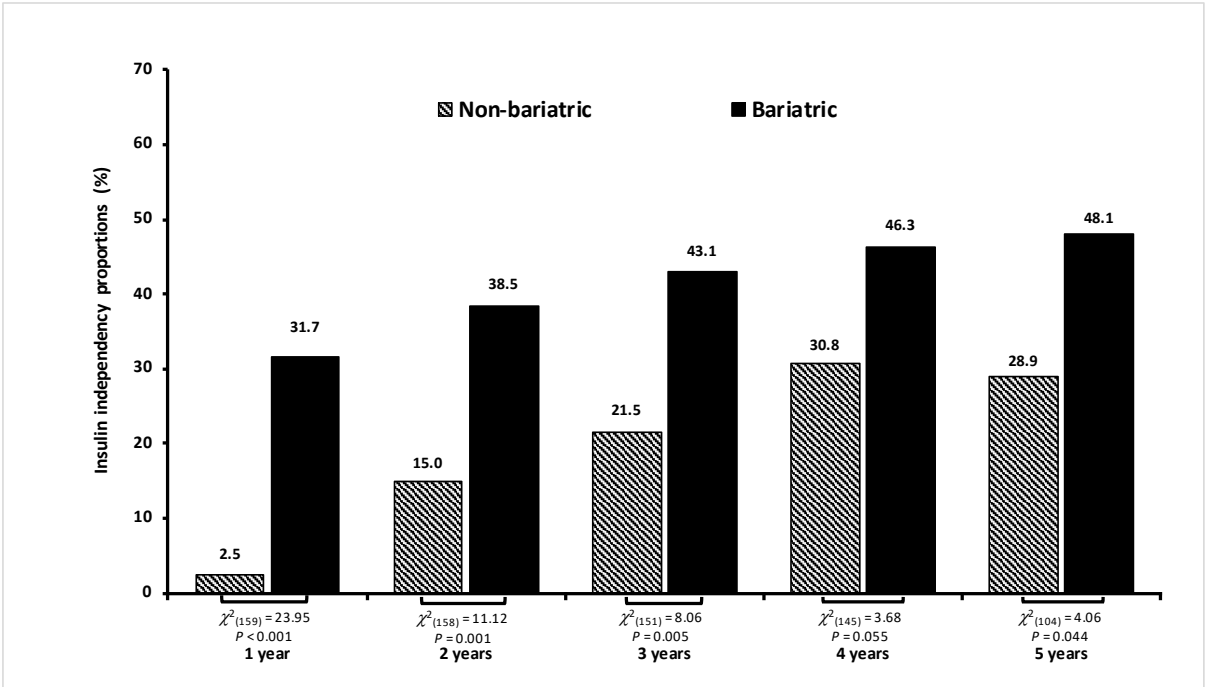

Figure 7.2 Insulin independency.
Insulin independency proportions comparing bariatric group to their matched non-bariatric.

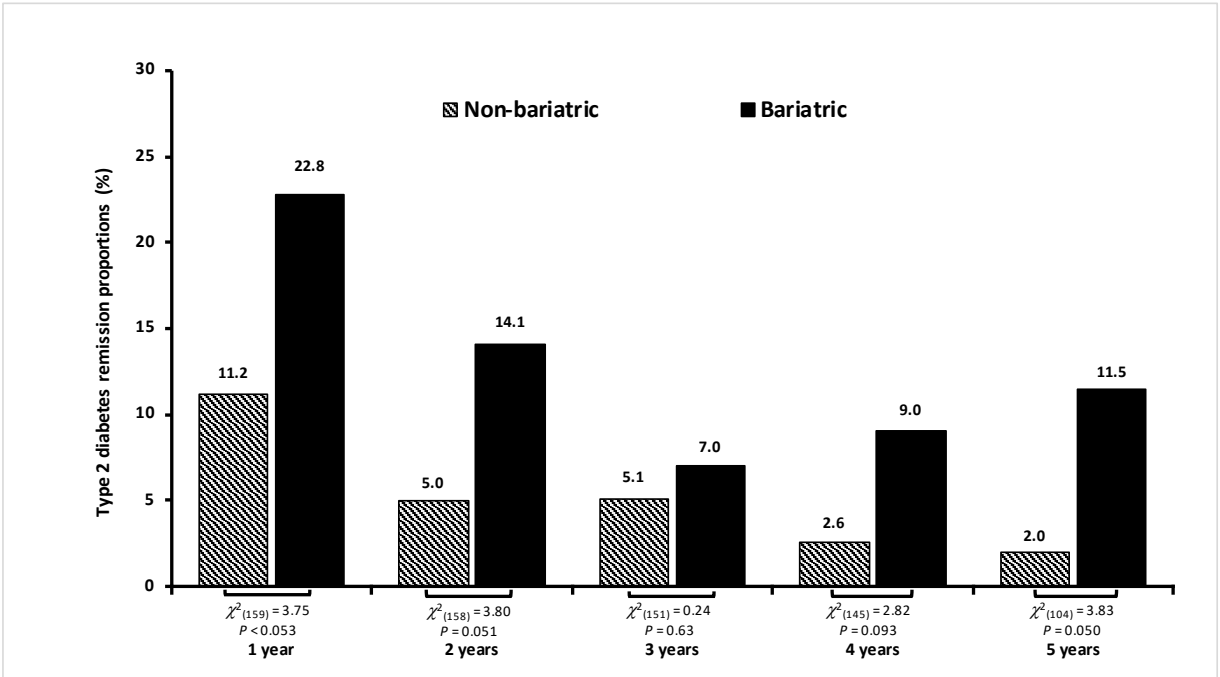

Figure 7.3 T2D remission proportions.
T2D remission proportions (i.e. off AD and with HbA1c < 48 mmol/mol) comparing bariatric to their matched non-bariatric group.

7.5 Discussion

Bariatric surgery is more effective, than medical or lifestyle intervention, for long-term weight loss and for achieving remission of diabetes [50,115]. However, it remains to be established whether bariatric surgery reduces expenditures sufficiently to achieve cost savings beyond three years of procedure [199]. The appreciation of significant cost reductions has received limited attention in regards of assessing different treatment strategies required by the various diabetic patients' subgroups [200]. In this cost-utilisation study, bariatric surgery was shown to be cost effective among insulin-treated T2D patients with obesity, driven by the significant reduction in the total cost of anti-diabetic drug therapy. In addition, total healthcare cost reduction is evident in the bariatric group, over a period of five years post-surgery. However, it should be noted that a subtle advantage exists for promoting bariatric surgery, despite its combined costs linked to the procedure, medical treatment and follow-up appointments. The reduction of a patient lifetime health expenditures is unlikely for a procedure that reduces mortality and morbidity in a complex, heterogeneous population, as was the case in this study. When taking into account the cost of surgery as well as the cost of medical treatment and follow-up of patients, bariatric surgery will not necessarily offer cost savings. However, it is noteworthy that our data highlighted how bariatric surgery could significantly protect against multifactorial obesity-related comorbidities, increased insulin independency rate and augmented the rates of diabetes remission post-surgery. The patients' quality of life improved significantly.

Previous studies have found that bariatric surgery was cost-effective for morbid obesity treatment [197-199]. The incremental cost-effectiveness ratio, ranging between £2,000 and £4,000 per QALY, was gained over a 20-year time period [204]. However, bariatric surgery costs are high: in the UK, £5,500 is the standard rate, based on current tariff, and higher price tags can be observed during the long analysis period in the present study. Therefore, predictably, bariatric surgery is less likely to achieve significant cost-saving advantages for most eligible patients. Further expenses accrued when the costs of medical follow-up, in-patient treatment, further surgery and complications management are added to the price of the initial surgery. In addition, supplementary costs are incurred when proactive individuals seek to ameliorate their health outcome, by pursuing a medical consultation and diligently attending follow-up clinics. This last statement should not be read as a detriment to the strife of these individuals taking ownership of their own health before it becomes absolutely necessary.

The UK National Bariatric surgery registry, which included data of 18,283 procedures from 2010 to 2013, revealed that, 61% patients with sleep apnoea were able to come off their treatment one year after surgery. Additionally, 65% T2D patients were in remission of T2D after two years from surgery, with significantly higher rates of insulin independencies [205]. Thus, an important policy question is whether bariatric surgery needs to be cost-effective (i.e. more effective but more costly than usual care), or does it need to achieve the higher standard of cost savings (i.e. more effective and less costly than usual care) to justify its

increased commissioning throughout the UK. Although bariatric surgery does not appear to produce economical savings, it is associated with substantial health gains at expenses that are below the accepted thresholds for cost-effectiveness. Furthermore, true cost savings may only accrue over a longer follow up of patients, which include the unaccounted expense in the improvement of patients' mental health and general well-being. For example, in the United States, for patients with a BMI of 35 or greater, annual health care costs are between $3000 and $10 000 per year [198,200]. Hence, even if total healthcare (drugs and clinical visits) expenses are reduced by 50% after surgery, cost neutrality may be achieved only after 20 years.

It has to be recognised that a variety of factors hinder the ability to execute a thorough assessment of the immediate and longer-term post bariatric surgery costs. These factors include the reduced patients' number in the database, beyond 5 years after surgery, as well as poorly recorded details, relating to costs of surgical complications, follow-up and re-operations. Nevertheless, studies have reported cost savings for bariatric surgery, when analysing longer-term follow-up and health economic models [206,207]. Further analysis is required to ascertain whether better cost efficiency could be achieved in different patients' subgroups or with specific types of bariatric surgery. The identification of this potential saving would be invaluable for informing clinical commissioners during the decision making process. Procedures, such as sleeve gastrectomy, was thought to yield cost savings, due to the relatively low complication rates and early evidence of clinical outcomes

that are comparable with RYGB [51,57]. However, the long-term outcome of sleeve gastrectomy, on diabetes remission and insulin independence, remains unclear.

This chapter main advantage derives from the inclusion of a specific insulin-treated T2D cohort in a real-world population. This enables the generalised application of our results to the rest of the UK population, as well as to a similar demographic community. The analysed patients' cohort provides adequate statistical power and contains sufficient information on other time-varying covariates for adjusting for possible co-founders. Adjustments were made for a large set of factors, which could have differed at the baseline, through a robust PS-matching protocol. This is very important, because it is routine clinical practice that bariatric surgery implementation depends on a multifaceted decision-making process, which exceeds the UK NICE guidelines.

This research was based on empirical data for health care utilisation costs, estimated from the electronic health records of a large participants' sample, managed in primary care in the UK. We have used conservative assumptions, including health care utilisation costs after surgery not associated with weight loss or other unreported forms of morbidity. These include psychological and mental health benefits, productivity at work or any positive surgery 'spill over' effects, which are transmitted to other family members, such as lifestyle changes and health behaviours of the entire family. In addition, this study has only covered a small clinical part of the whole real picture of formal and informal cost utilisation.

Patients' quality of life, productivity and psychological or mental status are all, among other aspects, economically worthy.

In conclusion, cost efficiency appears to be evident when bariatric surgery is performed. Specifically, the saving appears to stem from the reduced need for prescribing antidiabetic medications. Additionally, it is an effective measure in protecting insulin-treated T2D patients with severe obesity against composite obesity-related comorbidities. Patients, who underwent bariatric surgery, displayed an increased likelihood of becoming independent from insulin treatment and appeared to acquire a greater tendency towards subsequent diabetes remission.

7.6 Limitations

In this study, some residual shortcomings may persist, because of our inability to measure and adjust for insulin therapy dosage or for diabetes duration, due to ongoing issues of identifying incidents versus prevalent diabetes. The exposure classification, into broad kind of bariatric surgery, may have masked the effects of the individual procedure type and could have driven our study away, or closer, to the null hypothesis. Nonetheless, previous high-profile studies, on cardiovascular benefits of bariatric surgery, have not examined individual procedure types for the same objectives. For the purpose of this study, it is worth clarifying that, in the UK, both types of bariatric surgery procedures incur the same costs.

Chapter Eight: General Discussion and Final Conclusions

8.1 Discussion

The preceding chapters have focused on the clinical impact of comorbidities associated with obesity together with the clinical service requirement to cater for these issues. Given that the obesity epidemic has significant implications for the NHS, the aforementioned disease states have been evaluated from both practical and economic perspectives.

Obesity is a complex condition. It seldom presents in isolation and typically co-exists with one or more comorbidity. Thus, UK citizens with elevated BMI are 2.5 times more likely to develop CKD, for example, than are individuals with BMIs within the normal range [208]. Any guideline designed to tackle obesity must consider the presence of concurrent medical conditions. The extent of this issue is under-represented within adult admission criteria for entry into Tier 3, with a tight criteria of BMI 40 kg/m^2, BMI ≥ 35 kg/m^2 existing alongside comorbidities or BMI ≥ 30 kg/m^2 and T2D onset within the last decade. Hence, it remains unclear whether Tier 3 can reduce the current burdensome demand for Tier 4 surgical intervention.

The viability of short- to medium-term success has been demonstrated in a number of observational studies into British obesity, as outlined in **Chapter 2**, albeit with the possibility of bias and perceptible patient loss during the follow-up stages. The full extent of this field of interest was revealed during the literature review, which explored studies into obesity-related comorbidities. This empowered a better understanding to acquire more in-depth knowledge of the

work required in the current thesis. Later chapters in this thesis explore potential solutions to the clinical problems. Thus, **Chapter 3** postulates that the loss of patients beyond the six-month follow-up stage might be a consequence of their being discharged into the care of their own GPs, a lack of interest in their condition, or their onward referral to Tier 4 bariatric intervention.

Morbid obesity is a complicated clinical condition. Those patients who, despite their best efforts, have failed to achieve BMI reductions are often referred for Tier 4 intervention. Yet, to ensure success at this stage, patients must be sufficiently motivated and equipped with the knowledge necessary to manage post-operative requirements. Only patients in whom significant clinical improvement can be anticipated should be selected for bariatric procedures. Moreover, bariatric surgery is an extremely specialised field and should preferably be performed in dedicated centres by surgeons with demonstrable expertise in this area. In addition, support from specialist multi-disciplinary teams is highly desirable [55].

In addition to issues of accessibility and availability, the level of intervention provided by Tier 3 services may be inadequate for such patients if recovery from comorbidities is also to be achieved. Hence, the referral criteria for Tier 3 services should be modified to include subjects with BMI ≥ 35 kg/m^2 alone or with BMI ≥ 30 kg/m^2 with T2D or with pre-diabetic syndrome (e.g. HbA1c of 42–47 mmol/mol). This proposal is in keeping with the literature in that it has demonstrated that such patients already possess an increased probability of presenting with significant obesity-related comorbidities. The presence of diabetes, hypertension, and

hypercholesterolaemia were found to be related to excess body weight in male and female subjects from a wide range of socioeconomic and ethnic backgrounds [209].

The work presented in **Chapter 4** illustrates that specialist surgical intervention has failed to mitigate the risk of AMI, stroke, and HF. These results accord with the acknowledged CV and metabolic effects of bariatric procedures. The current research, however, focuses on subjects with insulin-treated T2D who have a greater CV risk. Although a lower incidence of CV-related disease or death is associated with the performance of bariatric surgery, the post-operative risk of death in patients with T2D remains over a third higher than expected [136].

In patients with microalbuminuria and who are thus at significant risk of renal disease, there was an observed tendency towards a reduction of composite CVD risk following bariatric surgery. However, as shown in **Chapter 5**, this effect did not reach statistical significance. A new method to evaluate composite CVD risk was devised. This involved evaluating survivability based on the patient's initial kidney function status.

Furthermore, patients with liver cirrhosis not only have a greater risk from bariatric procedures, but also experience poorer clinical outcomes. The presence of T2D in these patients is an additional and independent risk factor [187]. Furthermore, hyperinsulinaemia and insulin resistance have been implicated in the aetiology of NAFLD [166,170]. The risk of hepatic complications in diabetic patients undergoing bariatric surgery has yet to be fully described in the literature. However, it has been

observed that bariatric surgery can accelerate cirrhotic progression over a five year period, which suggests that hyperinsulinaemia is an independent risk factor for liver function deterioration [179]. The work discussed in **Chapter 6**, however, demonstrated improvements in respect of clinical measurements of body weight, HbA1c, and the stability of hepatic fibrosis scores. Moreover, there was no significant rise in incidences of hepatic failure or associated complications, such as cirrhosis, hepatoma, encephalopathy, or variceal bleeding, amongst bariatric insulin-dependent T2D patients with NAFLD at baseline.

Tier 4 bariatric procedures significantly reduce the risk of developing PAD, CHD, and CKD, irrespective of the presence of microalbuminuria at baseline. Clinical improvements are also seen in terms of body weight, glycaemic control, eGFR, insulin dependency, and diabetes remission. In addition to the similar improvements in respect of metabolic parameters for patients with NAFLD at baseline. Surgery appears to reduce the likelihood of obesity-related comorbidities, as per the 13 components of composite chronic disease outlined in **Chapter 7**. However, BP, total cholesterol, albumin and serum creatinine either remain constant or demonstrate only short-term improvements.

Whilst statistically significant short- to medium-term metabolic improvements were evident in patients in receipt of Tier 3 care, the clinical outcomes were somewhat checked. That is, any improvements were fleeting. Moreover, not only was the available data pertaining to the six-month follow-up stage limited, but the service capabilities were sporadically endangered.

Only short- to medium-term improvements in body weight, glycaemic control, and BP occurred with a modest benefit in terms of physical activity. This finding confirms the need to query the ability of Tier 3 services to help patients transition to bariatric intervention. In addition, it indicates the possibility that intervention which is both multifaceted and multidisciplinary might impact potential clinical outcomes in post-bariatric surgery contexts when referral to Tier 4 services were implemented.

Commissioning guidelines act to standardise the elements of the Tier 3 service offered by EMBMI. The outcome considerations employed in **Chapter 3** refer to baseline comorbidities. This is deemed a more preferable approach to conventional weight-focused metrics as a means of evaluating the effectiveness of therapeutic intervention. Tier 3 services are expected to play an important role in optimising the management of comorbidities prior to bariatric surgery, either through the implementation of referrals to appropriate clinicians or through the utilisation of multi-disciplinary teams. The volume of patients with comorbidity issues lends weight to the earlier proposal to improve patient access to Tier 3 care, even in respect of patients with class I obesity (i.e. BMI ≥ 30 kg/m^2).

The current research confirms the contention that the primary fiscal drain is associated with conditions which coexist with obesity. Hence, there is a clear need to explore the economic impact of therapeutic interventions. As a bare minimum this appraisal should incorporate cost per capita considerations [103]. However, it seems likely that a more inclusive strategy is required, perhaps akin to that

outlined in **Chapter 7**. Comparing 160 PS-matched cohort revealed only minimal cost-saving emerging from bariatric intervention, although there was added cost-efficiency when the study was extended to encompass composite obesity-related comorbidities.

Wang et al. (2011) anticipate that by 2030, there will be an extra 11 million adults with obesity in the UK. It is projected that this will create an additional 6–8.5 million cases of diabetes, 5.7–7.3 million instances of heart disease, and 0.49–0.7 million incidences of cancer. Accompanying this is the forecast loss of between 26 and 55 million quality-adjusted life years [210]. These scenarios could be almost entirely eradicated if relevant health care measures were implemented. However, this would require an estimated increase in spending of £1.9–2 billion per annum until 2030 [210]. According to Wang et al. (2011), it would be possible to reduce this expenditure through the introduction of multimodal lifetime treatment pathways that includes medical assessment, psychological evaluation, as well as bariatric intervention.

In cases where bariatric intervention is considered, as mentioned previously, the choice of patient, their awareness, the effective treatment of comorbidities, and psychological evaluation are all paramount to the success of any surgical options. Bariatric procedures must be offered more consistently in the UK. Moreover, they should be tailored to the physiological needs of individual patients. In addition, any non-surgical interventions for patients with severe obesity should not exceed a reasonable length of time (e.g. six months in duration based on inferences made

in **Chapters 2** and **3**) in cases where less invasive options have been fully explored and considered within a multi-targeted management strategy.

8.2 Research recommendations

In light of the guidelines explored in the preceding chapters, it is clear that the assessment of obesity-related comorbidities comprises a valuable gauge against which to measure the effectiveness of service provision. The monitoring of the extent to which patients absorb advice pertaining to diet and exercise can help to ensure that they possess enough information to enable them to adopt appropriate calorie intake and lifestyle changes. Moreover, management strategies can be tailored to take into account the unique risk factors and problems associated with each patient.

Further randomised control studies are required to evaluate the clinical outcomes of specific therapeutic interventions. Liaison with ethical approval bodies is required to ensure that randomisation in study control groups does not deny patients access to any clinically necessary treatments. Another option would be to conduct prospective studies designed to assess the impact bespoke therapeutic interventions for patients with obesity-associated comorbidities.

Evaluating the viability of the present tiered system from a policy perspective represents another useful approach. The current thesis contends that Tier 3 services produce moderate, albeit unstainable, metabolic improvements. Moreover, this paper recommends the incorporation within existing Tier 4 services

of a multidisciplinary weight management programme, comparable to that currently used within Tier 3 service provisions. It is proposed that this could enhance and accelerate access to surgical interventions.

In patients selected for bariatric surgery who also present with existing liver pathology, it is essential to implement protocols for pre- and post-interventional screening. Patients would also benefit from psychological input and clinical care after specialist surgery in order to address any new issues arising from their procedures, including the presence of loose or excess skin as a consequence of weight loss.

I also suggest the detailed documentation of data related to bariatric interventions and potential complications, including the type of surgery performed, 7-day and 30-day readmission rates, 30-day reoperation rates, in-hospital mortality, and day case use. The acquisition of data relating to in-patient readmissions, follow-up procedures, length of hospital stay, intensive care admissions, out-patient visits, use of additional medical services, and the impact on associated comorbidities could assist in the identification of financial burdens on the NHS associated with this clinical issue. Thus, this analytical strategy could provide clear insights for both budget holders and policy makers.

8.3 Final conclusions

The evaluation of obesity-related pathologies should be incorporated within the monitoring of clinical progress for all patients. This can be accomplished using

standardised clinical outcome metrics and through the consistent documenting of evaluations in patient records. Whilst the non-invasive interventions offered as part of Tier 3 services tend only to generate time-limited benefits in respect of body weight, glycaemic control, BP, and physical activity, they are associated with less sustained, almost imperceptible, positive progress in patients.

Medical literature supports the notion that the prevention of related pathologies, such as advanced T2D, represents a rational clinical approach to the management of patients with morbid obesity. The risk of serious CVD, such as PAD or CHD, can be significantly reduced by performing bariatric procedures. Surgery is also reno-protective in patients with a risk of CKD, such as those with baseline microalbuminuria. Furthermore, bariatric intervention promotes the optimisation of metabolic parameters in NAFLD patients. Substantial improvements in body weight also have a significant positive correlation with the normalisation of eGFR, cholesterol, BP and HbA1c. It is reasonable to assume that the subsequent improvements in patient well-being also generate enhancements in life quality and work performance. The satisfactory resolution of comorbidities and the generation of lower insulin requirements also reduce the need for clinic appointments and the demand for numerous related health services. Bariatric intervention, therefore, has positive financial implications for both the British economy and the NHS.

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10 Appendices

10.1 Search strategy example.

10.2 PRISMA checklist.

10.3 THIN database.

10.4 Ethical approval.

10.5 THIN READ codes.

10.6 Survival analysis.

10.7 Screened drugs.

10.8 Obesity-related comorbidities.

10.9 Drug use frequency.

Appendix 10.1 Search strategy example.

```
(((‘tier 3’) OR (‘weight reduc*’) OR (‘weight manag*’) OR (‘weight program*’) OR (‘overweight program*’) OR (‘MWMS’) OR (’specialist weight management’) OR (‘SWM’) OR (‘weight reduction program*’) OR (‘weight management interven*’) OR (‘multidisciplinary weight loss initiatives’) OR (‘multicomponent weight loss schemes’) AND ((‘UK’) OR (‘england’) OR (‘british’) OR (‘wales’) OR (‘scotland’) OR (‘north irland’)))
```

Appendix 10.2 PRISMA checklist for Tier 3 systematic review.

Section/topic	#	Checklist item	Reported
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	YES
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	YES
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	YES
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	YES
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	YES
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	YES
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	YES
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	YES
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	YES
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	YES
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	YES
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	YES
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	YES
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	YES

Section/topic	#	Checklist item	Reported
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	YES
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	YES
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	YES
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	YES
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	YES
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	YES
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	YES
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	YES
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	YES
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NO

Appendix 10.3 THIN database.

The longitudinal database, The Health Improvement Network (THIN), comprises extensive anonymised primary care records, provided by a significant number of participating UK general practices. It was established in 2002, by the Epidemiology and Pharmacology Information Core (EPIC) in partnership with In Practice Systems (IPS), London. EPIC recruited Primary Care practices and began data collection in 2003. It regulates the participating practices by setting, upgrading and monitoring adherence to stipulated standards on data collection, quality, handling and storage, in line with NHS guidelines. Currently, THIN represents a collaboration between INPS and Cegedim Healthcare Software (the company that writes the data collection software used).

The initial data management of THIN dataset was done under the guidance of Uchenna Anyanwagu, a senior PhD candidate during 2018. This entailed using the Drug and BNF codes to extract information from the dataset on all significant drug prescriptions and store these in separate data-files. Similarly, Additional Health Data (AHD) codes were used to extract important covariates, with their record dates. Separate data files were created for each covariate. Time-dependent covariates, such as weight, height, HbA1c levels, and laboratory investigations, were stratified yearly according to the detection dates. Individual data files were established to include READ codes for significant medical diagnoses and their

dates. Specifically, these records encompass details for coronary heart disease (CHD), acute myocardial infarction (MI), cerebrovascular disease (stroke), peripheral arterial disease (PAD), heart failure (HF), CKD and composite obesity-related comorbidities.

On 27th February 2018, the version numbered 14THIN031 (termed "THIN1709") was obtained for this thesis. This version contains updated data for 11,125 active insulin-treated T2D patients, up to September 15th, 2017. The raw data-files are in a simplified flexible structure format, organised by practice and by patients in the form of flat ASCII (American Standard Code for Information Interchange). Each practice data is split into four standard ASCII fixed width text files and three linked files (**Tables 10.2.1, 10.2.2 and 10.2.3**). These comprise records relating to patient, medical, therapy and AHD information. The linked files include postcode variable indicators (PVI), consultation and staff files (**Figure 10.2.1**). Additionally, a series of dictionaries and look-up tables are present, allowing the interpretation of the coded information. The obtained data slice is in SAS format. We converted it to Stata format for all carried management and analyses.

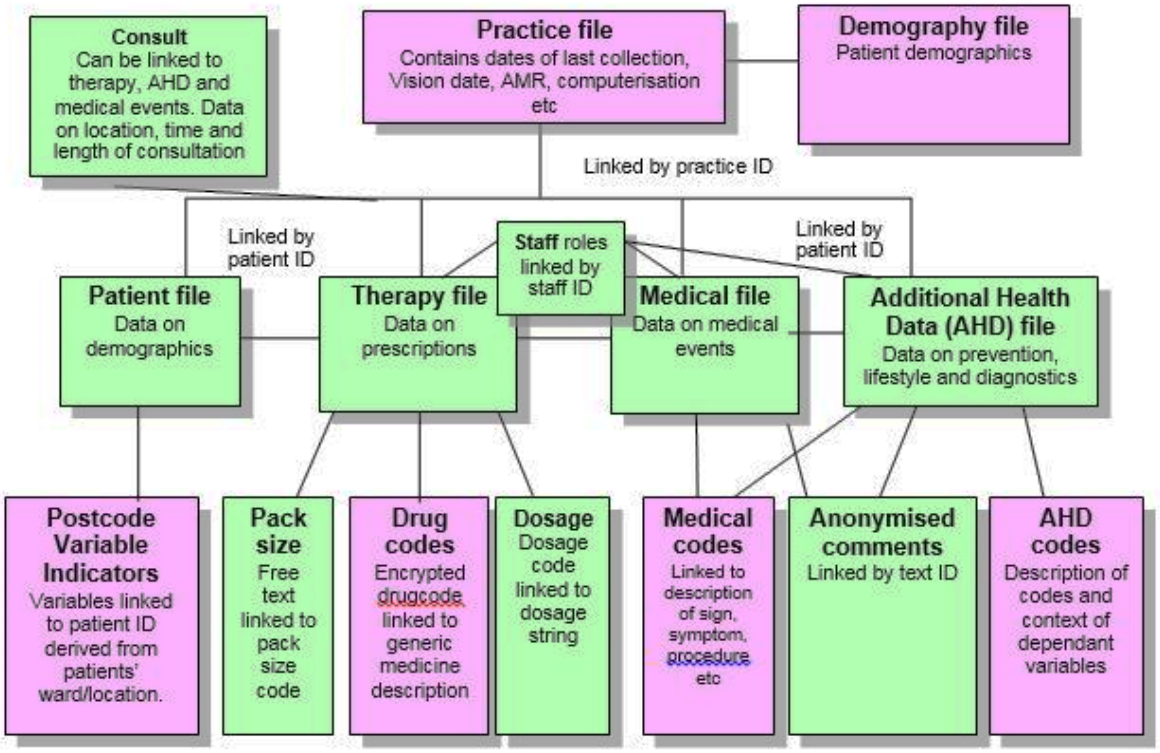

Figure 10.2.1 THIN database structure.

Table 10.3.1 *THIN Data SAS Files.*

File Name	Description	File Size
ahd.sas7bdat	Additional Health Information	1.5 GB
medical.sas7bdat	Medical File	389.6 MB
patient.sas7bdat	Patient File	896 KB
staff.sas7bdat	Staff File	25.2 MB
therapy.sas7bdat	Therapy Data File	1.4 GB
consult.sas7bdat	Consult File	431.5 MB

Table 10.3.2 *THIN Data Ancillary TXT Files.*

File name	Description
AHDCodeFrequencyEver1709.txt	Frequency of all AHDcodes found in the AHD file ever
AHDCodes1709.txt	Additional Health Data codes, in excel and Access
AHDLookups1709.txt	AHD tables lookups, in excel
AHDReadcodeFrequencyEver1709.txt	Frequency count of all Read codes found in the AHD file ever
ATCterms.1709.txt	Anatomical Therapeutic Chemical Classification System code
BNFcodes1709.txt	Lookup of all BNF chapters
DeathAHDcomments1709.txt	List of Death AHD comments available
Dosage1709.txt	Complete list of all dosage codes and dosage instructions
DrugcodeFrequencyEver1709.txt	Frequency of all drug codes found in the Therapy file ever
Drugcodes1709.txt	Drug dictionary, in access and text
FileList1709.txt	List of files on external hard drive
FirstAndLast1709.txt	First and last records for each file on external hard drive, in excel
MedicalReadcodeFrequencyEver1709.txt	Frequency count of all Read codes found in the medical file ever
MidYearCounts1709.txt	Breakdown of population in 1 year age bands
NHSspeciality1709.txt	Clinical specialty lookup, in excel and text
Pack1709.txt	Lookup for detailed information at pack level
Packsize1709.txt	Look up for pack size information in excel and text
PatientStats1709.txt	Count of patients within each practice
Readcodes1709.txt	Medical dictionary, in access and text
THINlookups.txt	Application readable THIN and AHD Lookup values
THINDataFormat1709.docx	Format for THIN Data
THINDataGuide1709.pdf	Guide to using the database
THINPrac1709.txt	Practice file for data

Table 10.3.3 *THIN Data Ancillary SAS Files.*

File name	Description
AHDCodeFrequencyEver1709.sas7bdat	Frequency of all AHDcodes found in the AHD file
AHDCodes1709.sas7bdat	Additional Health Data codes, in excel and Access
AHDLookups1709.sas7bdat	AHD tables lookups, in excel
AHDReadcodeFrequencyEver1709.sas7bdat	Frequency count of all Read codes found in the AHD file
ATCterms1709.sas7bdat	Anatomical Therapeutic Chemical Classification System code
BNFcodes1709.sas7bdat	Lookup of all BNF chapters
DeathAHDcomments1709.sas7bdat	List of Death AHD comments available
Dosage1709.sas7bdat	Complete list of all dosage codes and dosage instructions
DrugcodeFrequencyEver1709.sas7bdat	Frequency of all drug codes found in the Therapy file
Drugcodes1709.sas7bdat	Drug dictionary, in access and text
THIN_SAS file list 1709.xlsx	List of files on external hard drive
FirstAndLast1709.sas7bdat	First and last records for each file on external hard drive, in excel
MedicalReadcodeFrequencyEver1709.sas7bdat	Frequency count of all Read codes found in the medical file
MidYearCounts1709.sas7bdat	Breakdown of population in 1 year age bands
NHSspeciality1709.sas7bdat	Clinical specialty lookup, in excel and text
Pack1709.sas7bdat	Lookup for detailed information at pack level
Packsize1709.sas7bdat	Look up for pack size information in excel and text
PatientStats1709.sas7bdat	Count of patients within each practice
Readcodes1709.sas7bdat	Medical dictionary, in access and text
THINlookups1709.sas7bdat	Application readable THIN and AHD Lookup values
THINPrac1709.sas7bdat	Practice file for data
THINDataFormatSAS1709.docx	Format for THIN Data
THINDataGuide1709.pdf	Guide to using the database

Appendix 10.4 Ethical approval.

NHS

National Research Ethics Service

South East Research Ethics Committee
South East Coast Strategic Health Authority
Preston Hall
Aylesford
Kent
ME20 7NJ

Telephone: 01622 713097
Facsimile: 01622 885966

06 March 2008

Mrs Alison Bourke
Managing Director
EPIC
Regeneration House
York Way
London
N1 0UZ

Dear Mrs Bourke

Full title of study: **The Health Improvement network (Data Collection Scheme)**
REC reference number: **07/H1102/103**

Thank you for your letter of 13 February 2008, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair and named members who were present at the meeting.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

In point (a) of our letter dated 18 October 2007, we said that the Committee would draw up a set of conditions. These are as follows:

The Committee need assurance that the details will either be incorporated into, presumably, the contract they have between them, or some other acknowledgement that the researchers will comply with the requirements. If sent by letter, a signed copy of the letter would be sufficient. If sent by email, a definite reply, printed out and kept, would be needed or something like that. The same applies to researchers outside the UK (as per your point 5 bullet point 3).

Ethical review of research sites

The Committee has designated this study as exempt from site-specific assessment (SSA. There is no requirement for [other] Local Research Ethics Committees to be informed or for site-specific assessment to be carried out at each site.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Application		19 September 2007
Investigator CV		
Protocol		
Advertisement	Poster content for GP surgeries	
Response to Request for Further Information		13 February 2008
SRC ← Protocol review checklist	1	01 February 2008
Letter to Inps		31 January 2008
Practice visit checklist	1	01 February 2008
Suggested wording for practice patient leaflet	2	01 February 2008
Practice poster	2	01 February 2008
Research agreement for supply of THIN data subsets		
sub licence agreement		
Data audit procedures		
SRC ← Scientific review of research		

R&D approval

All researchers and research collaborators who will be participating in the research at NHS sites should apply for R&D approval from the relevant care organisation, if they have not yet done so. R&D approval is required, whether or not the study is exempt from SSA. You should advise researchers and local collaborators accordingly.

Guidance on applying for R&D approval is available from http://www.rdforum.nhs.uk/rdform.htm.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

Here you will find links to the following

a) Providing feedback. You are invited to give your view of the service that you have received from the National Research Ethics Service on the application procedure. If you wish to make your views known please use the feedback form available on the website.

b) Progress Reports. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
c) Safety Reports. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
d) Amendments. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
e) End of Study/Project. Please refer to the attached Standard conditions of approval by Research Ethics Committees.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nationalres.org.uk .

07/H1102/103	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely

pp **Dr L. Alan Ruben**
Chair

Email: nicki.watts@nhs.net

Enclosures: *Standard approval conditions*

Copy to:

Appendix 10.5 READ codes from THIN database.

Table 10.5.1 *Screened Acute Myocardial Infarction (AMI).*

Description	Code
Acute ST segment elevation myocardial infarction	G30X000
Acute anterolateral infarction	G300.00
Acute anteroseptal infarction	G301100
Acute coronary syndrome	G311500
Acute inferolateral infarction	G302.00
Acute myocardial infarction	G30..00
Acute myocardial infarction NOS	G30z.00
Acute non-ST segment elevation myocardial infarction	G307100
Attack - heart	G30..11
Coronary thrombosis	G30..12
Heart attack	G30..14
Inferior myocardial infarction NOS	G308.00
MI - acute myocardial infarction	G30..15
Other specified anterior myocardial infarction	G301.00
Posterior myocardial infarction NOS	G304.00
Silent myocardial infarction	G30..17
Subsequent myocardial infarction	G35..00

Table 10.5.2 *Screened Coronary Heart Diseases (CHD).*

Description	Code
Acute coronary insufficiency	G31y000
Acute inferoposterior infarction	G303.00
Angina at rest	G311200
Angina on effort	G33z300
Angina pectoris	G33..00
Angina pectoris NOS	G33zz00
Anterior myocardial infarction NOS	G301z00
Arteriosclerotic heart disease	G3...11
Asymptomatic coronary heart disease	G34z000
Atherosclerotic cardiovascular disease	G342.00
Atherosclerotic heart disease	G3...12
Chronic myocardial ischaemia	G34y100
Coronary artery disease	G340.12
Coronary artery spasm	G332.00
Coronary atherosclerosis	G340.00
Crescendo angina	G311.11
Double coronary vessel disease	G340100
Dressler's syndrome	G310.11
IHD - Ischaemic heart disease	G3...13
Ischaemic cardiomyopathy	G343.00
Ischaemic chest pain	G33z400

Ischaemic heart disease	G3...00
Ischaemic heart disease NOS	G3z..00
Lateral myocardial infarction NOS	G305.00
Mural thrombosis	G30A.00
New onset angina	G33z600
Old myocardial infarction	G32..00
Other acute and subacute ischaemic heart disease	G31..00
Other chronic ischaemic heart disease	G34..00
Other specified ischaemic heart disease	G3y..00
Prinzmetal's angina	G331.00
Single coronary vessel disease	G340000
Stable angina	G33z700
Triple vessel disease of the heart	G340.11
Unstable angina	G311.13
Worsening angina	G311400

Table 10.5.3 *Screened Cerebrovascular Accident (Stroke).*

Description	Code
Amaurosis fugax	F423600
Brain stem stroke syndrome	G663.00
CVA - Cerebrovascular accident unspecified	G66..13
CVA - cerebral artery occlusion	G64..11
CVA - cerebrovascular accid due to intracerebral haemorrhage	G61..11
CVA unspecified	G66..11
Carotid artery occlusion	G631.00
Carotid artery stenosis	G634.00
Cerebellar haemorrhage	G613.00
Cerebellar infarction	G64z.12
Cerebral aneurysm, nonruptured	G673.00
Cerebral arterial occlusion	G64..00
Cerebral embolism	G641.00
Cerebral infarct due to thrombosis of precerebral arteries	G63y000
Cerebral infarction NOS	G64z.00
Cerebral infarction due to embolism of cerebral arteries	G641000
Cerebral infarction due to embolism of precerebral arteries	G63y100
Cerebral infarction due to thrombosis of cerebral arteries	G640000
Cerebral thrombosis	G640.00
Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs	G6X..00
Cerebrovascular disease	G6...00
Cerebrovascular disease NOS	G6z..00
Chronic cerebral ischaemia	G671100
Drop attack	G65..11
Extradural haemorrhage - nontraumatic	G620.00
Hypertensive encephalopathy	G672.00
Infarction - cerebral	G64..12
Infarction - precerebral	G63..11
Infarction of basal ganglia	G64z400
Intracerebral haemorrhage	G61..00

Intracerebral haemorrhage NOS	G61z.00
Intracerebral haemorrhage, intraventricular	G617.00
Left sided CVA	G667.00
Left sided cerebral infarction	G64z200
Middle cerebral artery syndrome	G660.00
Other transient cerebral ischaemia	G65y.00
Pontine haemorrhage	G614.00
Posterior cerebral artery syndrome	G662.00
Pure motor lacunar syndrome	G665.00
Right sided CVA	G668.00
Right sided cerebral infarction	G64z300
Stenosis, carotid artery	G631.11
Stroke and cerebrovascular accident unspecified	G66..00
Stroke due to cerebral arterial occlusion	G64..13
Stroke due to intracerebral haemorrhage	G61..12
Stroke unspecified	G66..12
Subclavian steal syndrome	G652.00
Subdural haematoma - nontraumatic	G622.00
Subdural haemorrhage - nontraumatic	G621.00
Subdural haemorrhage NOS	G623.00
Transient cerebral ischaemia	G65..00
Transient cerebral ischaemia NOS	G65z.00
Transient global amnesia	G655.00
Transient ischaemic attack	G65..12
Vertebrobasilar insufficiency	G656.00

Table 10.5.4 *Screened Heart Failure.*

Description	Code
Acute congestive heart failure	G580000
Acute heart failure	G582.00
Acute left ventricular failure	G581000
Biventricular failure	G580.14
Cardiac failure	G58..11
Cardiac failure NOS	G58z.12
Chronic congestive heart failure	G580100
Congestive cardiac failure	G580.11
Congestive heart failure	G580.00
Decompensated cardiac failure	G580200
Heart failure	G58..00
Heart failure NOS	G58z.00
Heart failure confirmed	1O1..00
Impaired left ventricular function	G581.13
Left ventricular diastolic dysfunction	G5yyA00
Left ventricular failure	G581.00
Left ventricular systolic dysfunction	G5yy900
New York Heart Association classification - class I	662f.00
New York Heart Association classification - class II	662g.00
New York Heart Association classification - class III	662h.00

New York Heart Association classification - class IV	662i.00
Pulmonary oedema - acute	G581.12
Right heart failure	G580.12
Right ventricular failure	G580.13

Table 10.5.5 *Screened Peripheral Arterial Disease (PAD).*

Description	Code
AAA - Abdominal aortic aneurysm without mention of rupture	G714.11
Abdominal aortic aneurysm without mention of rupture	G714.00
Aortic aneurysm	G71..00
Aortic aneurysm repair	7A14.11
Aortic atherosclerosis	G700.00
Arterial embolism and thrombosis	G74..00
Arterial leg ulcer	M271300
Axillo-unifemoral PTFE bypass graft	7A10300
Bypass femoral artery by fem/pop art anast c vein graft NEC	7A48200
Cardiac failure therapy	8B29.00
Chronic peripheral venous hypertension	G8y3.00
Claudication	G73z011
Diabetic peripheral angiopathy	G73y000
Dissecting aortic aneurysm	G710.00
Embolism and thrombosis of the axillary artery	G74y700
Embolism and thrombosis of the femoral artery	G742400
Embolism and thrombosis of the iliac artery unspecified	G74y300
Embolism and thrombosis of the subclavian artery	G74y500
Extremity artery atheroma	G702.00
Femoro-femoral prosthetic cross over graft	7A48E00
Gangrene of finger	G732200
Gangrene of foot	G732100
Gangrene of toe	G732000
Intermittent claudication	G73z000
Ischaemia of legs	G73..12
Ischaemic leg ulcer	M271.12
Ischaemic ulcer diabetic foot	M271000
Mixed venous and arterial leg ulcer	M271400
Other bypass of common femoral artery	7A48.12
Other bypass of femoral artery	7A48.14
Other bypass of femoral artery or popliteal artery	7A48.00
Other bypass of femoral artery or popliteal artery NOS	7A48z00
Other bypass of femoral artery or popliteal artery OS	7A48y00
Other bypass of superficial femoral artery	7A48.16
Other emergency bypass of femoral artery	7A47.16
Other emergency bypass of popliteal artery	7A47.14
Other peripheral vascular disease	G73..00
Other specified peripheral vascular disease NOS	G73yz00
Percutaneous transluminal balloon angioplasty of aorta	7A1A000
Peripheral gangrene	G732.00
Peripheral ischaemia	G73..13

Peripheral ischaemic vascular disease	G73..11
Peripheral vascular disease NOS	G73z.00
Peripheral vascular disease monitoring	662U.00
Raynaud's disease	G730000
Raynaud's phenomenon	G730100
Raynaud's syndrome	G730.00
Ruptured abdominal aortic aneurysm	G713.11
Ruptured aortic aneurysm NOS	G715.00
Saddle embolus	G740.14
Thoracic aortic aneurysm which has ruptured	G711.00
Thoracic aortic aneurysm without mention of rupture	G712.00
Thrombosis - arterial	G74..12

Table 10.5.6 *Screened bariatric READ codes.*

Description	Code
Bariatric operative procedure	14NE.00
Roux-en-y oesophagogastrectomy	7600111
Total gastrectomy	7610.12
Total gastrectomy and anastomosis oesophagus to jejunum NEC	7610400
Polya partial gastrectomy and anastomosis stomach to jejunum	7611215
Partial gastrectomy and gastrojejunostomy	7611216
Sleeve gastrectomy and duodenal switch	7611400
Sleeve gastrectomy NEC	7611500
Laparoscopic sleeve gastrectomy	7611600
Plastic operations on stomach	7613.00
Gastroplasty NEC	7613000
Laparoscopic adjustable gastric banding	7613200
Partitioning of stomach using band	7613300
Bypass of stomach by anastomosis of stomach to duodenum	7614100
Bypass of stomach by anastomosis of stomach to jejunum NEC	7616000
Laparoscopic gastric bypass	7616600
Gastrostomy operations	7617.00
Gastrostomy operation NOS	7617z00
Gastropexy NEC	7618000
Pyloromyotomy	761B.11
Ramstedt pyloromyotomy	761B011
Pyloroplasty NEC	761B200
Pyloromyotomy and wedge resection	761B500
Gastroscopy and extirpation of lesion	761D.11
Fibreoptic endoscopic laser destructn lesion upper GI tract	761D100
Other therapeutic gastroscopy	761E.11
Temporary percutaneous endoscopic gastrostomy	761E300
Other operations on stomach	761H.00
Insertion of gastric balloon	761H500
Other operation on stomach NOS	761Hz00
Other fibre endos extirp lesion upper gastrointestinal tract	761M.00
Stomach and pylorus operations NOS	761z.00
Closure of perforation of duodenum NEC	7623100

Roux-en-y cholecystojejunostomy	7811212
Roux-en-y procedure for biliary atresia	7824400
Roux-en-y pancreaticojejunostomy	7835.12

Table 10.5.7 *Screened Chronic Kidney Disease (CKD).*

Description	Code
Kidney disease	14D..11
Chronic kidney disease stage 1	1Z10.00
Chronic kidney disease stage 3	1Z12.00
Chronic kidney disease stage 4	1Z13.00
Chronic kidney disease stage 5	1Z14.00
Chronic kidney disease stage 3B without proteinuria	1Z1G.00
Kidney and ureter disease NOS	K13z.00
Injury to kidney	S76..00
Kidney injury without open wound into cavity, unspecified	S760000
Kidney injury without mention of open wound into cavity NOS	S760z00

Table 10.5.8 *Screened liver diseases.*

Description	Code
alcoholic fatty liver	J610.00
acute alcoholic hepatitis	J611.00
alcoholic cirrhosis of liver	J612.00
alcoholic liver damage unspecified	J613.00
alcoholic hepatic failure	J613000
alcoholic hepatitis	J617.00
local ligation of oesophageal varices	7609300
fibreoptic endoscopic banding of oesophageal varices	760C500
glycogenosis with hepatic cirrhosis	C310400
oesophageal varices in cirrhosis of the liver	G852200
gastric varices	G857.00
cirrhosis and chronic liver disease	J61..00
chronic hepatitis	J614.00
chronic active hepatitis	J614100
chronic lobular hepatitis	J614400
chronic hepatitis nos	J614z00
cirrhosis - non alcoholic	J615.00
non-alcoholic cirrhosis nos	J615z00
macronodular cirrhosis of liver	J615z11
cryptogenic cirrhosis of liver	J615z12
cirrhosis of liver nos	J615z13
biliary cirrhosis	J616.00
primary biliary cirrhosis	J616000
other non-alcoholic chronic liver disease	J61y.00
non-alcoholic fatty liver	J61y100
hepatosplenomegaly	J61y200

hepatic fibrosis	J61y400
hepatic sclerosis	J61y500
steatosis of liver	J61y700
nonalcoholic steatohepatitis	J61y800
fatty change of liver	J61y900
chronic liver disease nos	J61z.00
[x]other and unspecified cirrhosis of liver	Jyu7100
hepatitis c status	2J1..00
hepatitis c immune	2J11.00
viral hepatitis	A70..00
viral (infectious) hepatitis a	A701.00
viral (serum) hepatitis b	A703.00
viral hepatitis c without mention of hepatic coma	A705000
acute hepatitis e	A705200
hepatitis non a non b	A705400
chronic viral hepatitis c	A707200
chronic viral hepatitis, unspecified	A707X00
hepatitis c genotype 3	A70C.00
unspecified viral hepatitis	A70z.00
hepatitis c	A70z000
right iliac fossa pain	1977.00
malignant neoplasm of liver and intrahepatic bile ducts	B15..00
primary carcinoma of liver	B150000
hepatocellular carcinoma	B150300
malignant neoplasm of liver unspecified	B152.00
secondary malignant neoplasm of liver	B153.00
malignant neoplasm of common bile duct	B161200
malignant neoplasm of ampulla of vater	B162.00
secondary malignant neoplasm of liver	B577.00
liver metastases	B577.11
benign neoplasm of gallbladder	B715200
focal nodular hyperplasia of liver	B715800
[m]cholangiocarcinoma	BB5D100
[m]hepatoma nos	BB5D511
[m]hepatoma, malignant	BB5D512
[m]hepatobiliary adenoma or carcinoma nos	BB5Dz00
acute hepatic failure	J600000
[x] hepatic failure	J625.00
[x] liver failure	J625.11
hepatic failure nos	J62y.11
liver failure as a complication of care	SP14211
[so]liver	7N33000
portal vein thrombosis	G81..00
portal hypertension	J623.00

Table 10.5.9 *Screened Additional Health Data (AHD).*

Description	AHD Code
Alanine Aminotransferase	1001400006
Albumin	1001400002
Albumin Creatinine Ratio	1001400319
Alkaline Phosphatase	1001400004
Ambulatory blood pressure	1001400253
Aspartate Aminotransferase	1001400007
Asthma status	1009581000
Bilirubin	1001400009
Blood Group	1012000000
Blood glucose	1001400067
Blood pressure	1005010500
C Reactive protein	1001400144
Creatinine clearance	1001400020
Differential white cell count	1001400178
Ethnicity	1082000000
Fasting glucose	1001400139
Full blood count	1001400081
Glomerular filtration rate	1001400326
Haematology screening tests	1001400317
HbA1C - Diabetic control†	1001400140
Height	1005010100
High Density Lipoprotein	1001400031
Lactate Dehydrogenase	1001400033
Liver enzymes	1001400235
Low Density Lipoprotein	1001400035
Packed Cell Volume	1001400213
Platelets	1001400064
Serum cholesterol	1001400017
Serum creatinine	1001400019
Serum globulin	1001400248
Smoking	1003040000
Total protein	1001400043
Triglycerides	1001400045
Urea - blood	1001400051
Urea and Electrolytes	1001400112
Urine microalbumin	1001400311
Very low density lipoprotein	1001400054
Waist circumference	1006100000
Weight	1005010200

† HbA1c is reported in per cent and in mmol/mol. A decision was made to convert all units from per cent to mmol/mol.

Appendix 10.6 Survival analysis.

The development of a predicted outcome of interest is observed and analysed within a set time period during cohort studies: to accomplish this objective, anonymised patients records were harvested and investigated utilising the THIN database (see **Chapters 4**, **5**, and **7**). These studies measure specific outcomes incidence, usually, expressed as a rate. For example, the incidence of new CKD event in a population can be measured according to the following formula:

$$\text{Rate} = \frac{Number\ of\ new\ CKD\ events}{Total\ person{-}time\ from\ the\ specified\ index\ date}$$

This is presented as rates per 100, or 1,000, or 10,000 person-time. The person-time denotes the 'at risk' period: the sum total of the period during which each participant is at risk of the predicted outcome.

In longitudinal data, the collected information comprises the length of follow-up time during which participants are examined. One great advantage of the Cox regression over linear, logistic or Poisson regression models, lays in the ability to not make assumptions that incidence rates are constant over the study period, or constant within specific calendar-time periods or age bands. This is useful, since specific outcomes rates may be subject to rapid change over time. For example, following insulin use, CKD events rate varies with the treatment duration.

The Cox regression model sits within a framework of examinations for time to event data, known as survival analysis. It is noteworthy that an actual survival time period (time to event occurrence) could not be ascertained for all patients. Therefore, the Cox regression data model is useful for analysing varied information of events occurring during the studied set time period. The merit of the Cox model is that it allows these specific patients to be included in the analysis. Additionally, it is robust, flexible, powerful, and able to cope with complex survival data subject to multiple unpredictable factors, and it can handle many covariates and interactions.

The Cox proportional hazards model is used to compute risk rates. It uses a conditional likelihood procedure to take account of particular observations. Additionally, it derives hazard ratios in which the risk rates are compared in different exposure groups. The Cox regression model is based on the hazard rate during a specific time, *t*, within the follow-up period, *h(t)*. Interestingly, during the set follow-up time period, any change value can be observed within the hazard rate, which is intrinsically not a constant factor.

The following steps are involved in fitting a Cox regression model:

i. Survival analysis: this first step analyses the time to the outcome of interest occurrence, e.g. the CKD event, and the loss to follow-up or the predicting loss date. It is worth mentioning that a follow-up time is known for all analysed patients. However, it is not possible to have an actual survival time (time to even occurrence) for all patients. This represents a significant shortcoming.

ii. Kaplan-Meier plots: in building a Cox regression model, this second step allows for simple comparisons between different study-groups, using the log rank test, which provides a direct way of comparing survival curves. All survival times, exact or predicted, were used to compare treatment groups (i.e. bariatric) during the period after the cohort start until the study end point. It is based on calculations of survival probabilities and median survival time, throughout the study. The log rank test is used to compare the probabilities of survival within the entire follow-up duration, by computing the observed survival within the different groups and comparing it with the expected events, if all groups had similar survival.

iii. Fitting the Cox model first for unadjusted and for adjusted measures of effect.

Hazard ratio represents the scale of events risks in individuals exposed (i.e. bariatric) vs those not subjected (non-bariatric) to treatment. When comparing groups of individuals exposed and non-exposed to treatment, an increased hazard rate is suggested when the ratio value is greater than 1. This implies that survival is decreased. Conversely, values below 1 indicate a lower hazard rate and increased chance of survival (i.e. protective effect from treatment or exposure). Likelihood ratio tests (LRT) and Wald's tests can be calculated for the Cox proportional hazards model, to determine statistical significance. Additionally, both categorical and continuous covariates can be included in the Cox model during adjustment, to obtain a tailored hazard ratio with a 95% confidence interval.

Appendix 10.7 Screened drug categories and pharmacological genericnames.

Table 10.7.1 *Insulin.*

	genericname
Insulin	Human insulin 100iu/ml preloaded injection pen
	Human insulin 1mg unit dose blisters
	Human insulin 3mg unit dose blisters
	Human isophane insulin 100iu/ml injection cartridges
	Human isophane insulin 100iu/ml preloaded injection pen
	Insulin aspart 100units/ml solution for injection 1.6ml cartridges
	Insulin aspart 100units/ml solution for injection 10ml vials
	Insulin aspart 100units/ml solution for injection 3ml cartridges
	Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices
	Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml cartridges
	Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices
	Insulin aspart human pyr 100 iu/ml injection 1 10ml vial(s)
	Insulin biphasic 100 units/ml injection
	Insulin biphasic aspart human pyr 30:70; 100 units/ml injection 5 3ml disposable pen(s)
	Insulin biphasic isophane human emp 30:70; 100 units/ml injection
	Insulin biphasic isophane human prb 10:90; 100 units/ml injection
	Insulin biphasic isophane human prb 20:80; 100 units/ml injection
	Insulin biphasic isophane human prb 30:70; 100 units/ml injection
	Insulin biphasic isophane human prb 40:60; 100 units/ml injection
	Insulin biphasic isophane human prb 50:50; 100 units/ml injection
	Insulin biphasic isophane human pyr 10:90; 100 units/ml injection
	Insulin biphasic isophane human pyr 20:80; 100 units/ml injection
	Insulin biphasic isophane human pyr 30:70; 100 units/ml injection
	Insulin biphasic isophane human pyr 30:70; 100 units/ml injection 5 3ml cartridge(s)
	Insulin biphasic isophane human pyr 40:60; 100 units/ml injection
	Insulin biphasic lispro human prb 25:75; 100 units/ml injection 5 3ml disposable pen(s)
	Insulin biphasic lispro human prb 50:50; 100 units/ml injection 5 3ml disposable pen(s)
	Insulin degludec 100units/ml solution for injection 3ml cartridges
	Insulin degludec 100units/ml solution for injection 3ml pre-filled disposable devices
	Insulin degludec 200units/ml solution for injection 3ml pre-filled disposable devices
	Insulin detemir 100units/ml solution for injection 3ml cartridges
	Insulin detemir 100units/ml solution for injection 3ml pre-filled disposable devices
	Insulin glargine 100units/ml solution for injection 10ml vials
	Insulin glargine 100units/ml solution for injection 3ml cartridges
	Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices
	Insulin glargine 300units/ml solution for injection 1.5ml pre-filled disposable devices
	Insulin glulisine 100units/ml solution for injection 10ml vials

Insulin glulisine 100units/ml solution for injection 3ml cartridges

Insulin glulisine 100units/ml solution for injection 3ml pre-filled disposable devices

Insulin human 1mg inhalation powder blisters

Insulin human 3mg inhalation powder blisters

Insulin isophane biphasic Porcine 30/70 Mix 100units/ml suspension for injection 1.5ml cartridges

Insulin isophane biphasic Porcine Isophane 100units/ml suspension for injection 1.5ml cartridges

Insulin isophane biphasic human 10/90 100units/ml suspension for injection 3ml cartridges

Insulin isophane biphasic human 10/90 100units/ml suspension for injection 3ml pre-filled disposable devices

Insulin isophane biphasic human 15/85 100units/ml suspension for injection 3ml cartridges

Insulin isophane biphasic human 15/85 100units/ml suspension for injection 3ml pre-filled disposable devices

Insulin isophane biphasic human 20/80 100units/ml suspension for injection 3ml cartridges

Insulin isophane biphasic human 20/80 100units/ml suspension for injection 3ml pre-filled disposable devices

Insulin isophane biphasic human 25/75 100units/ml suspension for injection 3ml cartridges

Insulin isophane biphasic human 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices

Insulin isophane biphasic human 25/75 100units/ml suspension for injection 5ml vials

Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials

Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges

Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices

Insulin isophane biphasic human 40/60 100units/ml suspension for injection 3ml cartridges

Insulin isophane biphasic human 40/60 100units/ml suspension for injection 3ml pre-filled disposable devices

Insulin isophane biphasic human 50/50 100units/ml suspension for injection 1.5ml cartridges

Insulin isophane biphasic human 50/50 100units/ml suspension for injection 10ml vials

Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml cartridges

Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices

Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 1.5ml cartridges

Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 10ml vials

Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 3ml cartridges

Insulin isophane bovine 100units/ml suspension for injection 10ml vials

Insulin isophane bovine 100units/ml suspension for injection 3ml cartridges

Insulin isophane human 100units/ml suspension for injection 1.5ml cartridges

Insulin isophane human 100units/ml suspension for injection 10ml vials

Insulin isophane human 100units/ml suspension for injection 3ml cartridges

Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices

Insulin isophane human 100units/ml suspension for injection 5ml vials

Insulin isophane human crb 100iu/ml injection

Insulin isophane human emp 100unit/ml injection

Insulin isophane human prb 100iu/ml injection

Insulin isophane human vial 100unit/ml sterile suspension injection

Insulin isophane porcine 100units/ml suspension for injection 1.5ml cartridges

Insulin isophane porcine 100units/ml suspension for injection 10ml vials
Insulin isophane porcine 100units/ml suspension for injection 3ml cartridges
Insulin isophane porcine 100units/ml suspension for injection 3ml cartridges 5 3ml cartridge(s)
Insulin lispro 100units/ml solution for injection 1.5ml cartridges
Insulin lispro 100units/ml solution for injection 1.5ml pre-filled disposable devices
Insulin lispro 100units/ml solution for injection 10ml vials
Insulin lispro 100units/ml solution for injection 3ml cartridges
Insulin lispro 100units/ml solution for injection 3ml pre-filled disposable devices
Insulin lispro 200units/ml solution for injection 3ml pre-filled disposable devices
Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml cartridges
Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices
Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml cartridges
Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices
Insulin protamine zinc bovine 100units/ml suspension for injection 10ml vials
Insulin soluble bovine 100units/ml solution for injection 10ml vials
Insulin soluble bovine 100units/ml solution for injection 3ml cartridges
Insulin soluble human 100units/ml solution for injection 10ml vials
Insulin soluble human 100units/ml solution for injection 3ml cartridges
Insulin soluble human 100units/ml solution for injection 3ml cartridges 5 cartridge
Insulin soluble human prb 100unit/ml injection
Insulin soluble human pyr 100unit/ml injection 5 3ml cartridge(s)
Insulin soluble porcine 100units/ml solution for injection 1.5ml cartridges
Insulin soluble porcine 100units/ml solution for injection 1.5ml cartridges 5 3ml vial(s)
Insulin soluble porcine 100units/ml solution for injection 10ml vials
Insulin soluble porcine 100units/ml solution for injection 3ml cartridges
Insulin zinc crystalline human 100units/ml suspension for injection 10ml vials
Insulin zinc lente 100iu/ml injection
Insulin zinc mixed bovine 100units/ml suspension for injection 10ml vials
Insulin zinc suspension amorphous porcine 100unit/ml injection
Insulin zinc suspension mixed human pyr 100unit/ml injection
Insuman comb 25 100iu/ml Injection
Isophane insulin 100iu/ml injection
Neutral insulin 100iu/ml injection
Neutral insulin 100iu/ml injection cartridges

Table 10.7.2 *Oral Antidiabetic drugs.*

	Genericname
Oral Antidiabetic drugs	Acarbose 100mg tablets
	Acarbose 50mg tablets
	Alogliptin 12.5mg / Metformin 1g tablets
	Alogliptin 12.5mg tablets
	Alogliptin 25mg tablets
	Alogliptin 6.25mg tablets
	Canagliflozin 100mg tablets
	Canagliflozin 300mg tablets
	Chlorpropamide 100mg tablets
	Chlorpropamide 250mg tablets
	Dapagliflozin 10mg tablets
	Dapagliflozin 5mg / Metformin 1g tablets
	Dapagliflozin 5mg tablets
	Empagliflozin 10mg tablets
	Empagliflozin 12.5mg / Metformin 1g tablets
	Empagliflozin 25mg tablets
	Glibenclamide 2.5mg tablets
	Glibenclamide 5mg tablets
	Glibenclamide 5mg/5ml oral suspension
	Gliclazide 30mg modified-release tablets
	Gliclazide 40mg tablets
	Gliclazide 40mg/5ml oral suspension
	Gliclazide 60mg modified-release tablets
	Gliclazide 80mg tablets
	Glimepiride 1mg tablets
	Glimepiride 2mg tablets
	Glimepiride 3mg tablets
	Glimepiride 4mg tablets
	Glipizide 2.5mg tablets
	Glipizide 5mg tablets
	Gliquidone 30mg tablets
	Guar gum 5g granules sachets sugar free
	Guar gum 5g/sachet granules
	Guar gum 90% granules
	Linagliptin 2.5mg / Metformin 1g tablets
	Linagliptin 2.5mg / Metformin 850mg tablets
	Metformin & rosiglitazone 1g+2mg tablets
	Metformin & rosiglitazone 1g+4mg tablets
	Metformin & rosiglitazone 500mg+1mg tablets
	Metformin & rosiglitazone 500mg+2mg tablets
	Metformin 1g / Sitagliptin 50mg tablets

	Metformin 1g modified-release tablets
	Metformin 1g oral powder sachets sugar free
	Metformin 500mg modified-release tablets
	Metformin 500mg oral powder sachets sugar free
	Metformin 500mg tablets
	Metformin 500mg/5ml oral solution
	Metformin 500mg/5ml oral solution sugar free
	Metformin 750mg modified-release tablets
	Metformin 850mg tablets
	Metformin hydrochloride 500mg sachets
	Metformin with rosiglitazone 1000mg + 2mg tablet
	Metformin with rosiglitazone 1000mg + 4mg tablet
	Metformin with rosiglitazone 500mg + 1mg tablet
	Metformin with rosiglitazone 500mg + 2mg tablet
	Nateglinide 120mg tablets
	Nateglinide 180mg tablets
	Nateglinide 60mg tablets
	Pioglitazone 15mg / Metformin 850mg tablets
	Pioglitazone 15mg tablets
	Pioglitazone 30mg tablets
	Pioglitazone 45mg tablets
	Repaglinide 1mg tablets
	Repaglinide 2mg tablets
	Repaglinide 500microgram tablets
	Rosiglitazone 1mg / metformin 500mg tablets
	Rosiglitazone 2mg / metformin 1g tablets
	Rosiglitazone 2mg / metformin 500mg tablets
	Rosiglitazone 4mg / metformin 1g tablets
	Rosiglitazone 4mg tablets
	Rosiglitazone 8mg tablets
	Saxagliptin 2.5mg / Metformin 1g tablets
	Saxagliptin 2.5mg / Metformin 850mg tablets
	Saxagliptin 2.5mg tablets
	Saxagliptin 5mg tablets
	Sitagliptin 100mg tablets
	Sitagliptin 25mg tablets
	Sitagliptin 50mg tablets
	Tolazamide 100mg tablet
	Tolazamide 250mg tablets
	Tolbutamide 500mg tablets
	Vildagliptin 50mg / Metformin 1g tablets
	Vildagliptin 50mg / Metformin 850mg tablets
	Vildagliptin 50mg tablets

Table 10.7.3 *GLP-1 analogues.*

	Genericname
GLP-1 analogues	Dulaglutide 0.75mg/0.5ml solution for injection pre-filled disposable devices Dulaglutide 1.5mg/0.5ml solution for injection pre-filled disposable devices Exenatide 10micrograms/0.04ml solution for injection 2.4ml pre-filled disposable devices Exenatide 2mg powder and solvent for prolonged-release suspension for injection pre-filled disposable devices Exenatide 5micrograms/0.02ml solution for injection 1.2ml pre-filled disposable devices Insulin degludec 100units/ml / Liraglutide 3.6mg/ml solution for injection 3ml pre-filled disposable devices Liraglutide 6mg/ml solution for injection 3ml pre-filled disposable devices Lixisenatide 10micrograms/0.2ml solution for injection 3ml pre-filled disposable devices Lixisenatide 10micrograms/0.2ml solution for injection 3ml pre-filled disposable devices and Lixisenatide 20micrograms/0 Lixisenatide 20micrograms/0.2ml solution for injection 3ml pre-filled disposable devices

Table 10.7.4 *Antihypertensive drugs.*

	Genericname
Antihypertensive drugs	Acebutolol 100mg capsules
	Acebutolol 200mg capsules
	Acebutolol 400mg tablets
	Aliskiren 150mg tablets
	Aliskiren 300mg tablets
	Amiodarone 100mg tablets
	Amiodarone 200mg tablets
	Amlodipine 10mg / Valsartan 160mg tablets
	Amlodipine 10mg tablets
	Amlodipine 5mg / Valsartan 160mg tablets
	Amlodipine 5mg / Valsartan 80mg tablets
	Amlodipine 5mg tablets
	Amlodipine 5mg/5ml oral suspension
	Atenolol & co-amilozide 50mg+2.5mg+25mg capsules
	Atenolol 100mg tablets
	Atenolol 25mg tablets
	Atenolol 25mg/5ml oral solution sugar free
	Atenolol 50mg / Nifedipine 20mg modified-release capsules
	Atenolol 50mg tablets
	Atenolol 5mg/10ml solution for injection ampoules
	Atenolol with amiloride and hydrochlorothiazide capsules
	Azilsartan medoxomil 40mg tablets
	Bendroflumethiazide 5mg with propanolol 160mg modified-release capsules
	Betaxolol 20mg tablets
	Bisoprolol 1.25mg tablets
	Bisoprolol 10mg tablets
	Bisoprolol 2.5mg tablets
	Bisoprolol 3.75mg tablets
	Bisoprolol 5mg tablets
	Bisoprolol 7.5mg tablets
	Candesartan 16mg tablets
	Candesartan 2mg tablets
	Candesartan 32mg tablets
	Candesartan 4mg tablets
	Candesartan 8mg tablets
	Captopril 12.5mg tablets
	Captopril 25mg tablets
	Captopril 50mg tablets
	Carvedilol 12.5mg tablets
	Carvedilol 25mg tablets

Carvedilol 3.125mg tablets
Carvedilol 6.25mg tablets
Celiprolol 200mg tablets
Celiprolol 400mg tablets
Celiprolol hydrochloride 200mg tablets
Cilazapril 1mg tablets
Cilazapril 2.5mg tablets
Cilazapril 500microgram tablets
Cilazapril 5mg tablets
Cilostazol 100mg tablets
Cilostazol 50mg tablets
Cinnarizine 75mg capsules
Clonidine 100microgram tablets
Clonidine 250microgram modified-release capsules
Clonidine 300microgram tablets
Co-prenozide 160mg+0.25mg modified release tablets
Co-tenidone 100mg/25mg tablets
Co-tenidone 50mg/12.5mg tablets
Co-zidocapt 25mg/50mg tablets
Diltiazem 120mg modified-release capsules
Diltiazem 120mg modified-release tablets
Diltiazem 180mg modified-release capsules
Diltiazem 200mg modified-release capsules
Diltiazem 240mg modified-release capsules
Diltiazem 300mg modified-release capsules
Diltiazem 360mg modified-release capsules
Diltiazem 60mg modified-release capsules
Diltiazem 60mg modified-release tablets
Diltiazem 90mg modified-release capsules
Diltiazem 90mg modified-release tablets
Diltiazem hydrochloride 120mg modified release capsules
Diltiazem hydrochloride 180mg modified release capsules
Diltiazem hydrochloride 300mg modified release capsules
Diltiazem hydrochloride 60mg modified release tablets
Diltiazem hydrochloride 90mg modified release capsules
Disopyramide 100mg capsules
Doxazosin 1mg tablets
Doxazosin 2mg tablets
Doxazosin 4mg modified-release tablets
Doxazosin 4mg tablets
Doxazosin 4mg/5ml oral suspension
Doxazosin 8mg modified-release tablets
Dronedarone 400mg tablets

	Enalapril 10mg tablets
	Enalapril 2.5mg tablets
	Enalapril 20mg / Hydrochlorothiazide 12.5mg tablets
	Enalapril 20mg tablets
	Enalapril 5mg tablets
	Enalapril 5mg/5ml oral suspension
	Enalapril maleate starter pack
	Enalapril titration pack
	Eprosartan 300mg tablets
	Eprosartan 400mg tablets
	Eprosartan 600mg tablets
	Felodipine 10mg modified-release tablets
	Felodipine 2.5mg modified-release tablets
	Felodipine 5mg modified-release tablets
	Flecainide 100mg tablets
	Flecainide 200mg modified-release capsules
	Flecainide 50mg tablets
	Fosinopril 10mg tablets
	Fosinopril 20mg tablets
	Generic Tritace titration pack tablets
	Generic tritace titration pack capsules
	Glyceryl trinitrate 10mg/24hours transdermal patches
	Glyceryl trinitrate 15mg/24hours transdermal patches
	Glyceryl trinitrate 1mg modified release buccal tablets
	Glyceryl trinitrate 1mg modified-release buccal tablets sugar free
	Glyceryl trinitrate 2% ointment
	Glyceryl trinitrate 2.5mg/24hours transdermal patches
	Glyceryl trinitrate 2.6mg modified release tablets
	Glyceryl trinitrate 2mg modified release buccal tablets
	Glyceryl trinitrate 2mg modified-release buccal tablets sugar free
	Glyceryl trinitrate 300microgram sublingual tablets
	Glyceryl trinitrate 3mg modified release buccal tablets
	Glyceryl trinitrate 3mg modified-release buccal tablets sugar free
	Glyceryl trinitrate 400mcg spray
	Glyceryl trinitrate 400micrograms/dose aerosol sublingual spray
	Glyceryl trinitrate 400micrograms/dose pump sublingual spray
	Glyceryl trinitrate 500microgram injection
	Glyceryl trinitrate 500microgram sublingual tablets
	Glyceryl trinitrate 5mg modified release buccal tablets
	Glyceryl trinitrate 5mg modified-release buccal tablets sugar free
	Glyceryl trinitrate 5mg/24hours transdermal patches
	Glyceryl trinitrate 600microgram sublingual tablets
	Glyceryl trinitrate pump 400mcg CFC-free spray

	Hydralazine 25mg tablets
	Hydralazine 50mg tablets
	Hydralazine hydrochloride 50mg tablets
	Imidapril 10mg tablets
	Imidapril 20mg tablets
	Imidapril 5mg tablets
	Indoramin 25mg tablets
	Inositol nicotinate 500mg tablets
	Inositol nicotinate 750mg tablets
	Irbesartan 150mg / Hydrochlorothiazide 12.5mg tablets
	Irbesartan 150mg tablets
	Irbesartan 300mg / Hydrochlorothiazide 12.5mg tablets
	Irbesartan 300mg / Hydrochlorothiazide 25mg tablets
	Irbesartan 300mg tablets
	Irbesartan 75mg tablets
	Isosorbide dinitrate 1.25mg spray
	Isosorbide dinitrate 10mg tablets
	Isosorbide dinitrate 20mg modified release capsules
	Isosorbide dinitrate 20mg modified-release capsules
	Isosorbide dinitrate 20mg modified-release tablets
	Isosorbide dinitrate 20mg tablets
	Isosorbide dinitrate 30mg tablets
	Isosorbide dinitrate 40mg modified release capsules
	Isosorbide dinitrate 40mg modified-release capsules
	Isosorbide dinitrate 40mg modified-release tablets
	Isosorbide dinitrate 5mg chewable tablets
	Isosorbide dinitrate 5mg sublingual tablet
	Isosorbide dinitrate 5mg tablets
	Isosorbide mononitrate & aspirin 60mg+75mg modified release tablets
	Isosorbide mononitrate 10mg tablets
	Isosorbide mononitrate 10mg+20mg starter pack
	Isosorbide mononitrate 20mg tablets
	Isosorbide mononitrate 25mg modified-release capsules
	Isosorbide mononitrate 25mg modified-release tablets
	Isosorbide mononitrate 40mg modified release capsules
	Isosorbide mononitrate 40mg modified-release capsules
	Isosorbide mononitrate 40mg modified-release tablets
	Isosorbide mononitrate 40mg tablets
	Isosorbide mononitrate 50mg modified-release capsules
	Isosorbide mononitrate 50mg modified-release tablets
	Isosorbide mononitrate 60mg modified-release capsules
	Isosorbide mononitrate 60mg modified-release tablets
	Isradipine 2.5mg tablets

	Ivabradine 5mg tablets
	Ivabradine 7.5mg tablets
	Labetalol 100mg tablets
	Labetalol 100mg/20ml solution for injection ampoules
	Labetalol 200mg tablets
	Labetalol 400mg tablets
	Labetalol 50mg tablets
	Lacidipine 2mg tablets
	Lacidipine 4mg tablets
	Lercanidipine 10mg tablets
	Lercanidipine 20mg tablets
	Lidocaine 200mg/10ml (2%) solution for injection ampoules
	Lisinopril 10mg / Hydrochlorothiazide 12.5mg tablets
	Lisinopril 10mg tablets
	Lisinopril 2.5mg tablets
	Lisinopril 20mg / Hydrochlorothiazide 12.5mg tablets
	Lisinopril 20mg tablets
	Lisinopril 5mg tablets
	Lisinopril 5mg/5ml oral solution
	Losartan 100mg / Hydrochlorothiazide 12.5mg tablets
	Losartan 100mg / Hydrochlorothiazide 25mg tablets
	Losartan 100mg tablets
	Losartan 12.5mg tablets
	Losartan 25mg tablets
	Losartan 50mg / Hydrochlorothiazide 12.5mg tablets
	Losartan 50mg tablets
	Methyldopa 125mg tablets
	Methyldopa 250mg tablets
	Methyldopa 500mg tablets
	Metoprolol 100mg / hydrochlorothiazide 12.5mg tablets
	Metoprolol 100mg tablets
	Metoprolol 200mg modified-release / hydrochlorothiazide 25mg tablets
	Metoprolol 200mg modified-release tablets
	Metoprolol 50mg tablets
	Metoprolol 50mg/5ml oral suspension
	Metoprolol 5mg/5ml solution for injection ampoules
	Metoprolol tartrate & chlortalidone 100mg+12.5mg tablets
	Metoprolol tartrate & hydrochlorothiazide 100mg+12.5mg tablets
	Metoprolol tartrate & hydrochlorothiazide 200mg+25mg modified release tablets
	Metoprolol tartrate 200mg modified release tablets
	Mexiletine 200mg capsules
	Mexiletine 50mg capsules
	Mibefradil 100mg tablets

Mibefradil 50mg tablet
Mibefradil 50mg tablets
Midodrine 2.5mg tablets
Midodrine 5mg tablets
Minoxidil 10mg tablets
Minoxidil 2.5mg tablets
Minoxidil 5mg tablets
Moxisylyte 40mg tablets
Moxonidine 200microgram tablets
Moxonidine 300microgram tablets
Moxonidine 400microgram tablets
Nadolol 80mg tablets
Naftidrofuryl 100mg capsules
Nebivolol 2.5mg tablets
Nebivolol 5mg tablets
Nicardipine 20mg capsules
Nicardipine 30mg capsules
Nicardipine 30mg modified-release capsules
Nicardipine 45mg modified-release capsules
Nicofuranose 250mg gastro-resistant tablets
Nicorandil 10mg tablets
Nicorandil 20mg tablets
Nicotinyl alcohol 25mg tablet
Nicotinyl alcohol 25mg tablets
Nifedipine 10mg capsules
Nifedipine 10mg modified release tablets
Nifedipine 10mg modified-release capsules
Nifedipine 10mg modified-release tablets
Nifedipine 10mg/5ml oral suspension
Nifedipine 20mg modified release tablets
Nifedipine 20mg modified-release capsules
Nifedipine 20mg modified-release tablets
Nifedipine 30mg modified release tablets
Nifedipine 30mg modified-release capsules
Nifedipine 30mg modified-release tablets
Nifedipine 40mg modified-release tablets
Nifedipine 5mg capsules
Nifedipine 60mg modified-release capsules
Nifedipine 60mg modified-release tablets
Nimodipine 30mg tablets
Nisoldipine 10mg modified-release tablets
Nisoldipine 20mg modified-release tablets
Nisoldipine 30mg modified-release tablets

Olmesartan medoxomil 10mg tablets
Olmesartan medoxomil 20mg / Hydrochlorothiazide 12.5mg tablets
Olmesartan medoxomil 20mg / Hydrochlorothiazide 25mg tablets
Olmesartan medoxomil 20mg tablets
Olmesartan medoxomil 40mg / Hydrochlorothiazide 12.5mg tablets
Olmesartan medoxomil 40mg tablets
Oxerutins 250mg capsules
Oxprenolol 160mg modified-release tablets
Oxprenolol 20mg tablets
Oxprenolol 40mg tablets
Oxprenolol 80mg tablets
Oxprenolol hydrochloride 80mg tablets
Pentoxifylline 400mg modified-release tablets
Perhexiline maleate 100mg tablet
Perindopril arginine 10mg tablets
Perindopril arginine 2.5mg tablets
Perindopril arginine 5mg / Indapamide 1.25mg tablets
Perindopril arginine 5mg tablets
Perindopril erbumine & indapamide 4mg+1.25mg tablets
Perindopril erbumine 2mg tablets
Perindopril erbumine 4mg / indapamide 1.25mg tablets
Perindopril erbumine 4mg tablets
Perindopril erbumine 4mg/5ml oral suspension
Perindopril erbumine 8mg tablets
Phenoxybenzamine 10mg capsules
Pindolol 10mg / Clopamide 5mg tablets
Pindolol 15mg tablets
Pindolol 5mg tablets
Prazosin 1mg tablets
Prazosin 1mg tablets and prazosin 500microgram tablets
Prazosin 2mg tablets
Prazosin 500microgram tablets
Prazosin 5mg tablets
Prazosin hydrochloride 500mcg+1mg starter pack
Propafenone 150mg tablets
Propafenone 300mg tablets
Propranolol & bendroflumethiazide 160mg+5mg modified release capsules
Propranolol & bendroflumethiazide 80mg+2.5mg capsules
Propranolol 10mg tablets
Propranolol 160mg modified-release / bendroflumethiazide 5mg capsules
Propranolol 160mg modified-release capsules
Propranolol 160mg tablets

	Propranolol 40mg tablets
	Propranolol 40mg/5ml oral solution sugar free
	Propranolol 5mg/5ml oral solution sugar free
	Propranolol 80mg modified-release capsules
	Propranolol 80mg tablets
	Propranolol hydrochloride 10mg tablets
	Propranolol hydrochloride 160mg tablets
	Propranolol hydrochloride 40mg tablets
	Propranolol hydrochloride 80mg tablets
	Quinapril 10mg / Hydrochlorothiazide 12.5mg tablets
	Quinapril 10mg tablets
	Quinapril 20mg tablets
	Quinapril 40mg tablets
	Quinapril 5mg tablets
	Quinidine bisulfate 250mg modified-release tablets
	Quinidine sulfate 200mg tablets
	Quinidine sulfate 300mg tablets
	Ramipril 1.25mg capsules
	Ramipril 1.25mg tablets
	Ramipril 10mg capsules
	Ramipril 10mg tablets
	Ramipril 10mg/5ml oral suspension
	Ramipril 2.5mg capsules
	Ramipril 2.5mg tablets
	Ramipril 2.5mg/5ml oral suspension
	Ramipril 5mg capsules
	Ramipril 5mg tablets
	Ranolazine 375mg modified-release tablets
	Ranolazine 500mg modified-release tablets
	Ranolazine 750mg modified-release tablets
	Sacubitril 24mg / Valsartan 26mg tablets
	Sacubitril 49mg / Valsartan 51mg tablets
	Sacubitril 97mg / Valsartan 103mg tablets
	Sotalol 160mg tablets
	Sotalol 160mg with hydrochlorothiazide 25mg tablet
	Sotalol 200mg tablets
	Sotalol 40mg tablets
	Sotalol 80mg tablets
	Sotalol hydrochloride & hydrochlorothiazide 80mg+12.5mg tablets
	Telmisartan 20mg tablets
	Telmisartan 40mg / Hydrochlorothiazide 12.5mg tablets
	Telmisartan 40mg tablets
	Telmisartan 80mg / Hydrochlorothiazide 12.5mg tablets

	Telmisartan 80mg / Hydrochlorothiazide 25mg tablets
	Telmisartan 80mg tablets
	Terazosin 10mg tablets
	Terazosin 2mg tablets
	Terazosin 2mg tablets and Terazosin 1mg tablets
	Terazosin 5mg tablets
	Timolol 10mg / Amiloride 2.5mg / Hydrochlorothiazide 25mg tablets
	Timolol 10mg / Bendroflumethiazide 2.5mg tablets
	Timolol 10mg tablets
	Timolol maleate & bendroflumethiazide 20mg+5mg tablets
	Timolol maleate & co-amilozide 10mg+2.5mg+25mg tablets
	Timolol maleate 10mg tablets
	Trandolapril & verapamil hydrochloride 2mg+180mg modified release capsules
	Trandolapril 1mg capsules
	Trandolapril 2mg capsules
	Trandolapril 4mg capsules
	Trandolapril 500microgram capsules
	Trandolapril with verapamil 2mg + 180mg modified-release capsule
	Valsartan 160mg / Hydrochlorothiazide 12.5mg tablets
	Valsartan 160mg / Hydrochlorothiazide 25mg tablets
	Valsartan 160mg capsules
	Valsartan 160mg tablets
	Valsartan 320mg tablets
	Valsartan 40mg capsules
	Valsartan 40mg tablets
	Valsartan 80mg / Hydrochlorothiazide 12.5mg tablets
	Valsartan 80mg capsules
	Valsartan 80mg tablets
	Verapamil 120mg modified-release capsules
	Verapamil 120mg modified-release tablets
	Verapamil 120mg tablets
	Verapamil 160mg tablets
	Verapamil 180mg modified-release / trandolapril 2mg capsules
	Verapamil 180mg modified-release capsules
	Verapamil 240mg modified-release capsules
	Verapamil 240mg modified-release tablets
	Verapamil 40mg tablets
	Verapamil 80mg tablets
	Verapamil hydrochloride 120mg modified release capsules
	Verapamil hydrochloride 120mg tablets
	Verapamil hydrochloride 180mg modified release capsules
	Verapamil hydrochloride 240mg modified release capsules
	Xamoterol fumarate 200mg tablets

Table 10.7.5 *Lipids lowering drugs.*

	Genericname
Lipids lowering drugs	Acipimox 250mg capsules
	Atorvastatin 10mg chewable tablets sugar free
	Atorvastatin 10mg tablets
	Atorvastatin 20mg chewable tablets sugar free
	Atorvastatin 20mg tablets
	Atorvastatin 40mg tablets
	Atorvastatin 60mg tablets
	Atorvastatin 80mg tablets
	Bezafibrate 200mg tablets
	Bezafibrate 400mg modified-release tablets
	Cerivastatin 100microgram tablets
	Cerivastatin 200microgram tablets
	Cerivastatin 300microgram tablets
	Cerivastatin 400microgram tablets
	Cerivastatin sodium 100mcg tablets
	Cerivastatin sodium 200mcg tablets
	Cerivastatin sodium 300mcg tablets
	Cerivastatin sodium 400mcg tablets
	Ciprofibrate 100mg tablets
	Clofibrate 500mg capsules
	Colesevelam 625mg tablets
	Colestipol 5g granules sachets sugar free
	Colestyramine 4g oral powder sachets
	Colestyramine 4g oral powder sachets sugar free
	Eicosapentaenoic acid 170mg / Docosahexaenoic acid 115mg capsules
	Eicosapentaenoic acid 170mg/g / docosahexaenoic acid 115mg/g oral liquid
	Eicosapentaenoic acid 460mg / Docosahexaenoic acid 380mg capsules
	Ezetimibe 10mg tablets
	Fenofibrate 100mg capsule
	Fenofibrate 100mg capsules
	Fenofibrate micronised 160mg tablets
	Fenofibrate micronised 200mg capsules
	Fenofibrate micronised 267mg capsules
	Fenofibrate micronised 67mg capsules
	Fish oil concentrate 1g capsules
	Fish oil concentrate oral liquid
	Fluvastatin 20mg capsules
	Fluvastatin 40mg capsules
	Fluvastatin 80mg modified-release tablets
	Gemfibrozil 300mg capsules

	Gemfibrozil 600mg tablets
	Ispaghula husk 3.5g sugar free granules
	Nicotinic acid & laropiprant 1g+20mg tablets
	Nicotinic acid 1g / laropiprant 20mg modified-release tablets
	Nicotinic acid 1g modified release tablets
	Nicotinic acid 1g modified-release tablets
	Nicotinic acid 25mg tablet
	Nicotinic acid 375mg + 500mg + 750mg modified-release tablet
	Nicotinic acid 500mg modified-release tablets
	Nicotinic acid 50mg tablets
	Nicotinic acid 750mg modified release tablets
	Nicotinic acid 750mg modified-release tablets
	Nicotinic acid pack
	Pravastatin 10mg tablets
	Pravastatin 20mg tablets
	Pravastatin 40mg tablets
	Rosuvastatin 10mg tablets
	Rosuvastatin 20mg tablets
	Rosuvastatin 40mg tablets
	Rosuvastatin 5mg tablets
	Simvastatin 10mg tablets
	Simvastatin 20mg / Ezetimibe 10mg tablets
	Simvastatin 20mg tablets
	Simvastatin 20mg/5ml oral suspension sugar free
	Simvastatin 40mg / Ezetimibe 10mg tablets
	Simvastatin 40mg tablets
	Simvastatin 40mg/5ml oral suspension sugar free
	Simvastatin 80mg / Ezetimibe 10mg tablets
	Simvastatin 80mg tablets

Table 10.7.6 *Diuretics.*

	Genericname
Diuretics	Amiloride 2.5mg / Cyclopenthiazide 250microgram tablets
	Amiloride 5mg / Bumetanide 1mg tablets
	Amiloride 5mg / hydrochlorothiazide 50mg/5ml solution
	Amiloride 5mg tablets
	Amiloride hydrochloride 5mg tablets
	Bendroflumethiazide & potassium 2.5mg+7.7mmol modified release tablets
	Bendroflumethiazide & potassium 2.5mg+8.4mmol modified release tablets
	Bendroflumethiazide 2.5mg / potassium chloride 630mg (potassium 8.4mmol) modified-release tablets
	Bendroflumethiazide 2.5mg tablets
	Bendroflumethiazide 2.5mg/5ml oral suspension
	Bendroflumethiazide 5mg tablets
	Bumetanide & potassium 500mcg+7.7mmol modified release tablets
	Bumetanide 1mg tablets
	Bumetanide 1mg/5ml oral solution sugar free
	Bumetanide 500microgram / potassium chloride 573mg (potassium 7.7mmol) modified-release tablets
	Bumetanide 5mg tablets
	Chlorothiazide 500mg tablets
	Chlortalidone 100mg tablets
	Chlortalidone 50mg tablets
	Co-amilofruse 10mg/80mg tablets
	Co-amilofruse 2.5mg/20mg tablets
	Co-amilofruse 5mg/40mg tablets
	Co-amilozide 2.5mg/25mg tablets
	Co-amilozide 5mg+50mg tablets
	Co-amilozide 5mg+50mg/5ml oral solution
	Co-amilozide 5mg/50mg tablets
	Co-flumactone 25mg/25mg tablets
	Co-flumactone 50mg/50mg tablets
	Co-triamterzide 50mg/25mg tablets
	Cyclopenthiazide -k tablets
	Cyclopenthiazide 500mcg tablets
	Cyclopenthiazide 500microgram tablets
	Eplerenone 25mg tablets
	Eplerenone 50mg tablets
	Furosemide & modified release potassium 40mg+10mmol tablets
	Furosemide & potassium 20mg+10mmol modified release tablets
	Furosemide 20mg tablets
	Furosemide 20mg/2ml solution for injection ampoules
	Furosemide 20mg/5ml oral solution
	Furosemide 250mg/25ml solution for injection ampoules

	Furosemide 40mg / Potassium chloride 600mg (potassium 8mmol) modified-release tablets
	Furosemide 40mg tablets
	Furosemide 40mg/5ml oral solution sugar free
	Furosemide 500mg tablets
	Furosemide 50mg/5ml injection
	Furosemide 50mg/5ml oral solution
	Furosemide 50mg/5ml solution for injection ampoules
	Hydrochlorothiazide 25mg tablets
	Indapamide 1.5mg modified-release tablets
	Indapamide 2.5mg tablets
	Metolazone 500mcg tablets
	Metolazone 5mg tablets
	Spironolactone 100mg capsule
	Spironolactone 100mg tablets
	Spironolactone 25mg tablets
	Spironolactone 25mg/5ml oral suspension
	Spironolactone 50mg / Furosemide 20mg capsules
	Spironolactone 50mg tablets
	Spironolactone 50mg/5ml oral suspension
	Torasemide 10mg tablets
	Torasemide 2.5mg tablets
	Torasemide 5mg tablets
	Triamterene 50mg / Furosemide 40mg tablets
	Triamterene 50mg / benzthiazide 25mg capsules
	Triamterene 50mg capsules
	Xipamide 20mg tablets

Table 10.7.7 *Aspirin.*

	Genericname
Aspirin	Aspirin 100mg effervescent tablets
	Aspirin 100mg modified release tablets
	Aspirin 300mg effervescent tablets
	Aspirin 75mg dispersible tablets
	Aspirin 75mg gastro-resistant tablets
	Aspirin 75mg tablets
	Clopidogrel 300mg tablets
	Clopidogrel 75mg tablets
	Dipyridamole 100mg tablets
	Dipyridamole 100mg/5ml oral suspension
	Dipyridamole 200mg modified-release / Aspirin 25mg capsules
	Dipyridamole 200mg modified-release capsules
	Dipyridamole 25mg tablets
	Dipyridamole 50mg/5ml oral suspension sugar free
	Prasugrel 10mg tablets
	Prasugrel 5mg tablets
	Ticagrelor 90mg tablets
	Ticlopidine 250mg tablets

Appendix 10.8 Obesity-related comorbidity events.

Table 10.8.1 *Frequency of obesity-related comorbidity events, with READ codes, among a cohort of 160 participants (related to **Chapter 7**).*

Patient ID	Observed Comorbidity	READ code	Bariatric (Yes/No)	Observed event date	Baseline date
a665801vZ	gall	J651000	Yes	29-Jun-12	01-Jun-12
a665801vZ	cvd	G66..00	Yes	20-Jan-16	01-Jun-12
a665901i5	cvd	G66..00	No	27-May-11	29-Oct-10
a665901i5	cvd	G66..00	No	18-Jun-11	29-Oct-10
a677504qw	gall	J64..15	Yes	16-Jan-17	13-Dec-15
a680201OQ	depdem	Eu32z11	Yes	08-Feb-12	27-Jun-09
a689700D1	asthma	Fy03.11	Yes	01-Apr-10	27-Jan-10
a777809pN	gord	J10y412	No	31-Jul-15	03-Dec-12
a783200Pj	hypert	G2...00	No	12-Aug-04	17-Oct-03
a793903oV	depdem	E200300	No	19-Jan-15	21-Mar-11
a793903oV	depdem	E200300	No	19-Mar-15	21-Mar-11
a980001rV	cvd	G33..00	No	25-Jan-17	22-Oct-14
a980001rV	cvd	G581.13	No	16-Jan-17	22-Oct-14
a980001rV	cvd	662T.00	No	17-Jan-17	22-Oct-14
a980001rV	cvd	G58..00	No	11-Apr-17	22-Oct-14
a984900dD	arthritis	N05..11	No	27-Jan-17	31-Dec-12
a987001dh	ckd	1Z12.00	No	10-Aug-15	21-Jan-13
a987001dh	cholath	C320.00	No	19-Jan-15	21-Jan-13
a987001dh	gord	J10y500	No	09-Mar-16	21-Jan-13
a987001dh	ckd	K053.00	No	16-Dec-15	21-Jan-13
a991000pM	depdem	Eu32z11	No	31-Aug-12	20-Mar-12
a991000pM	depdem	Eu32z11	No	03-Oct-12	20-Mar-12
a991000pM	depdem	Eu32z11	No	30-Aug-12	20-Mar-12
b668701TR	depdem	E200.00	No	10-Jan-11	14-Dec-10
b668701TR	depdem	E135.00	No	24-Jan-11	14-Dec-10
b688200YT	ckd	1Z11.00	No	09-Dec-08	15-Jul-05
b688200YT	ckd	1Z12.00	No	19-Mar-08	15-Jul-05
b688204Tj	gout	C34..00	Yes	22-Oct-08	02-Jul-08
b688204Tj	gout	C34..00	Yes	05-Oct-11	02-Jul-08
b688300Zc	gout	C34..00	No	02-Apr-15	01-Dec-10
b688300Zc	depdem	Eu32z11	No	30-Dec-13	01-Dec-10
b688702UM	ckd	1Z11.00	No	29-Sep-08	03-Nov-05
b688702UM	ckd	1Z11.00	No	02-May-08	03-Nov-05
b793803rB	hypert	G20..11	Yes	21-Jul-09	26-Jan-09

b793803rB	hypert	G20..11	Yes	01-Nov-12	26-Jan-09
b982301P3	ckd	1Z10.00	No	18-May-11	06-Jul-09
b982301P3	ckd	1Z10.00	No	12-Feb-10	06-Jul-09
b982301P3	ckd	1Z10.00	No	13-Jan-14	06-Jul-09
b982301P3	ckd	1Z10.00	No	05-Mar-12	06-Jul-09
b982301P3	ckd	1Z10.00	No	25-Mar-13	06-Jul-09
b9857038i	cvd	G581.13	Yes	15-Oct-16	15-Feb-15
b988400gy	cvd	G3...00	No	01-Jul-00	03-May-00
b988401LE	gall	7810500	No	19-Jul-11	07-Nov-08
b988401LE	gall	J64..15	No	08-Apr-11	07-Nov-08
b9925017D	cvd	G6...00	Yes	06-Feb-08	04-Feb-08
b996400IB	depdem	E200300	Yes	17-Jan-11	02-Nov-07
b996400IB	cholath	C320.00	Yes	12-Aug-10	02-Nov-07
b996400IB	cholath	C320.00	Yes	08-Dec-08	02-Nov-07
b996400IB	arthritis	N053512	Yes	25-Oct-12	02-Nov-07
b996400IB	depdem	E113.11	Yes	15-Feb-12	02-Nov-07
b998900ia	gout	C34..00	Yes	04-Jan-05	04-Jan-02
b999801Dx	gout	C34..00	No	22-Feb-11	26-Jan-09
b999801Dx	ckd	1Z15.00	No	27-Nov-13	26-Jan-09
b999801Dx	gout	C34..00	No	24-May-11	26-Jan-09
c678400PE	ckd	1Z12.00	No	27-Oct-10	21-Jul-09
c6830001U	depdem	E200.00	Yes	26-Jul-07	14-Aug-06
c6830001U	depdem	E200.00	Yes	27-Nov-08	14-Aug-06
c6830001U	depdem	E200.00	Yes	29-Jul-11	14-Aug-06
c6830001U	depdem	E200.00	Yes	24-Aug-10	14-Aug-06
c6830001U	depdem	E135.00	Yes	19-Dec-08	14-Aug-06
c778105dw	gord	J15..00	No	13-Jun-11	05-Dec-07
c778105dw	cholath	8BAG.00	No	08-Oct-08	05-Dec-07
c780500Sc	cholath	C320.00	No	31-Oct-11	25-Feb-11
c780502DM	ckd	1Z1..00	Yes	21-Aug-13	05-Aug-11
c780502DM	ckd	K050.00	Yes	13-Jul-12	05-Aug-11
c989406l5	arthritis	N05..11	Yes	06-Jul-07	16-Nov-04
c9896013T	depdem	E200.00	Yes	01-Dec-15	28-Apr-15
c989603LZ	arthritis	N05..11	Yes	11-Jan-17	07-Apr-12
c989700EG	arthritis	N05..11	No	09-Jul-13	24-Dec-12
c999602NY	asthma	R005311	Yes	01-May-12	30-Apr-09
c999608hx	cvd	G573000	No	18-Sep-14	02-Nov-12
c999608hx	ckd	1Z12.00	No	08-Jul-15	02-Nov-12
c999608hx	cvd	G573000	No	18-Sep-14	02-Nov-12
c999806f6	cvd	G3...00	No	15-May-07	13-Jun-06
c999806f6	arthritis	N05z.00	No	19-Oct-07	13-Jun-06
c999806f6	arthritis	N05z.00	No	06-Aug-07	13-Jun-06
d671903PU	cvd	G58..00	Yes	06-Mar-06	09-Dec-04

d671903PU	cvd	G58..00	Yes	29-Jun-06	09-Dec-04
d671903PU	cvd	G58..00	Yes	05-Mar-06	09-Dec-04
d671903PU	gout	C34..00	Yes	08-Oct-09	09-Dec-04
d671903PU	cvd	G58..00	Yes	18-Jul-06	09-Dec-04
d671903PU	gout	C34..00	Yes	03-Sep-09	09-Dec-04
d671903PU	cvd	G58..00	Yes	09-May-06	09-Dec-04
d671903PU	cvd	G58..00	Yes	30-Mar-06	09-Dec-04
d671903PU	cvd	G58..00	Yes	07-Apr-06	09-Dec-04
d671903PU	gout	C34..00	Yes	22-Oct-09	09-Dec-04
d672702AN	cvd	G573000	Yes	12-Feb-14	26-May-11
d672702AN	hypert	G20..11	Yes	04-Jun-13	26-May-11
d675301nN	arthritis	N11D.00	No	06-Oct-15	25-Sep-12
d676402bu	gout	C34..00	Yes	09-Jul-07	20-Jul-04
d676402bu	ckd	1Z13.00	Yes	14-Sep-06	20-Jul-04
d676402bu	cvd	G86..11	Yes	10-Nov-06	20-Jul-04
d676402bu	gout	C34..00	Yes	02-Dec-04	20-Jul-04
d676402bu	gout	C34..00	Yes	07-Jun-07	20-Jul-04
d676402bu	ckd	1Z16.00	Yes	04-Sep-07	20-Jul-04
d683803FG	ckd	K054.00	No	11-Nov-13	19-Oct-11
d687801xE	depdem	E200300	Yes	03-Nov-09	28-Jul-09
d779300xa	cvd	G65..12	Yes	06-Jan-04	26-Jan-01
d779300xa	cvd	G64..00	Yes	06-Jan-04	26-Jan-01
d779300xa	depdem	Eu32z11	Yes	09-Oct-03	26-Jan-01
d779300xa	cvd	G65..12	Yes	06-Jan-04	26-Jan-01
d779300xa	hypert	G2...00	Yes	17-Feb-04	26-Jan-01
d794100Wf	ckd	1Z11.00	Yes	28-Feb-07	01-Jul-05
d980305Cm	gord	J17z.00	Yes	01-Jul-12	07-Dec-11
d980305rl	gord	J101100	No	24-Jan-12	08-Jun-09
d980305rl	gord	J10y412	No	23-Aug-10	08-Jun-09
d980305rl	ckd	1Z10.00	No	01-Jul-09	08-Jun-09
d980305rl	gord	J17z.00	No	01-Jul-11	08-Jun-09
d98030A@w	arthritis	N051B00	No	18-Jun-13	08-Jun-13
d9844012v	cvd	G64..11	Yes	10-May-05	16-Jun-04
d987702Vy	gall	J671.00	No	04-May-16	13-Jun-11
d992804vj	cvd	G573000	No	25-Mar-11	08-Oct-10
d992804vj	cancer	B141.00	No	08-Dec-14	08-Oct-10
d992804vj	cvd	G580.11	No	03-Feb-11	08-Oct-10
d992804vj	cvd	G580.11	No	24-Dec-10	08-Oct-10
d992804vj	cvd	G573000	No	11-Jun-12	08-Oct-10
d992804vj	cvd	G573000	No	29-Sep-11	08-Oct-10
d992804vj	gord	J10y412	No	23-Nov-10	08-Oct-10
d992804vj	cvd	G580.11	No	23-Nov-10	08-Oct-10
d992804vj	cvd	G573000	No	02-Nov-10	08-Oct-10

d992804vj	cvd	G580.11	No	21-Dec-10	08-Oct-10
d992804vj	cvd	G580.11	No	23-Nov-10	08-Oct-10
d992804vj	cvd	G573000	No	11-Jun-12	08-Oct-10
d992804vj	gord	J10y412	No	12-Nov-10	08-Oct-10
d992804vj	cvd	G573000	No	11-Jun-12	08-Oct-10
d99570031	cvd	G87..00	Yes	09-Jul-13	13-Jul-12
d99570031	cvd	G87..00	Yes	23-May-13	13-Jul-12
d99570031	arthritis	N05..11	Yes	18-Jul-13	13-Jul-12
d99570031	cvd	G87..00	Yes	21-May-13	13-Jul-12
d99570031	arthritis	N05..11	Yes	04-Feb-14	13-Jul-12
d997000gO	depdem	E113.11	No	23-Apr-15	21-Feb-12
d997000gO	depdem	E113.11	No	10-Apr-15	21-Feb-12
e681704xK	ckd	1Z12.00	No	13-Nov-12	29-Aug-12
e681704xK	ckd	1Z12.00	No	25-Sep-12	29-Aug-12
e977602Vj	hypert	G2...00	Yes	03-Jun-16	19-Aug-14
f670400VL	arthritis	N11D.00	Yes	28-Nov-13	08-Aug-13
f670401AN	arthritis	N05zH00	No	17-Jul-13	06-Jul-12
f673702cw	cvd	G3...00	No	04-Oct-07	02-Aug-07
f673702cw	depdem	E200300	No	29-Jul-11	02-Aug-07
f673702cw	cvd	G3...00	No	03-Oct-07	02-Aug-07
f674900js	cholath	8CA4700	No	18-Dec-06	19-Aug-04
f674900js	cholath	8CA4700	No	24-Aug-04	19-Aug-04
f680300dA	cholath	C320.00	Yes	13-Dec-07	19-Sep-06
f680300dA	cholath	C320.00	Yes	24-Aug-07	19-Sep-06
f680300dA	ckd	1Z12.00	Yes	04-Sep-08	19-Sep-06
f6818047O	hypert	G2...00	No	14-May-09	07-Sep-05
f681804PX	gall	J64..15	No	31-Mar-14	06-Jun-12
f977201x0	ckd	1Z11.00	No	20-Nov-07	16-Aug-05
f986600SB	depdem	E200300	Yes	12-Dec-15	14-Nov-12
f986600du	gord	J10y412	No	10-Sep-12	16-Jul-12
f986605qV	cvd	G86..11	Yes	07-Dec-12	09-Nov-09
f989201xi	ckd	1Z12.00	Yes	23-Jan-07	07-Oct-05
f991301FL	asthma	H5B..00	No	17-Oct-14	25-Mar-13

Appendix 10.9 Exact count of prescribed drugs with pharmacological genericnames.

Table 10.9.1 *Frequency of drug use for a cohort of 160 patients throughout 5 years of follow-up (related to **Chapter 7**).*

Insulin	
Genericname	Frequency
Insulin aspart 100units/ml solution for injection 3ml cartridges	169
Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices	518
Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml cartridges	145
Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices	356
Insulin biphasic isophane human prb 30:70; 100 units/ml injection	3
Insulin detemir 100units/ml solution for injection 3ml cartridges	68
Insulin detemir 100units/ml solution for injection 3ml pre-filled disposable devices	435
Insulin glargine 100units/ml solution for injection 10ml vials	23
Insulin glargine 100units/ml solution for injection 3ml cartridges	135
Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices	877
Insulin glargine 300units/ml solution for injection 1.5ml pre-filled disposable devices	19
Insulin glulisine 100units/ml solution for injection 10ml vials	1
Insulin glulisine 100units/ml solution for injection 3ml pre-filled disposable devices	23
Insulin isophane biphasic human 25/75 100units/ml suspension for injection 3ml cartridges	40
Insulin isophane biphasic human 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices	23
Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges	257
Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices	403
Insulin isophane human 100units/ml suspension for injection 3ml cartridges	259
Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices	174
Insulin lispro 100units/ml solution for injection 1.5ml pre-filled disposable devices	3
Insulin lispro 100units/ml solution for injection 3ml cartridges	90
Insulin lispro 100units/ml solution for injection 3ml pre-filled disposable devices	77
Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml cartridges	24
Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices	65
Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml cartridges	77
Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices	23
Insulin soluble human 100units/ml solution for injection 3ml cartridges	5

OAD	
Genericname	Frequency
Acarbose 100mg tablets	11
Canagliflozin 100mg tablets	13
Dapagliflozin 10mg tablets	127
Dapagliflozin 5mg tablets	9
Glibenclamide 5mg tablets	14
Gliclazide 30mg modified-release tablets	36
Gliclazide 40mg tablets	16
Gliclazide 80mg tablets	958
Glimepiride 1mg tablets	1
Glimepiride 2mg tablets	48
Glimepiride 3mg tablets	13
Glimepiride 4mg tablets	19
Glipizide 5mg tablets	13
Metformin & rosiglitazone 1g+4mg tablets	19
Metformin 1g modified-release tablets	208
Metformin 500mg modified-release tablets	597
Metformin 500mg oral powder sachets sugar free	16
Metformin 500mg tablets	2098
Metformin 500mg/5ml oral solution	34
Metformin 750mg modified-release tablets	4
Metformin 850mg tablets	395
Pioglitazone 15mg tablets	114
Pioglitazone 30mg tablets	48
Pioglitazone 45mg tablets	54
Repaglinide 1mg tablets	8
Repaglinide 500microgram tablets	2
Rosiglitazone 4mg tablets	70
Rosiglitazone 8mg tablets	22
Saxagliptin 5mg tablets	3
Sitagliptin 100mg tablets	330
Sitagliptin 25mg tablets	13
Sitagliptin 50mg tablets	7
Vildagliptin 50mg tablets	6
GLP-1 Analogues	
Genericname	Frequency
Exenatide 10micrograms/0.04ml solution for injection 2.4ml pre-filled disposable devices	78
Exenatide 5micrograms/0.02ml solution for injection 1.2ml pre-filled disposable devices	21
Liraglutide 6mg/ml solution for injection 3ml pre-filled disposable devices	235
Lixisenatide 10micrograms/0.2ml solution for injection 3ml pre-filled disposable devices	2
Lixisenatide 20micrograms/0.2ml solution for injection 3ml pre-filled disposable devices	10

Antihypertensive drugs	
Genericname	Frequency
Aliskiren 150mg tablets	84
Amlodipine 10mg tablets	398
Amlodipine 5mg tablets	441
Atenolol 100mg tablets	135
Atenolol 25mg tablets	95
Atenolol 25mg/5ml oral solution sugar free	33
Atenolol 50mg tablets	317
Bisoprolol 1.25mg tablets	9
Bisoprolol 10mg tablets	88
Bisoprolol 2.5mg tablets	97
Bisoprolol 3.75mg tablets	53
Bisoprolol 5mg tablets	182
Bisoprolol 7.5mg tablets	110
Candesartan 16mg tablets	267
Candesartan 2mg tablets	4
Candesartan 32mg tablets	141
Candesartan 4mg tablets	43
Candesartan 8mg tablets	46
Captopril 50mg tablets	33
Carvedilol 12.5mg tablets	10
Carvedilol 25mg tablets	64
Carvedilol 3.125mg tablets	8
Carvedilol 6.25mg tablets	25
Diltiazem 120mg modified-release capsules	4
Diltiazem 120mg modified-release tablets	28
Diltiazem 180mg modified-release capsules	3
Diltiazem 200mg modified-release capsules	56
Diltiazem 240mg modified-release capsules	53
Diltiazem 300mg modified-release capsules	31
Diltiazem 90mg modified-release capsules	2
Doxazosin 1mg tablets	47
Doxazosin 2mg tablets	25
Doxazosin 4mg modified-release tablets	10
Doxazosin 4mg tablets	198
Doxazosin 4mg/5ml oral suspension	1
Doxazosin 8mg modified-release tablets	200
Enalapril 10mg tablets	64
Enalapril 20mg tablets	89
Enalapril 5mg tablets	30
Eprosartan 600mg tablets	24
Felodipine 10mg modified-release tablets	30

Felodipine 2.5mg modified-release tablets	7
Felodipine 5mg modified-release tablets	33
Glyceryl trinitrate 400micrograms/dose aerosol sublingual spray	47
Glyceryl trinitrate 400micrograms/dose pump sublingual spray	45
Glyceryl trinitrate 500microgram sublingual tablets	33
Glyceryl trinitrate pump 400mcg CFC-free spray	2
Irbesartan 150mg tablets	38
Irbesartan 300mg tablets	42
Irbesartan 75mg tablets	15
Isosorbide mononitrate 10mg tablets	14
Isosorbide mononitrate 20mg tablets	13
Isosorbide mononitrate 25mg modified-release capsules	5
Isosorbide mononitrate 25mg modified-release tablets	55
Isosorbide mononitrate 50mg modified-release capsules	30
Isosorbide mononitrate 60mg modified-release tablets	191
Ivabradine 5mg tablets	29
Labetalol 100mg tablets	1
Lacidipine 4mg tablets	2
Lercanidipine 10mg tablets	3
Lercanidipine 20mg tablets	2
Lidocaine 200mg/10ml (2%) solution for injection ampoules	3
Lisinopril 10mg tablets	54
Lisinopril 2.5mg tablets	107
Lisinopril 20mg tablets	238
Lisinopril 5mg tablets	174
Lisinopril 5mg/5ml oral solution	1
Losartan 100mg tablets	197
Losartan 25mg tablets	28
Losartan 50mg / Hydrochlorothiazide 12.5mg tablets	1
Losartan 50mg tablets	58
Methyldopa 250mg tablets	20
Methyldopa 500mg tablets	2
Metoprolol 50mg tablets	54
Nicorandil 10mg tablets	70
Nicorandil 20mg tablets	40
Nifedipine 20mg modified-release tablets	18
Nifedipine 30mg modified-release capsules	216
Nifedipine 30mg modified-release tablets	33
Nifedipine 40mg modified-release tablets	33
Nifedipine 5mg capsules	3
Nifedipine 60mg modified-release capsules	4
Olmesartan medoxomil 10mg tablets	55
Olmesartan medoxomil 20mg tablets	8

Perindopril arginine 10mg tablets	4
Perindopril erbumine 2mg tablets	28
Perindopril erbumine 4mg tablets	127
Perindopril erbumine 8mg tablets	17
Propranolol 40mg tablets	37
Propranolol 80mg modified-release capsules	1
Ramipril 1.25mg capsules	111
Ramipril 10mg capsules	588
Ramipril 10mg tablets	35
Ramipril 2.5mg capsules	328
Ramipril 2.5mg tablets	35
Ramipril 5mg capsules	406
Sacubitril 24mg / Valsartan 26mg tablets	1
Telmisartan 40mg tablets	17
Timolol 10mg tablets	40
Verapamil 120mg modified-release tablets	7
Verapamil 40mg tablets	2

Lipids lowering drugs

Genericname	Frequency
Atorvastatin 10mg tablets	484
Atorvastatin 20mg tablets	226
Atorvastatin 40mg tablets	790
Atorvastatin 80mg tablets	327
Bezafibrate 200mg tablets	17
Bezafibrate 400mg modified-release tablets	33
Colestyramine 4g oral powder sachets	1
Eicosapentaenoic acid 460mg / Docosahexaenoic acid 380mg capsules	109
Ezetimibe 10mg tablets	179
Fenofibrate micronised 160mg tablets	5
Fenofibrate micronised 200mg capsules	3
Fenofibrate micronised 267mg capsules	24
Fenofibrate micronised 67mg capsules	1
Fluvastatin 80mg modified-release tablets	36
Nicotinic acid 1g / laropiprant 20mg modified-release tablets	1
Pravastatin 10mg tablets	3
Pravastatin 20mg tablets	11
Pravastatin 40mg tablets	19
Rosuvastatin 10mg tablets	61
Rosuvastatin 20mg tablets	26
Rosuvastatin 40mg tablets	17
Rosuvastatin 5mg tablets	10
Simvastatin 10mg tablets	123
Simvastatin 20mg / Ezetimibe 10mg tablets	17

Simvastatin 20mg tablets	291
Simvastatin 40mg tablets	970
Simvastatin 40mg/5ml oral suspension sugar free	1
Simvastatin 80mg tablets	5

Diuretics

Genericname	Frequency
Amiloride 5mg / Bumetanide 1mg tablets	31
Bendroflumethiazide 2.5mg tablets	379
Bumetanide 1mg tablets	71
Chlortalidone 50mg tablets	74
Co-amilofruse 5mg/40mg tablets	22
Eplerenone 25mg tablets	3
Eplerenone 50mg tablets	2
Furosemide 20mg tablets	102
Furosemide 40mg tablets	857
Furosemide 40mg/5ml oral solution sugar free	3
Indapamide 1.5mg modified-release tablets	94
Indapamide 2.5mg tablets	7
Spironolactone 25mg tablets	142
Spironolactone 50mg tablets	18

Aspirin

Genericname	Frequency
Aspirin 75mg dispersible tablets	977
Aspirin 75mg gastro-resistant tablets	163
Aspirin 75mg tablets	63
Clopidogrel 75mg tablets	390
Dipyridamole 100mg tablets	3
Dipyridamole 200mg modified-release capsules	24