BARIATRIC SURGERY OUTCOMES IN PEOPLE WITH AND WITHOUT TYPE 2 DIABETES: POPULATION BASED STUDIES AND A SYSTEMATIC REVIEW.

By

PUSHPA SINGH

A thesis submitted to the University of Birmingham for the degree of

DOCTOR OF PHILOSOPHY

Institute of metabolism and system research

University of Birmingham

November 2021

UNIVERSITY OF
BIRMINGHAM

University of Birmingham Research Archive

e-theses repository

This unpublished thesis/dissertation is copyright of the author and/or third parties. The intellectual property rights of the author or third parties in respect of this work are as defined by The Copyright Designs and Patents Act 1988 or as modified by any successor legislation.

Any use made of information contained in this thesis/dissertation must be in accordance with that legislation and must be properly acknowledged. Further distribution or reproduction in any format is prohibited without the permission of the copyright holder.

Abstract

Background

Impact of bariatric surgery on vascular complications and mortality using real-world data are lacking. In addition, there is lack of robust prediction model to predict diabetes remission. Hence, in this thesis I undertook series of population- based studies examining outcomes of bariatric surgery and a systematic review to recognise prediction-model for diabetes remission following bariatric surgery.

Methods

Retrospective cohort matched controlled studies utilising IQVIA Medical Research Data (IMRD)database to assess the impact of bariatric surgery on 1) incident cardiovascular disease (CVD), and all-cause mortality in patients with obesity; 2) diabetes related microvascular complications in patients with obesity and type 2 diabetes compared to routine care.

Systematic literature search was undertaken. Studies developing or validating prediction model for diabetes remission in adults after bariatric surgery were included and performance assessed

Results

Project 1- Bariatric surgery was associated with a lower incident composite CVD (adjusted HR 0.79, 95% CI 0.62 to 1.02, p=0.074), which was statistically significant in the RYGB group mainly driven by reduction in incidence heart failure. It was also associated with 30% reduction in all-cause mortality compared to routine care.

Project 2- Bariatric surgery was associated with reduction in incident composite microvascular complications (adjusted HR 0.63, 95% CI 0.51-0.78, p<0.001), better glycaemic status, higher proportion achieving target HbA1c on less glucose lowering medications.
Project 3- Identified 16 prediction model. ABCD and DiaRem had been widely externally validated. Newer prediction model showed excellent performance in limited validation studies.

Conclusions

Bariatric surgery was associated with reduction in incidence cardiovascular and diabetes related microvascular complications, and all- cause mortality. Improvements in provision of bariatric surgery can help reduce the burden of obesity. Further validation studies are needed.

Acknowledgements

I am grateful to endless list of people and their contribution without which this project had been unattainable. To begin I would like to thank my three supervisors: Dr Abd A Tahrani, Senior Lecturer in University of Birmingham, NIHR clinical scientist and Consultant Endocrinology and Diabetes at University Hospital Birmingham NHS Trust; Prof. Krishnarajah Nirantharakumar, Senior Lecturer at University of Birmingham, and Dr Srikanth Bellary reader at Aston University and Consultant Endocrinology and Diabetes at University Hospital Birmingham NHS Trust for supervising me and providing me the opportunity to undertake research work.

I am eternally grateful to Dr Tahrani for introducing me to academic field. It must be hard and challenging for him to guide me as I had no academic experience before entering this field. He gave me tremendous time and valuable support throughout and even till date. I have disturbed him before my presentations on multiple occasions, and he happily guided and helped even out of hours. I appreciate his vast knowledge in field of academic research and weight management and his assistance in all forms of writing including conference abstracts, posters, and scientific papers.

I am fortunate to have Prof. Nirantharakumar as one of my supervisors. I value the regular teachings and guidance given by Prof. Nirantharakumar on research methods, analysis, and statistics. He patiently supported me and guided me.

I would like to thank Prof. Nirantharakumar and his whole team for teaching me the new world of data-based research. I appreciate the help of his whole team especially Nicola Adderley, Anuradhaa Subramanian and Krishna Gokhale. I am in debt to Dr Nicola Adderley for support professionally, and personally. She nurtured me like a mentor, supported me and stayed by my side like a sister. She reviewed, feedback and proofread different parts of my work throughout my PhD project.

I would like to thank Anu for helping me with analysis, Krishna for teaching the database. I am grateful to Malcolm Price from University of Birmingham for discussing and checking the analysis done in Systematic review project. I appreciate help of Dr Jonathan Hazlehurst,

Consultant Endocrinology and Diabetes at University Hospital Birmingham NHS Trust for continuous encouragement and contribution in systematic review project.
I am grateful to all other team members (Dr J Chandan, Dr Haider, Deepiksana, Jingya).
I would like to thank Dr S Bellary for encouraging and helping not only in the academic field, but also my clinical work. Under his supervision, I managed to continue my clinical work and maintain my clinical competences. There have been moments, I got stressed, tried to rush. Dr Bellary encouraged and raised me as a guardian.
I acknowledge the effort of all the lectures involved in delivering the courses at University of Birmingham especially Dr David Moore and Janine Dretzke.
I am grateful to Dr. Sayeed Haque from the University of Birmingham for his lecture series of statistic Lectures.
I appreciate the help of all the lecturers at Keele University involved in delivering the course on prediction model especially Kym Snell and Lucinda Archer.
I would like to thank Mr Rishi Singhal, Consultant Surgeon at Birmingham University Hospital Birmingham for reviewing bariatric surgery READ codes.
I would like to thank Sue Bayliss, Statistician at University of Birmingham for teaching me search strategy as a part of course “Statistical review and evidence synthesis” and reviewing my search strategy in the systematic review I conducted.
Thank you to the Research and development department at University of Birmingham (Heartland Hospital) and Dr Alice Turner for funding my research post.
Finally, I would like to thank my husband and my kids for the support and love. I must give special thanks to my husband. I gave him sleepless night, made him watch STATA videos till late night and looking after kids while I was doing my work. He taught me STATA, EPPI and DeStiller software. Thank you to my work colleagues at University of Birmingham and other students at University of Birmingham for encouragement and love.

Thesis Format

I have presented my thesis in accordance with the University of Birmingham alternative format thesis guidelines; Regulation 7.4.1 (g) (https://intranet.birmingham.ac.uk/as/studentservices/graduateschool/documents/public/rsa/alternative-format-thesis-guidelines.pdf).

I have included published papers (Chapter 3, 5 and 7) and manuscript under peer review (Chapter 6) directly into thesis. As advised in alternate thesis guideline, I have not included pages of the publications in the pagination sequence of the submission. I have inserted a sheet displaying the publication number, publication title, and the page number of the thesis.

Table of Contents

Abstract

Acknowledgements

Thesis Format

Table of Contents

Table of Figures

Table of Tables

Abbreviations

List of Achievements

1 Chapter 1: Introduction 1

1.1 Type 2 Diabetes mellitus 2

1.1.1 Definition 2

1.1.2 Pathophysiology 2

1.1.3 Epidemiology 5

1.1.4 Burden of diabetes related complications 6

1.1.5 Risk factors 8

1.1.6 Type 2 diabetes and obesity 8

1.2 Obesity 11

1.2.1 Epidemiology 12

1.2.2 Impact of Obesity 13

1.2.2.1 Metabolic impact 13

1.2.2.2 Physical impact 14

1.2.2.3 Psychological impact 15

1.2.2.4 Impact on quality of life 16

1.2.2.5 Financial impact 16

1.2.3 Pathogenesis of Obesity 17

1.2.3.1 Genetic factors 17
1.2.3.2 Environmental and behaviour factors 18
1.2.4 Management 20
1.2.4.1 Lifestyle and behavioural modification 20
1.2.4.2 Pharmacological approaches 23
1.2.4.3 Bariatric surgery 29
1.2.4.4 Guidelines and Recommendations 37
1.2.4.5 Diabetes remission and prediction model 38
1.3 Rationale for my thesis projects: 39
1.4 Layout of my chapters 42
1.5 References: 43
2 Chapter 2: Method 53
2.1 Ethical approval 54
2.2 Data source- IQVIA Medical Research Data (IMRD) – UK 55
2.2.1 The IMRD structure and presentation 55
2.2.1.1 Information presentation 55
2.2.2 Selection of general practice and study participants- 57
2.2.3 READ codes 57
2.2.4 Important dates 58
2.2.5 Data Extraction for Epidemiological Research (DExtER) 60
2.2.6 Validation of IMRD database 60
2.2.7 Strengths and Limitation of IMRD database: 61
2.3 Study design and study population 62
2.3.1 Project 1- Patients with obesity and had bariatric surgery 62
2.3.2 Project 2- Patients with obesity and type 2 diabetes and subsequently had bariatric surgery 62
2.4 Limitations of study design 63

2.5 Outcomes 64
2.5.1 Project 1 64
2.5.2 Project 2 64
2.6 Co-variates 64
2.7 Analysis 66
2.7.1 Baseline characteristics 66
2.7.2 Survival analysis 67
2.7.2.1 Cox Proportional hazard regression 67
2.7.2.2 Nelson–Aalen estimator graph 67
2.8 References: 69
3 Chapter 3: Impact of bariatric surgery on cardiovascular outcomes and mortality 71
3.1 Contents of chapter 3 72
3.2 References: 74
3.3 Manuscript 1: Impact of bariatric surgery on cardiovascular outcomes and mortality 75
4 Chapter 4: Impact of Bariatric Surgery in Elderly Population 76
4.1 Abstract 77
4.2 Introduction 78
4.3 Methods 79
4.3.1 Study design and data source 79
4.3.2 Population 80
4.3.3 Follow-up 81
4.3.4 Outcome 81
4.3.5 Statistical analysis 81
4.4 Results 83
4.4.1 Baseline characteristics 83

4.4.2 Weight loss 86
4.4.3 Cardiovascular disease and mortality 86
4.5 Discussion 89
4.6 Conclusion 92
4.7 References 93
5 Chapter 5: Impact of bariatric surgery on incident microvascular complications in patients with type 2 diabetes 96
5.1 Contents of chapter 5 97
5.2 References 99
5.3 Manuscript 2: Impact of bariatric surgery on incident microvascular complications in patients with type 2 diabetes 100
6 Chapter 6: Glycaemic outcomes in patients with type 2 diabetes following bariatric surgery 101
6.1 Contents of chapter 6 102
6.2 References 103
6.3 Manuscript 3: Glycaemic outcomes in patients with type 2 diabetes following bariatric surgery 104
6.3.1 Abstract 105
6.3.2 Backgrounds 106
6.3.3 Methods 107
6.3.3.1 Study design and data source 107
6.3.3.2 Study population 108
6.3.3.3 Outcome measures 109
6.3.3.4 Statistical analysis 109
6.3.4 Results 111
6.3.4.1 Baseline characteristics 111
6.3.4.2 Mean HbA1c and change in glycaemic status 113
6.3.4.3 Achieving glycaemic targets 115

6.3.4.4 Change in medications 117
6.3.4.5 Change in weight 118
6.3.5 Discussion 119
6.3.6 Limitations and strengths 123
6.3.7 Conclusion 123
6.3.8 References: 126
7 Chapter 7: Prognostic models for predicting remission of diabetes following bariatric surgery: A systematic review and meta-analysis 129
7.1 Contents of chapter 130
7.2 References 131
7.3 Manuscript 4: Prognostic models for predicting remission of diabetes following bariatric surgery: A systematic review and meta-analysis 132
8 Chapter 8: Summary and future direction 133
8.1 Summary of findings 134
8.2 Future studies 136
8.2.1 Prognosis of cardiovascular disease 136
8.2.2 Study comparing bariatric surgery vs newer pharmacotherapy or dietary intervention 137
8.2.3 Weight loss in elderly population 138
8.2.4 Prognosis of diabetes related microvascular complications 139
8.2.5 Adjuvant effect of glucose lowering medication in post- operative stage 140
8.2.6 Using term “diabetes remission” 141
8.2.7 Need for future prediction model 142
8.3 Future Plans 143
8.4 References 145
Appendices

Table of Figures

If the figure is within a published manuscript, the manuscript page number is given.

Chapter 1

Figure 1: Mechanism of β cell failure and progression to type 2 Diabetes 3

Figure 2: Mechanism of hyperglycaemia induced cellular dysfunction and damage 5

Figure 3: Mechanism binding type 2 diabetes and obesity 10

Figure 4 - Tackling obesities: future choices - full systems map 19

Chapter 2

Figure 1: IMRD database layout 56

Figure 2: Important dates 59

Chapter 3

Figure 1 - Distribution of bariatric surgery in different age groups over time 73

Manuscript 1

Figure 1: Flow diagram of participant selection 3

Figure 2: Forest plot of cardiovascular disease outcomes and mortality in all patients, and those with and without type 2 diabetes mellitus 7

Chapter 4

Figure 1: Number of elderly patients undergoing bariatric surgery from year 1997 to 2017 83

Chapter 6

Manuscript 3

Figure 1: a) Mean (SD) HbA1c in surgical vs control groups. b) Mean HbA1c change from baseline in surgical vs control groups; GB= Gastric band, SG= Sleeve gastrectomy, RYGB= Gastric bypass 114

Figure 2: Percentage of patients on glucose lowering medications before and after index date (pre- and post-surgery) in surgical and control groups. 118

Chapter 7

Manuscript 4

Figure 1: PRISMA flowchart 3

Figure 2: Meta-analysis 10

Table of Tables

If the figure is within a published manuscript, the manuscript page number is given.

Chapter 1

Table 1: Efficacy of anti-obesity drugs 28

Chapter 3

Manuscript 1

Table 1: Baseline characteristics of participants in exposed and control groups 4

Table 2: Impact of bariatric surgery on study outcomes across all surgical procedures and for individual procedures 5

Table 3: Impact of bariatric surgery on separate cardiovascular events across all surgical procedures and in individual procedures 6

Table 4: Impact of bariatric surgery on mortality for all surgical procedures 7

Chapter 4

Table 1: Baseline characteristics of surgical and control group 84

Table 2: The impact of bariatric surgery on cardiovascular disease and all- cause mortality 87

Chapter 5

Manuscript 2

Table 1: Baseline characteristics of participants in the surgical and nonsurgical groups 4

Table 2: Incidence of composite microvascular complications and DFD, STDR, and nephropathy in total population and subgroup analyses 5

Table 3: Incidence of DFD2 and DFD3, peripheral neuropathy, and PVD 6

Table 4: Incidence of eGFR <60 mL/min per 1.73 m2, eGFR <30 mL/min per 1.73 m2, ACR ǂ3 mg/mmol, and

ACR >30 mg/mmol and sensitivity analysis 6

Chapter 6

Manuscript 3

Table 1: Baseline characteristics of participants in surgical and non-surgical groups 112

Table 2: Achieving targeted HbA1c in surgical and control groups 116

Table 3: Change in glucose lowering medications before and after index date in surgical and control groups. 117

Chapter 7

Manuscript 4

Table 1: Model development studies with their predictors 4

Table 2: Study characteristics of model development studies 5

Table 3: Study characteristics of validation studies 7

Abbreviations

ABCD	Adiposity- based chronic disease
ADA	American Diabetes Association
AF	Atrial Fibrillation
BMI	Body Mass Index
CKD	Chronic Kidney Disease
CVD	Cardiovascular Disease
Dexter	Data Extraction for Epidemiological Research
DFD	Diabetes Foot Disease
DPN	Diabetic peripheral neuropathy
DPP	Diabetes prevention programme
DS	Duodenal Switch
DSE	Diabetes specific education
EOSS	Edmonton Obesity Staging System
ESRD	End stage renal disease
GB	Gastric Banding (Adjustable)
GP	General Practice
HF	Heart Failure
HTN	Hypertension
IDF	International Diabetes Federation
IHD	Ischaemic Heart Disease
ILS	Intensive lifestyle
IMRD	IQVIA Medical Research Data (IMRD)Database
IMRD	IQVIA Medical Research Data
IQR	Interquartile Range
NBSR	National Bariatric Surgery Registry
NHS	National Health Service

NICE	National Institute for Health and Care Excellence
OSA	Obstructive sleep apnoea
PHP	Painful heel pain
RYGB	Roux-En-Y Gastric Bypass
SD	Standard Deviation
SG	Sleeve Gastrectomy
SOS study	Swedish Obese Subject Study
STDR	Sight Threatening Diabetes Retinopathy Disease
STROBE	Strengthening the Reporting of Observational studies in Epidemiology
VLCD	Very-low calorie diet programs

List of Achievements

Posters

1) European Congress on Obesity (ECO) conference Glasgow, 2019
    a) The Impact of Bariatric surgery on Cardiovascular disease, mortality and weight in Elderly patients in the UK: A population-based matched controlled cohort study
    b) The Impact of Bariatric surgery on incident Cardiovascular disease in the UK: A population-based matched controlled cohort study'
    c) The impact of bariatric surgery on incident hypertension in the UK: a matched controlled population-based cohort study
2) European Association for the Study of Diabetes (EASD) conference, Barcelona, 2019
    a) The impact of bariatric surgery on incident cardiovascular disease and mortality in patients with and without type 2 diabetes in the UK: matched controlled cohort study
3) UK Congress on Obesity 2019
    a) Impact of bariatric surgery on diabetes related foot disease
4) West Midland Physician Association meeting
    a) Impact of bariatric surgery on elderly population

Oral presentations

1) Neurodiab conference 2019
    a) Bariatric surgery is associated with reduced risk of the development and progression of foot disease in patients with type 2 diabetes: a matched controlled cohort study
2) Midland Endocrinology club 2019
    a) Impact of bariatric surgery on cardiovascular outcomes and mortality: A population-based matched controlled cohort study in the UK

b) The Impact of Bariatric surgery on Cardiovascular disease, mortality and weight in older patients in the UK: A population-based matched controlled cohort study

3) East Midlands Bariatric & Metabolic Institute (EMBMI/ASO) Midlands Network Obesity Symposium - June 2019
   a) Bariatric surgery and real- world outcome
4) UK Congress on Obesity 2019
   a) Impact of bariatric surgery on diabetes related foot disease
5) European Association for the Study of Diabetes (EASD) Conference 2020-
   a) The impact of bariatric surgery on microvascular complications in patients with type 2 diabetes: a matched controlled population-based cohort study (https://www.easd.org/virtualmeeting/home.html#!resources/the-impact-of-bariatric-surgery-on-microvascular-complications-in-patients-with-type-2-diabetes-a-matched-controlled-population-based-cohort-study)
6) Midland Endocrinology club 2021
   a) Glycaemic outcomes in patients with type 2 diabetes following bariatric surgery: a population-based real-world UK cohort study
7) UKCO 2019
   a) Impact of bariatric surgery on cardiovascular disease and mortality
8) EMBMI/ASO Midlands 2019 Obesity Symposium-
   a) Impact of bariatric surgery on cardiovascular disease and mortality
9) British Obesity & Metabolic Surgery Society (BOMSS) 2019
   a) Impact of bariatric surgery on cardiovascular disease and mortality in elderly population

Publications

1) **Singh P.**, Subramanian A., Adderley N., Gokhale K., Singhal R., Bellary S., Nirantharakumar K., Tahrani A.A. Impact of bariatric surgery on cardiovascular outcomes and mortality: a population-based cohort study. British Journal of Surgery, Volume 107,

Issue 4, March 2020, Pages 432–442. (First published: 21 January 2020) https://doi.org/10.1002/bjs.11433

2) **Singh P.**, Adderley N., Subramanian A., Gokhale K., Singhal R., Toulis K.A., Bellary S., Nirantharakumar K., Tahrani A.A. The Impact of Bariatric Surgery on Incident Microvascular Complications in Patients With Type 2 Diabetes: A Matched Controlled Population-Based Retrospective Cohort Study. Diabetes Care 2021 Jan; 44(1): 116-124. (First published 10 Nov 2020) https://doi.org/10.2337/dc20-0571
3) **Singh P.**, Adderley N.J., Hazlehurst J., Price M., Tahrani A.A., Nirantharakumar K., Bellary S. Prognostic Models for Predicting Remission of Diabetes Following Bariatric Surgery: A Systematic Review and Meta-analysis. Diabetes Care 2021 Nov; 44(11): 2626-2641. (First published 20 October 2021) https://doi.org/10.2337/dc21-0166

Awards

1) West Midland Physician Association (WMPA) Spring meeting 2019 - 2nd prize for poster presentation
2) Midland Endocrinology and Diabetes Club Spring Meeting 2021 - 2nd prize for oral presentation

Chapter 1: Introduction

1.1 Type 2 Diabetes mellitus

1.1.1 Definition

Diabetes Mellitus is defined as “a metabolic disorder characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The long-term effects of diabetes mellitus include progressive development of the specific complications of retinopathy with potential blindness, nephropathy that may lead to renal failure, and/or neuropathy with risk of foot ulcers, amputation, Charcot joints, and features of autonomic dysfunction, including sexual dysfunction. People with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebrovascular disease” (1). The definition itself reflects the complicated nature of this condition.

Diabetes is broadly divided as type 1 diabetes mellitus, absolute insulin deficiency, and type 2 diabetes mellitus, which is a combination of insulin deficiency and insulin resistance. My study will focus on type 2 diabetes. Type 2 diabetes constitutes nearly 90% of all cases of diabetes.

1.1.2 Pathophysiology

Type 2 diabetes is complex metabolic disorder resulting from variable degree of insulin resistance and pancreatic beta cell dysfunction. Initially, there is beta cell compensation to fulfil the demand of increased insulin secondary to over accumulation of energy and insulin

resistance. With time, compensatory mechanism fails in patients with genetic predisposition or acquired environmental factors leading to type 2 diabetes (2).

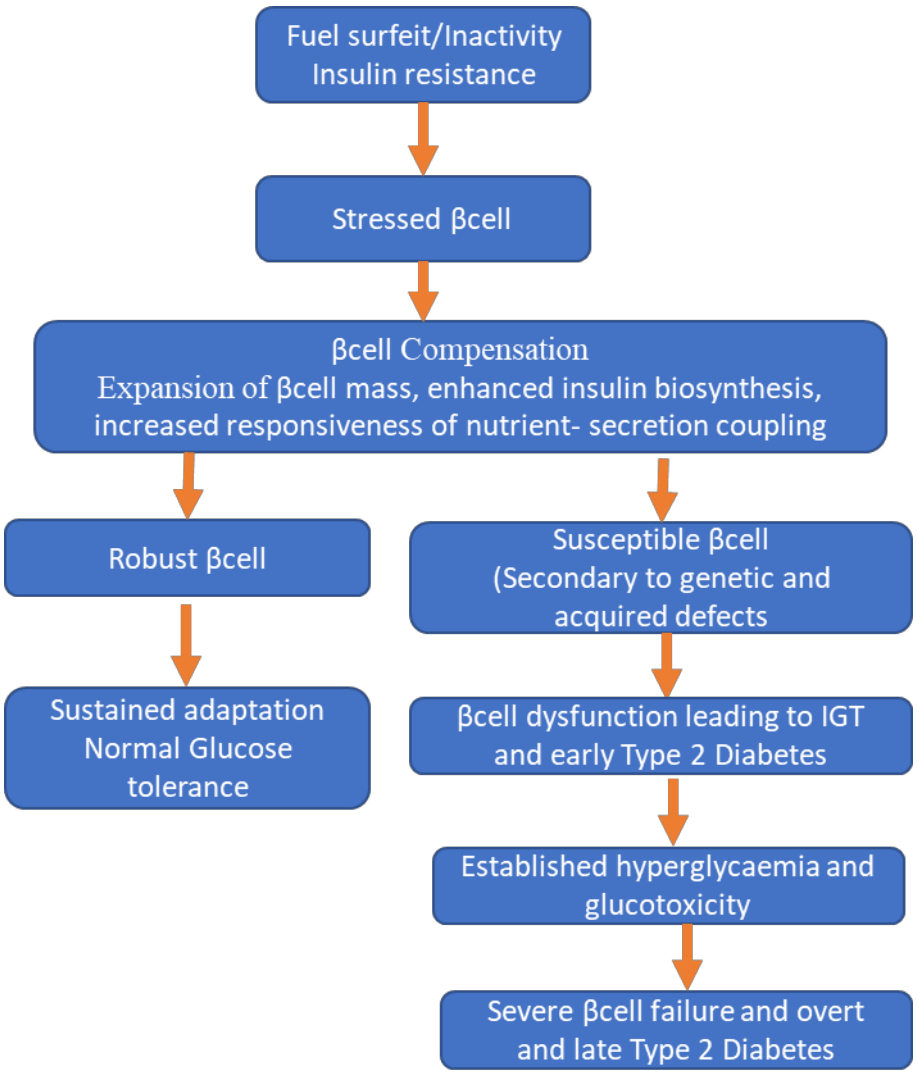


Figure 1: Mechanism of β cell failure and progression to type 2 Diabetes (2)

The major cause of morbidity and mortality in patients with type 2 diabetes are diabetes related complications. Microvascular complications include neuropathy (autonomic and peripheral), retinopathy, nephropathy which are leading cause of limb amputation,

blindness, and end-stage renal disease. Macrovascular complications include coronary artery disease, stroke, and peripheral vascular disease.

Hyperglycaemia causes overproduction of reactive oxygen species (ROS) leading to increased poly (ADP-ribose) polymerase (PARP) (3). PARP has an inhibitory effect on glyceraldehyde-3 phosphate dehydrogenase (GAPDH). Inhibition of GAPDH activates complex molecular mechanism leading to the activation of the polyol pathway, oxidative stress pathway, and the hexamine pathway, and overproduction of advanced glycation end-product and increased synthesis of diacylglycerol and activation of protein kinase C pathway (3, 4).These inflammatory responses and increased growth factors subsequently leads to cellular damage, endothelial dysfunction and eventually macrovascular and microvascular complications (3) (Figure 2).

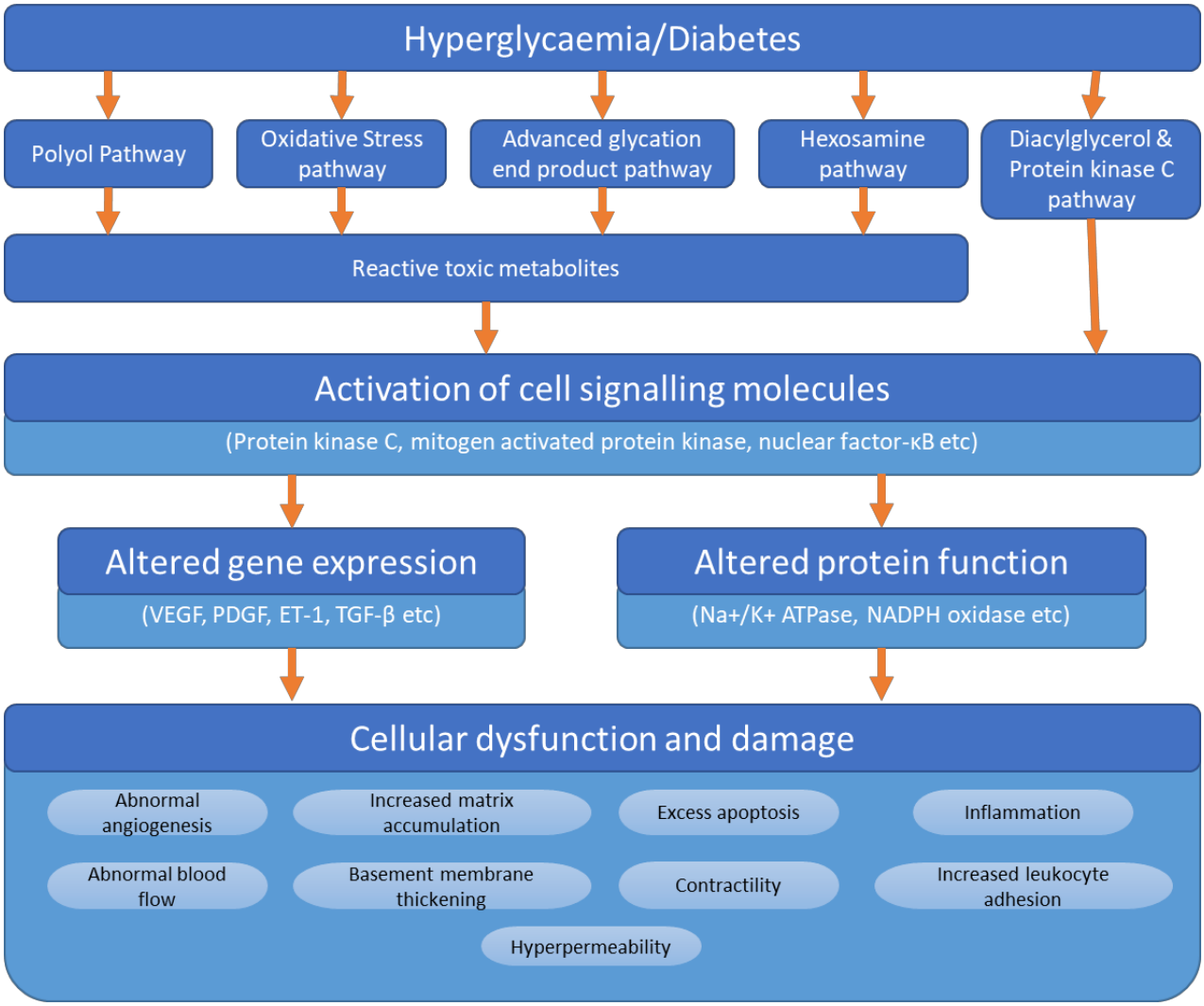


Figure 2: Mechanism of hyperglycaemia induced cellular dysfunction and damage (3, 4)

VEGF-vascular endothelial growth factor, PDGF-platelet-derived growth factor, ET-1-endothelin-1; TGF-b-transforming growth factor-b; NADPH- nicotinamide adenine dinucleotide phosphate

1.1.3 Epidemiology

Diabetes is a global health challenge. The prevalence of Diabetes worldwide had gone up from 108 million in 1980 to 422 million in 2014 (5). Recent International diabetes federation report has estimated 537 million adults (aged 20- 79 years) are living with diabetes worldwide (6).In the UK, 2.7 million people are already diagnosed with diabetes and further

1.4% of the population are undiagnosed (7). The prevalence of diabetes in male and female is 9.6% and 7.6% respectively. Prevalence increases as the age of population increases. <2% of people aged 16-34 years had been estimated to have type 2 diabetes compared to 16.5% in cohort aged >75 years (7). Type 2 diabetes is now being diagnosed even in childhood and adolescence age, driven by the increasing prevalence of obesity.

1.1.4 Burden of diabetes related complications

Cardiovascular diseases are major cause of mortality in patients with type 2 diabetes (8). Systematic review including 57 studies and 4549481 patients with type 2 diabetes found a third were affected by cardiovascular disease (8). CVD was the cause of mortality in 50 % of the total mortality recorded in this population (8). A recent systematic review including 52 studies found the prevalence of CVD in patients with type 2 diabetes ranging from 6.9% to 40.8%, with highest proportion of heart failure, followed by stroke and then peripheral artery disease (9).

Systematic review including 24 studies found CVD to contribute 20-49% of total direct cost toward treating type 2 diabetes (10). The median increase in cost of managing patients with type 2 diabetes and CVD was 112%, greatest CVD related cost were for hospital admission, followed by medications and outpatient care (10). Direct cost in patients with type 2 diabetes admitted for CVD was increased by >50% compared to patients with type 2 diabetes and no CVD (9)

Diabetic neuropathy is the most common cause of morbidity in diabetic patients. Diabetic neuropathy along with peripheral vascular disease can lead to lower limb ulcer, gangrene,

and amputation. According to a US study, diabetes is the most common cause of non-traumatic leg amputation (11, 12). Diabetic peripheral neuropathy (DPN) affects 50% of patients with type 2 diabetes and is a leading cause of increased morbidity (pain, foot ulcers, amputations, Charcot's arthropathy) and mortality (13). Painful neuropathy is associated with poor quality of sleep (13).Painful diabetic peripheral neuropathy gravely affects the quality of life of the patients and causes a major economic burden to the patient, their families and the health system. According to US data, nearly a third of diabetes and its complication cost was related to foot disease. The average cost of care of diabetic patients with ulcer in first year is 5.4 times higher than the diabetic without ulcer and 2.8times higher in second year (12).

Diabetic retinopathy (DR) is the most common cause of preventable blindness and moderate to severe visual impairment (14). Risk factors for DR are diabetes duration, poor glycaemic control, hypertension, high lipid profile (15). Good glycaemic control for long term is needed for DR management. However, it's well-established fact that intensive treatment usually as offered in pregnancy or achieved by insulin pump therapy or pancreatic transplant cause rapid deterioration in DR (16, 17).

Chronic kidney disease (CKD) is defined as a progressive loss of kidney function over the time. It is expected that 2.6 million people aged 16 years and older in England have CKD stage 3-5 (18). Evidence says that End stage renal disease (ESRD) is a marker of cardiovascular event (19). The common risk factors of chronic kidney disease include diabetes, hypertension, and smoking (20). Renal disease in subjects with high body mass

index is the combination of diabetes nephropathy, hypertensive nephropathy and obesity related glomerulopathy(21).

Social and financial impact: Diabetes affects the emotional and overall well- being of the patients and their family (22, 23). Because of diabetes induced complications and morbidity, the care cost for these patients goes up (24).Care for patients with type 2 diabetes enforces a major economic burden to the health system through direct medical care cost and indirectly though by affecting the ability and productivity of patients. As per WHO data, worldwide, the direct cost for diabetic management >$827 billion (25). As per UK data, type 2 diabetes and its complications management cost £8.8 billion a year which is under 9% of annual NHS budget (26). Patients with diabetes have increased sickness leave, less income and less productivity (24).

1.1.5 Risk factors

Type 2 diabetes is complex metabolic disorder. The cause of type 2 diabetes is usually multifactorial, and risk factors include increasing age, ethnicity, family history and history of gestational diabetes, lack of physical activity, high blood pressure, high cholesterol, and obesity.

1.1.6 Type 2 diabetes and obesity

Obesity is an established major modifiable risk factor for the development of type 2 diabetes and about 90% of individuals with type 2 diabetes have overweight or obesity (7). Obesity increases the risk of developing type 2 diabetes up to five times compared to a healthy

weight adult (7). The prevalence of type 2 diabetes is increasing in parallel to the obesity epidemic.

Three different hypotheses have been proposed to understand the mechanism linking type 2 diabetes and obesity (27), and it is likely that a combination of all these mechanisms may explain the links between obesity and type 2 diabetes.

1) Inflammation hypothesis – Obesity represents chronic inflammation where infiltrating macrophages in adipose tissue produce inflammatory molecule that leads to pathological changes in insulin sensitivity and beta cell.
2) Lipid overflow hypothesis or Adipose Tissue Expandability Hypothesis-

   Increased ectopic lipid stores (fat cells in organ like liver, muscle, and pancreas) cause cytotoxic effect on peripheral cells and impairing their function, survival, and regeneration.
3) Adipokine hypothesis

   Adipose cells function as endocrine organ producing hormones with auto and paracrine function. In patients with obesity, increased amount of adipose cell leads to disturbed hormonal function causing metabolic impairment and failure of beta cells.

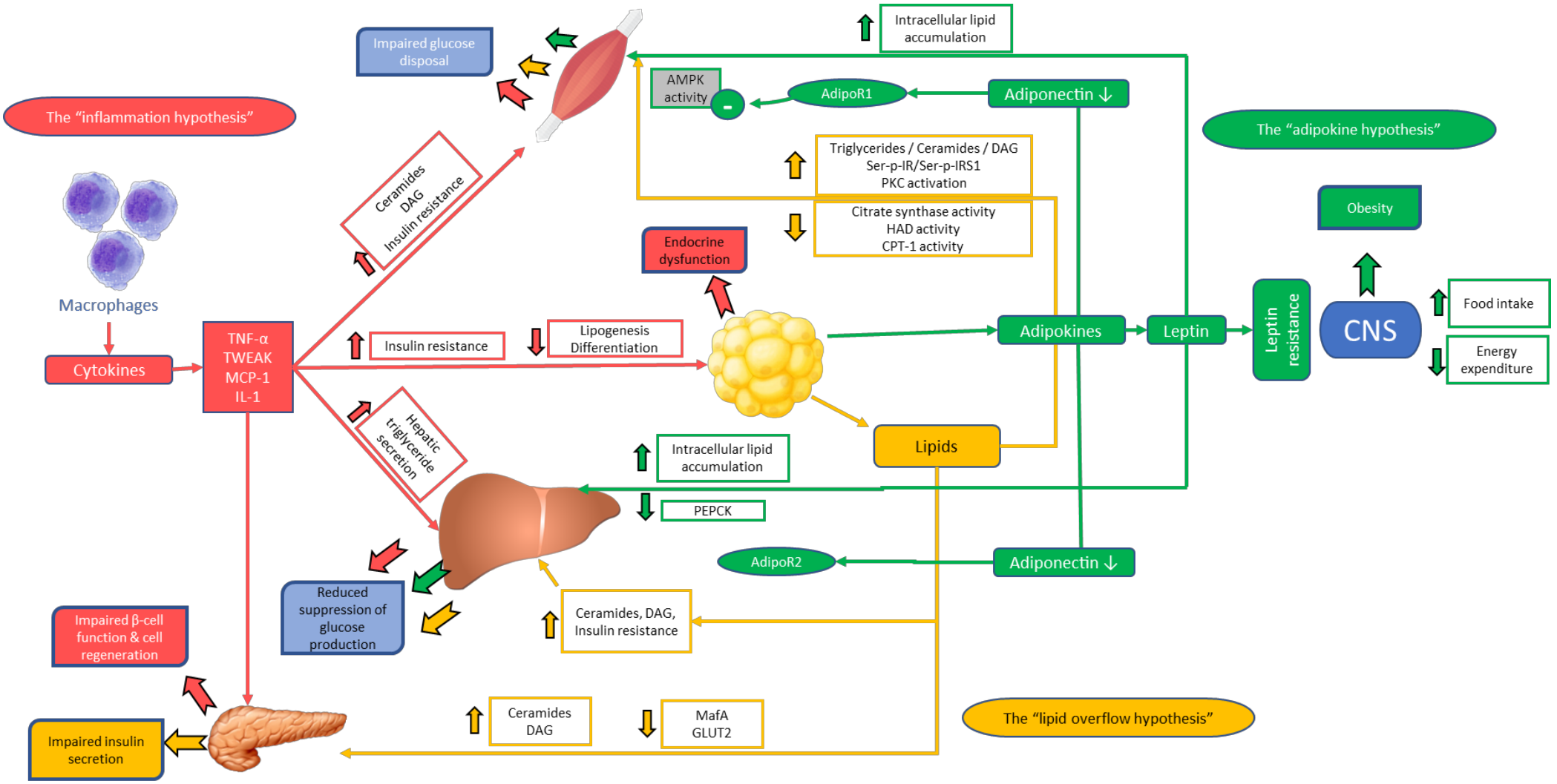


Figure 3: Mechanism linking type 2 diabetes and obesity (27)

1.2 Obesity

“Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health” (5). The fat mass depends on body composition and may vary depending on age, gender, and ethnicity.

There are various tools to measure obesity, most widely accepted and used is Body Mass Index (BMI). It is calculated as a person’s weight (in kilograms) divided by the square of their height (in metres), is a surrogate measure of adiposity in adult. It was given by Adolphe Quetelet in 1832 as a measure of obesity in population studies (28) and later called Body mass index by Ancel Keys in 1972. Waist circumference (29) and skin fold thickness are other way to measure adiposity, and can be used along with BMI to give more information (30). The severity of obesity has been classified based on BMI; a Healthy weight (18.5–24.9), Overweight (25–29.9), Obesity I (30–34.9), Obesity II (35–39.9), Obesity III (40 or more) (30). The impact of fat mass on metabolic system and inflammatory system depends on the type of fat and its distribution. BMI does not reflect the visceral and subcutaneous fat distribution ratio. The visceral and subcutaneous fat distribution differs by gender and ethnicity (31). Consequently, the classification based on anthropometric does not give information on metabolic profile, the detrimental impact of obesity on individual and guidance on the management.

In 2009, a classification Edmonton Obesity Staging System (EOSS) was proposed by Prof Sharma based on clinical and functional assessments (32). This classification has provided a holistic approach covering the physiological, psychological, and functional area. EOSS scoring was noted to be a strong predictor of all-cause mortality over 20 years follow up in US

civilian population (33). However, the definition of sub-clinical, established and end-stage is not well defined.

European Association for the Study of Obesity defined obesity as Adiposity- based chronic disease (ABCD) incorporating three dimensions of obesity namely aetiology, degree of adiposity and health risk (34).

1.2.1 Epidemiology

In 2016, more than 1.9 billion adults (≥18 years) were overweight or obese worldwide. Of these over 650 million were obese. Obesity rates have more than doubled since 1980 and are continuing to increase (5). The children and adolescents are also facing the health crisis of obesity. The prevalence of obesity in boys and girls has increased from 11 million in 1975 to 124 million in 2016 which is a 10-fold increase (35).

In the UK, two-thirds of adults are with either overweight or obesity (7). The 2014 England survey showed that 58% of women and 65% of man are overweight or obese. The prevalence of morbid obesity defined as BMI ≥40 kg/m^2 was 2% in men and 4% in women (36). The prevalence of obesity is high with increasing age in both genders (36) . Obesity in older adults is an emerging health issue with more detrimental effect on patient well-being. In elderly population with obesity, beside progressive increase in fat mass and fat redistribution, there is loss in lean mass and bone mass (37) contributing further negative impact to patients' morbidity and all-cause mortality (38).

On ethnicity analysis, highest mean BMI had been noted to be in the white men group and the black women group. Higher prevalence was recorded in the most deprived areas compared to least deprived areas in females(36).

1.2.2 Impact of Obesity

1.2.2.1 Metabolic impact

Obesity is a major risk factor for several health conditions and can lead to health crisis. The common conditions related to overweight, and obesity include type 2 diabetes, cancers (cancers of breast, endometrial, ovarian, colorectal, oesophageal, pancreatic, prostate), coronary artery disease, congestive heart failure, asthma, chronic back pain, osteoarthritis, pulmonary embolism and gallbladder diseases (39, 40).

The systematic review by Guh group analysing the data from 89 studies found the increased incidence of type 2 diabetes giving RR 6.7 (95% CI 3.10-4-97) in the male and 12.4 (95% CI 9.07-17.06) in the female population with obesity (39). The RR of coronary artery disease noted as 1.72 (95% CI 1.51-1.96) in males and 3.10 (95% CI 2.81-3.43) in females. Similar trends were noted in congestive cardiac failure, pulmonary embolism, and cancers (breast, colorectal, endometrial, oesophageal, prostate) in the overweight and obese population (39).

The Framingham study with 44 years of follow up found increased relative risk of incidence hypertension, cardiovascular events, hypercholesterolemia and diabetes in patients with obesity and overweight compared to normal weight (41). Pan- European prospective study showed positive linear association between BMI and coronary heart disease risk over a median follow up period of 12.2 years (42).

Obesity increases the susceptibility of sleep apnoea by increasing mechanical load in upper airway and decreases the compensatory neuromuscular responses. Neuromuscular signals are mediated by circulating adipokines, which is influenced by body fat distribution (43).

1.2.2.2 Physical impact

There is close relationship between obesity and decreased physical activity, representing a vicious cycle. Obesity and increased fat mass affects the body posture and function leading to decreased physical activity (44). Altered and adapted posture and gait puts them at increased risk of osteoarthritis and bone pain. A study done on 149 obese and overweight patients including 34 with painful heel pain (PHP) and 115 without found close relation between obesity and PHP (45). Lack of physical mobility leads to decreased bone mass density and can increase the risk of osteoporosis and fracture (46).

Obesity has been associated with osteoarthritis. A systematic review of 14 prospective study showed relative risk of knee osteoarthritis of 2.45 (95% CI 1.88 to 3.20, $p<0.001$) in overweight, and 4.55 (95% CI 2.90 to 7.13, $p<0.001$) in patients with overweight and obesity respectively (47). The study also calculated 35% increased risk of knee osteoarthritis with increase in BMI of 5kg/m^2 (47).

Because of above, patients with obesity are at risk of undertaking decreased physical activity and further contributing to obesity. The current culture appreciating the thin physique puts pressure and causes stigma to overweight people. Work of Jaroslava Kopcakova's et al have shown that adolescents boys (n= 3910) with negative body image are less likely to engage in physical activity (48). This dissatisfaction with body image can lead to further barrier for obese people to engage in physical activity.

1.2.2.3 Psychological impact

Obesity adversely affects mental health aspects of individuals (49). There is deep seated misconceptions that obesity is primarily caused by lack of physical activity, eating wrong type of food, inadequate discipline, and weak will power (50). These stereotypes put the patients with obesity at risk of discrimination, stigmatism right from the schooltime, noticed at work, and in public places.

A systematic review focussed on weight bias in children found 71% adolescent student with obesity experienced bullying, less liked as friend (51). The study also identified existence of overt and implied weight bias among teachers (51). Weight based bullying make these children feel self- conscious, unacknowledged and higher risk of depression compared to students without obesity (51).

People with obesity get discriminated at the work place during recruitment and are perceived as less efficient (52). These lead to various type of mental health problems, affecting their self-esteem (53). People with obesity get discriminated and perceived as less efficient in the workplace (52).

The meta-analysis which analysed 15 studies (58745 people) noted association between obesity and increased risk of depression with Odd ratio (OR) of 1.55 (95% CI 1.22-1.98) (54). The impact of obesity on an individual's mobility and chronic condition hinders their socialisation aspect and further negatively impacts their mental health.

1.2.2.4 Impact on quality of life

Increased incidence of metabolic disease including type 2 diabetes and cardiovascular disease and mental health disease in patients with obesity, obesity has been associated with decreased physical and mental quality of life. Meta-analysis of 8 published article found significant reduction in physical QoL in all BMI categories of obesity , though decreased mental QoL was only noticed in class III obesity (55).

Obesity has been identified as an independent risk factor for poor functional capacity and disability (defined as impaired ability to do activities daily living) in elderly populations (38). Elderly population with obesity has been reported to have poor recovery from other medical condition and more prone to institutionalization.(38). This may contribute to huge impact on patients' quality of life.

1.2.2.5 Financial impact

Obesity affects the financial status at various level including micro and macroeconomic. The excess per capita for overweight and obesity is higher compared with normal weight. These include both social care and health care. Severely obese individuals are three times more likely to require social care than those with a normal weight, resulting in increased risk of hospitalisation and associated health and social care costs (56). Overweight and Obesity related ill-health is estimated to have cost the NHS £6.1 billion in 2014/15 (57). This is more than the £3.3 billion attributed to smoking related ill health and £3.3 billion attributed to alcohol related ill health (56).

Overall productivity is lower for patients with obesity compared to normal weight patients due to loss of work secondary to higher absenteeism, long and short term disability and premature mortality (58). Patients with obesity may also experience discrimination at work (53) and are less likely to get a job, promotion and acknowledgement.

1.2.3 Pathogenesis of Obesity

The risk factors contributing to the current epidemiology of obesity is a complex system. In a given environment, there is a wide variation in weight and fat mass indicating that obesity is the result of complex interaction of genetic, environmental and behaviour factor including current lifestyle.

1.2.3.1 Genetic factors

From the animal studies, we know that the hypothalamus plays a pivotal role in energy balance and eating behaviour (59). The arcuate nucleus in the hypothalamus receives positive (orexigenic) and negative (anorexigenic) signals from the stomach, intestines, adipose tissue, and the pancreas (60). This complex system involves various neurons, hormones, and peptides. Mutation in these neurons and receptors gene can contribute to obesity (60, 61).

Role of genetics and heritability in obesity is mainly coming from studies done on twins, children reared together or in adopted environment (62, 63). The study showed the body weight is more closer to biological parent than the parent looking after them (63). 40-70% of obesity has been estimated to be hereditary (64). Various gene had been discovered and still

under investigation contributing to obesity (61). Genetic causes of obesity has been grouped as Monogenic, polygenic and syndromic (62).

Monogenic cause include mutation in single gene in leptin-melanocortin pathway. Polygenic gene include the combined effect of many genes amplified in weight gaining environment (62). Syndromic obesity is obesity associated with other organ/ system involvement e.g., Prader Willi Syndrome.

1.2.3.2 Environmental and behaviour factors

Obesity is strongly influenced by environmental and behavioural factors. From agricultural age, we transitioned to industrial age and currently living a deskbound life- style in digital age. The Foresight Tackling Obesities: Future Choices Project in 2007 provided an obesity system map highlighting the different factors leading to an obese society and their complex relationship (figure 3) (65).

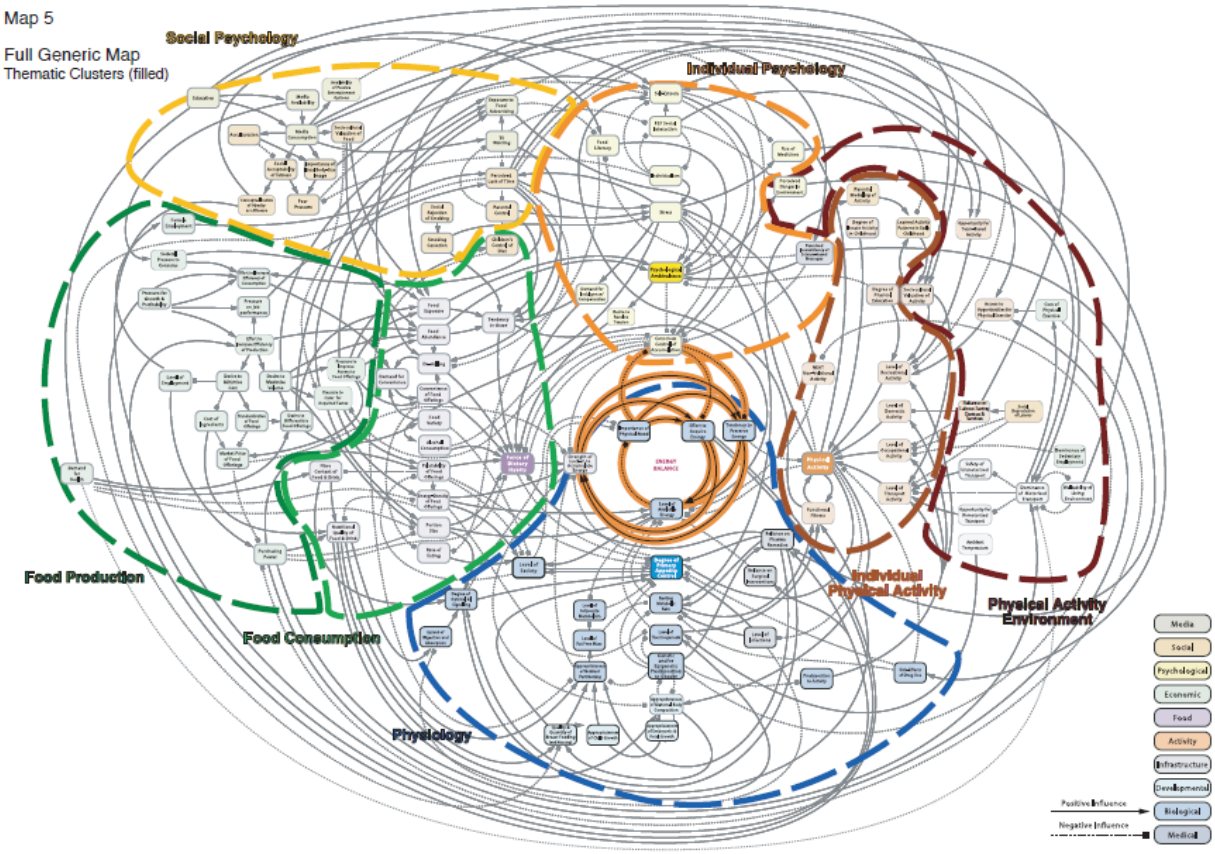


Figure 4 - Tackling obesities: future choices - full systems map (65)

The factors have been grouped as - food consumption, food production, physiology, individual psychology, social psychology, individual physical activity, and physical activity environment (65).

Adding to complexity of subject, recent studies showed the impact of these environmental factors on weight management differ modified by their genetic make-up. Studies done on 200 children aged 9-10 years showed that food consumption after watching food or toys advertisement was increased linearly in children with obesity associated genotype (66). The pooled result from Nurses' Health Study and Health Professionals Follow-up Study showed persons with higher genetic alleles associated with obesity appeared to be more susceptible to the adverse effects of sugar-sweetened beverages on BMI (67).

Impact of environment on BMI starts even before the child is born. Early adulthood obesity has been associated with high maternal BMI and higher maternal weight gain during pregnancy (68).

1.2.4 Management

Obesity is a chronic condition and will need intervention with long term follow up. Currently stepwise intensification management plan for obesity is - lifestyle intervention and behaviour therapy, pharmacotherapy, and bariatric surgery.

1.2.4.1 Lifestyle and behavioural modification

Lifestyle (+/- behavioural) interventions primarily involve counselling, dietary intervention, increased physical activity and behavioural therapy (40). These interventions can achieve 5-10% loss of body weight. There are various types of dietary interventions available for weight management with some focussing on carbohydrate restriction, some fat restriction and others reduction in total calorie intake. Patient culture, belief, associated comorbidities should be taken in to consideration and underlying cause of obesity should be targeted (69). There are several commercial lifestyle programs both at individual and community level like Slimming World, Weight Watcher UK, SlimFast, Atkins diet, Cambridge diet, Stillman diet, DASH diet.

1.2.4.1.1 Weight loss in patients with obesity

The systematic review published in 2015 analysed 45 trials representing 11 commercial weight loss programmes including self-directed programs (Atkins, Biggest Loser Club, eDiets,

Lose It, SlimFast), very-low calorie diet programs (VLCD) (Health management resources, Medifast, Optifast), Weight Watchers, Jenny Craig, Nurisystem and found weight loss ranging from 0.1-13% at 3-12 months (70).

Weight loss by dietary intervention had been associated with reduction in incidence of type 2 diabetes and cardiovascular risk factor (71, 72).

Systematic review and meta-analysis of seven RCTs, with study duration ranging from 1 year to 6 years, involving 4090 participants with impaired glucose tolerance found intervention with lifestyle changes lead to significant reduction in risk of progression to type 2 diabetes compared to control groups (RR = 0.53 (95% CI: 0.41, 0.67), $p < 0.001$) (73).

Diabetes Prevention programme (DPP) research group analysed 3234 participants with average follow up period of 2.8 years and noted more weight loss in lifestyle intervention group compared to metformin and placebo group (71). The crude incidence of diabetes per 100 person years was 4.8, 7.8 and 11 in lifestyle, metformin, and placebo groups, respectively. DPP group followed these participants further for median follow up of 5.7 years (IQR 5.5 to 5.8 years) and all participants were offered lifestyle modification and support (74). Overall incidence of diabetes in this 10 year follow- up study was lowest in lifestyle intervention group compared to metformin and placebo group showed the durability of lifestyle intervention (74).

1.2.4.1.2 Weight loss in patients with obesity and type 2 diabetes

Look AHEAD research group included participants with obesity and type 2 diabetes, randomised 2,496 participants on intensive lifestyle (ILS) and 2,463 on Diabetes specific education (DSE). They found more weight loss in ILS group compared to DSE group with net

difference of 7.9 % (7.6-8.3%) over 1 year follow up and 3.9% (3.5-4.4%) over 4 years follow up (75, 76). The prevalence of diabetes remission defined as HbA1c <6.5%, off glucose lowering medication was 11% during 1st year and 3.9% by 4 years in ILS group compared to <2% in DSE group (75). The positive impact on cardiovascular risk factor was also noted to be more pronounced in ILS compared to DSE at 1 year follow up (72).

Recently conducted cluster randomised trial DiRECT study compared the impact of lifestyle intervention and best practice care (77). 24% vs 0% managed to lose >15 kg body weight and 46% vs 4% managed to achieve Diabetes remission in intervention group compared to control group respectively (77). However, it was a small sample size 306 patients (149 in intervention) study, more than 98% were white ethnicity and were newly diagnosed with diabetes with max diabetes duration of 6 years and not on insulin (77).

1.2.4.1.3 Limitations

This degree of weight loss by dietary intervention although metabolically important is poorly sustained and patients usually regain weight over time (78).

DPP 10 years follow up, participants on lifestyle intervention group gained weight, crude incidence of diabetes increased from 4.8 to 5.9 per 100 person years while it was maintained in metformin group. Similarly in DiRECT study, over 2 years follow up, only 11% participants (24% at 1 year) maintained weight loss >15 kg and 36% (from 46%) maintained diabetes remission (79).

Long term compliance with life-style modification alone is difficult because of various reasons. Patients faces external barriers like lack of time and suitable environment for exercising, social and cultural beliefs (80) which may play role in weight management.

Weight loss by dietary intervention can lead to activation of compensatory biological pathway to encourage food intake and restore previous body weight. The rebound in weight gain had been explored at hormonal level. Weight is centrally controlled mainly in hypothalamus by many hormonal signals from gastrointestinal system and adipose tissue (60). Evidence showed that calorie restriction leads to reduction in satiety hormone like leptin, peptide YY, cholecystokinin, insulin, amylin and increased hunger hormones level like ghrelin, gastric inhibitory polypeptide (81). These changes cause increased hunger and decreased satiety signal leading to weight gain relapse (82). Hence, we need further adjuvant to reinforce the weight management. In clinical practice, pharmacotherapy is the second modality followed by bariatric surgery.

1.2.4.2 Pharmacological approaches

Pharmacotherapy approved by the Food and Drug Administration (FDA) for obesity includes Orlistat, Liraglutide, Phentermine-topiramate and Naltrexone- bupropion, but their use is limited because of cost, side-effects, lack of long- term safety data and cardiovascular outcomes (40, 83).

1.2.4.2.1 Orlistat

Orlistat is first approved weight management medication, is inhibitor of pancreatic, gastric, and carboxyl ester lipases and phospholipase A2, which are required for the hydrolysis of dietary fat in the gastrointestinal tract into fatty acids and monoacylglycerols. It can block ~30 % of fat absorption (69, 84). 10 % of the user can experience side effects like oily spotting, flatus with discharge, bowel urgency (69).

1.2.4.2.2 Naltrexone-bupropion

It is a combination of naltrexone and bupropion. Naltrexone is an opioid antagonist. It antagonises the feedback effect of β-endorphins. Bupropion is a norepinephrine/dopamine reuptake inhibitor. It stimulates the secretion of α-melanocyte stimulating hormone (MSH) and β-endorphin from hypothalamic proopiomelanocortin (POMC) neurons. α-MSH binds to MC3 and MC4 receptors leading to decreased food intake and increased satiety and resting energy expenditure (85). β-endorphin has got inhibitory feedback effects which get antagonised by Naltrexone. Common side effects are nausea with vomiting, constipation, headache, insomnia, dry mouth and transient rise in blood pressure (69). NICE guideline TA 494 published December last year rejected Naltrexone because it will need to be taken long term to get the benefit, hence not cost effective & absence of long term safety data (86).

1.2.4.2.3 Phentermine-topiramate

Combination therapy of phentermine and topiramate. Phentermine is a catecholamine releaser anorexiant drug, leads to decreased food intake. Topiramate is neurotransmitter gamma-aminobutyric acid (GABA) modulator leading to appetite suppression and augment satiety (69). Side effects are depression, anxiety, insomnia, dry mouth, constipation, dizziness, and dysgeusia (69). Its use is contraindicated in patients with established cardiac conditions.

1.2.4.2.4 Glucagon- like peptide-1 agonist/ analogue

Glucagon- like peptide-1 agonist/ analogues are incretin-based glucose lowering medications introduced in 2005. They act through G-proteins- coupled GLP-1 receptor. Peripherally, they

inhibit both gastric emptying, glucagon secretion, hepatic gluconeogenesis and improves insulin sensitivity (87). Centrally, they stimulate GLP-1 receptors and act on neurons as neurotransmitter located in hypothalamus and brainstem (88, 89). Evidence shows that central action of GLP-1 is beyond reduction in feeding and enhanced satiety. It has also been associated with regulation glucose and lipid metabolism, cardiovascular functions, mental function like cognitive functions, and emotional responses (88).

Currently available GLP1-analogues for weight management approved by FDA are liraglutide, and semaglutide. Liraglutide and semaglutide are glucagon-like peptide-1(GLP-1) analogue with 97% homology to human GLP-1. Higher dose Liraglutide (3 mg) and Semaglutide had been approved by FDA for weight management. SCALE diabetes RCT showed 5% and 10% of weight loss in 54.3% and 25.2% patients with obesity and type 2 diabetes taking liraglutide 3 mg at 56 weeks follow up (90). STEP (Semaglutide Treatment Effect in People with Obesity) trial conducted on patients with obesity without diabetes showed weight loss of 5% or more in 86.4% of patients,10% or more 69.1% of patients and 15% or more in 50.5% of patients at follow up period of week 68 (91). Cardiovascular outcome trial Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial with median follow up of 3.8 years (92) and Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) with follow up of 2 years (93) has reported Liraglutide and Semaglutide are associated with cardiovascular benefit in patients with type 2 diabetes.

Common side effects with GLP1A are injection site reaction, nausea, vomiting, pancreatitis, constipation, diarrhoea, gallbladder disease, increased resting heart rate, suicidal behaviour, worsening depression, unusual changes in mood or behaviour and hypoglycaemia when taken in combination with other medications for diabetes.

1.2.4.2.5 Combination therapy

Tirzepatide, dual glucagon like peptide and glucose dependent insulinotropic polypeptide receptor agonist, is a new emerging therapeutic option in field of diabetes management. RCT phase 3 trial including 478 patients with type 2 diabetes and randomised to weekly different doses of tirzepatide and placebo. Over a follow up period of 40 weeks, tirzepatide was associated with dose dependent weight loss of 7.0 to 9.5 kg (94).Frequent side effects reported were nausea, vomiting and diarrhoea (94).

1.2.4.2.6 Limitations

Most of the studies focussing on impact of pharmacotherapy on weight loss had follow up of <2 years and therefore the long-term data is lacking. Systematic review including RCT analysing the impact of weight lowering medications identified 28 studies (95). They found all medicines were associated with average < 5 kg weight loss compared with placebo at 1 year- with phentermine-topiramate offering weight loss of 8.8 kg, liraglutide 5.3 kg; naltrexone-bupropion 5.0 kg; and orlistat 2.6 kg (95). Systematic review included 21 RCT studies examining impact of pharmacotherapy on cardiovascular risk factor in patients with obesity reported orlistat produced improvement in cardiovascular risk factor (96). Newer medications like Liraglutide and Semaglutide have shown promising result on weight loss and better glycaemic control. However long- term data examining efficiency of pharmacotherapy is limited. Side effect and uncertainty around long term effect and cardiovascular safety had restricted the use of most of the pharmacological options.

Therefore, we need a more sustainable tool for weight management with promising long-term benefit on weight and metabolic outcomes.

Table 1: Efficacy of anti-obesity drugs (95)

Drug	**Mechanism of Action**	**Side Effect**	**Efficacy at 1 year**
Orlistat 1999- Long term	Inhibit lipases and phospholipase A2.(69) Blocks the digestion and absorption of ~30% of dietary fat	Oily spotting, flatus with discharge, bowel urgency (69)	2.6 kg (95%CI 2.16 to 3.04 kg) (95)
Naltrexone-bupropion FDA 2014	Inhibits dopamine and noradrenaline reuptake and activates POMC neurons. β-endorphin receptor antagonist Decreased food intake, increased satiety, and resting energy expenditure	Nausea with vomiting, constipation, headache, insomnia, dry mouth and transient rise in blood pressure	5.0 kg (95%CI 3.96 to 5.94 kg)(95)
Phentermine-topiramate 2012	GABA receptor modulator Appetite suppression and increases satiety	Insomnia, dry mouth, constipation, dizziness, and dysgeusia	8.8 kg (95%CI, -10.20 to -7.42 kg)(95)
GLP1A e.g- Liraglutide 2014- Semaglutide 2014	GLP-1 receptor agonist Induces the sensation of satiety when binding to the GLP-1 receptors present in neurons expressing POMC in the arcuate nucleus. Slows gastric emptying, increased satiety, and decreased food intake	Injection site reaction, nausea, vomiting, pancreatitis, constipation, diarrhoea, gallbladder disease, increased resting heart rate, suicidal behaviour, worsening depression, unusual changes in mood or behaviour and hypoglycaemia when taken in combination with other medications for diabetes	5.3 kg (95%CI, -6.06 to -4.52 kg) (95)
Tirzepatide	Dual GIP and GLP receptor agonist	Gastrointestinal side-effect- nausea, vomiting, diarrhoea	7- 9.5 kg, follow up 40 weeks(94)

1.2.4.3 Bariatric surgery

Bariatric surgery is currently the most durable treatment for obesity and the associated chronic diseases including type 2 diabetes. There are various surgical procedures being performed. Commonly done bariatric procedures world-wide are- Laparoscopic Adjustable Gastric Band (LAGB), sleeve gastrectomy (SG), Roux-en-Y gastric bypass (LRYGB), one anastomosis gastric bypass, and duodenal switch and pancreatic diversion. As per a survey participated by 50 countries the total number of metabolic/bariatric surgery done in 2011 was 340,768 (97) and is estimated to increase further (98).

Procedure descriptions of the common bariatric procedures covered in subsequent chapters:

Adjustable gastric band (GB)- In this procedure, a silicone is placed around the proximal part of stomach creating small pouch serving as mechanical fullness (99, 100).

Sleeve gastrectomy (SG)- Laparoscopically done sleeve gastrectomy is performed by stapling/ transecting ~70-80% of stomach (greater curvature) leaving banana shaped stomach (99, 100).

Gastric bypass (RYGB)- Stomach is stapled to create a proximal small pouch and distal stomach. Jejunum is transacted and the distal part is connected to the small proximal gastric pouch through a gastro-jejunostomy creating a Roux limb or alimentary limb. Distal stomach and proximal small intestine is left intact and re- anastomosed distal to gastrojejunostomy. RYGB leads ingested food to bypass the distal stomach, duodenum and proximal jejunum, and rapidly go through the small gastric pouch and flow into the jejunum (99-101).

Biliopancreatic diversion with duodenal switch (DS)- Biliopancreatic diversion with duodenal switch is multistep bariatric procedures. First step is sleeve gastrectomy with intact pylorus.

Ileum is anastomosed to pylorus bypassing duodenum and jejunum. Biliopancreatic loop consisting of bypassed small intestine loop and carrying bile and pancreatic juice joins the digestive tract proximal to ileo-caecal valve (100).

1.2.4.3.1 Impact of bariatric surgery on weight loss

Meta-analysis including 11 studies found mean weight reduction of 26 kg (95%CI 21-31 kg) in patients who had bariatric surgery compared to control with follow-up ranging from 40 weeks to 2 years (102). Another systematic review including 80 studies found excess weight loss % at 5 years of 47.94%, 62.5% and 53.25% after LAGB, LRYGB and LSG respectively (103). Systematic review with 33 studies included showed 56.7% excess weight loss in gastric bypass, 45.9% in LAGB, 74.1%in biliopancreatic bypass and 58.3% in sleeve gastrectomy with at least 10 years of follow-up (104).

The non-randomized matched controlled prospective Swedish Obese Subjects (SOS) intervention study included 2010 patients who underwent bariatric surgery and 2037 matched controls showed persistence weight loss of >15% over 20 years of follow up in all the surgical group (105). This study highlighted the durability of bariatric surgery.

1.2.4.3.2 Bariatric surgery and metabolic effect

Over the last 20 years, bariatric and metabolic surgery has emerged as an effective treatment for obesity and its associated comorbidities. In addition, bariatric surgery is also associated with significant improvements in metabolic outcomes, such as type 2 diabetes, hypertension, OSA, hyperlipidaemia, reduced mortality and cardiovascular disease (106).

Although initial data was from large observational trials, more recently, the superiority of bariatric surgery over medical therapy in patients with type 2 diabetes in terms of glycaemic control, and the impact on cardiovascular disease risk factors has been confirmed in randomised trials (107-109).

Several trial of up to 5-year duration showed the superiority of bariatric surgery to medical treatment in patients with type 2 diabetes in terms of glycaemic control, hypertension and lipids control as well as weight loss (108, 110, 111). Meta-analysis of RCT including four studies found the relative risk of diabetes remission was 22 times higher in surgical group compared to control group with relative risk 22.1 (3.2 to 154.3, P=0.002) (102). Similarly, the probability of attaining metabolic syndrome remission was found to be higher in surgical group compared to their control with relative risk 2.4 (1.6 to 3.6, P<0.001) (102).

1.2.4.3.3 Bariatric surgery and Diabetes related long term complications

Data from longitudinal studies showed possible favourable impact of bariatric surgery on glycaemic control and diabetes-related vascular complications in patients with type 2 diabetes (112, 113).

Swedish Obese Subject (SOS) study, a prospective matched controlled showed the reduction in the incidence rate of microvascular (eye, kidney, and peripheral nerves) and macrovascular (limb, heart, brain) complications in patients who had undergone bariatric surgery. The collective incidence of microvascular complications in control and surgery arm were 41.8 per 1000 person-years (95%CI, 35.3-49.5) and 20.6 per 1000 person-years (95%CI, 17.0-24.9) respectively (114). Similarly, the incidence of macrovascular complications in

control and surgical arm were 44.2 per 1000 person-years (95%CI, 37.5-52.1) and 31.7 per 1000 person-years (95%CI, 27.0-37.2) respectively (114).

Another paper from the same SOS group published by Carlsson et.al studied 1498 patients in the surgery arm and 1610 in the control arm, found the incidence of new onset albuminuria significantly reduced in post bariatric patients compared to control group over 10 years follow up with adjusted hazard ratio of 0.37 (95% CI, 0.30–0.47) (115).

The systematic review by Sheng group analysing the data from nine studies found the incidence of microvascular and macrovascular complication considerably lower in the surgery arm than the non-surgery arm (RR = 0.37; 95% CI 0.30-0.46 and RR = 0.52; 95% CI 0.44-0.61 respectively)(116).

Amin et.al studied 152 patients with type 2 diabetes from a single centre noted reduced progression of diabetic retinopathy (DR) and maculopathy in the surgical arm compared to routine care arm (117). The incidence of site threatening DR and maculopathy was 5.7% and 5.6% in surgical arm compared to 12.1% and 15.4% in routine care respectively (117).

Another study from the same hospital published a retrospective study analysing 163 patients with type 2 diabetes who underwent bariatric surgery and had pre and post eGFR available. They noted significant improvement in eGFR especially in patients with preoperative eGFR≤ 60 mL/min/1.73m^2 (118).

1.2.4.3.4 Mechanism

Given the extent of weight loss and improvements in glycaemic control following bariatric surgery, there has been considerable interest in the mechanisms leading to these effects. Historically, bariatric surgery was categorized as restrictive and/or malabsorptive. Restrictive

procedures restrict the amount of oral intake like Gastric band. In malabsorptive procedure, there is manipulation of gastrointestinal tract leading to malabsorption like gastric bypass. The effects of malabsorption understandably, has significant effects on weight loss but this theory could not explain the early metabolic benefits of bariatric surgery seen even before the substantial weight loss occurs. Then came the foregut and hindgut theory by Cumming et al defined as proximal intestinal exclusion. This theory focused on stimulation of L cells in small intestine and surge in level of glucose lowering incretin and appetite suppressing hormones GLP1A, peptide YY and oxyntomodulin. The rise in the level of theses hormones explains the early impact of bariatric surgery on glycaemic status (119).

The mechanisms by which malabsorption and changes in gut hormones influence weight loss and glucose control are discussed below.

1.2.4.3.4.1 Gut hormones

Bariatric surgery like RYGB, SG and DS has been associated with increased level of incretin hormones due to rapid nutrient entry in distal part of small intestine. Glucagon like peptide (GLP-1), glucose-dependent insulinotropic peptide (GIP) and Peptide YY (PYY) are secreted by Land K-cells mostly located in the ileum and colon (82, 120). GLP1 induces insulin secretion, insulin sensitivity, preservation of β cell function and mass and regulation of proliferation (121). It also slows down gastric emptying and gallbladder contraction, and reduces gastric, and pancreatic secretion (121).

Study conducted on 41 patients with obesity and type 2 diabetes who underwent gastric bypass, gastric band or very low-calorie diet found improved Insulin resistance measured as

HOMA-IR, insulin production, and GLP-1 responses after a standard meal test over 42 days follow up period in gastric bypass group (122).

1.2.4.3.4.2 Nervous system

Food intake and resting energy expenditure in hypothalamus is regulated by neuroendocrine system of anorexic and orexigenic neuronal signaling. Bariatric surgery has been associated with alteration in neuropeptide signaling and food reward system (123). Study done on five females demonstrated decreased dopamine receptor in patients post sleeve gastrectomy or gastric bypass leading to increased level of dopamine. Increased extracellular level of dopamine had been suggested as one of the pathway to achieve early satiety (124). Increased level of GLP-1, GIP and PYY induces anorexigenic effect on brain and suppress appetite (82, 120). Ghrelin is orexigenic peptide leading to increased appetite. Decreased level of ghrelin has been evidenced in patients post SG and RYGB (82, 120).
Peripheral nervous system plays vital role in food intake regulation. Vagal afferent nerve in stomach and duodenum area respond to stretch stimulus by luminal food material. Small stomach pouch leads to early satiety signal to brain via vagal neurons and reduces food intake (82, 125) which could be an important mechanism in gastric band beside restricting the amount of food intake.

1.2.4.3.4.3 Gut microbiota

Bariatric surgery causes change in dietary habit, luminal anatomy, and environment. Reduced gastric acid secretion post bariatric surgery can cause rise in pH in the colon. Bypassing parts of stomach and small intestine may lead of incompletely digested food.

These changes lead to alteration in gut microbiome and may contribute to weight loss (120, 126).

1.2.4.3.4.4 Bile acid adaptation

Due to change in anatomy after bariatric surgery, increased amount and change in composition of bile salt had also been noted in distal duodenum. Increased bile acid in ileum facilitates the secretion of fibroblast growth factor 19 (FGF19). FGF19 act on signaling pathway and farnesoid X receptor (FXR) to inhibit hepatic bile acid and stimulate GLP-1A, PYY and increases insulin sensitivity leading to weight loss and diabetes management (82, 126).

1.2.4.3.4.5 Change in food choices, taste, smell

Bariatric surgery was associated with shift in choice of food and less rewarding eating behavior (82). Study conducted on 58 patients in surgical group and 25 in control group found that there was lower activation in brain reward system to high calories food in RYGB group compared to GB and control group (127). This finding could explain the change in the food choice after bariatric surgery and shifting to healthier food choices

1.2.4.3.4.6 Malabsorption and enteroplasticity

The surface area of stomach and small intestine is decreased to various level depending on type of bariatric surgery. This leads to malabsorption of macro and micronutrients. Work of Carswell et al showed increased fat content in faecal material of patients post RYGB and DS (128). Protein malnutrition and anaemia secondary to iron and vitamin B12 deficiency has been associated with bariatric procedures (100).

Enteroplasticity is adaptation on lumen lining and cells to any stress, aging or change in environment. L cells proliferation has been evidenced post SG and RYGB in animal studies (82). These L cells are nutrient sensitive and has been associated with increased release of GLP1 for a given amount of nutrients.

1.2.4.3.5 Side effects

Short term side- effects

Like any surgical procedures, bariatric surgery is associated with peri-operative and post-operative complications and side-effects. A systematic review of 38 RCT involving 4030 patients found risk of short- term all-cause mortality defined as mortality (≤30 days) as 0.18% (95% CI, 0.04%-0.38%) (129). In early stage, bariatric surgery is associated with risk of anastomotic leak (0.6% to 7%), gastrointestinal gut stenosis leading to symptoms of dysphagia (130). There is 11% risk of bleeding in patients undergoing RYGB or SG during peri-operative stage (130). Slippage (8%) and band erosion (0.31% to 1.96%) are common complication in patients undergoing GB (130).

Long term side-effects

In late stage, due to alteration in enterohepatic circulation especially in RYGB and duodenal switch, patients are at increased risk of gall stone. There is high risk of malignant ulcer (5%), spontaneous bowel perforation, small bowel obstruction and hernia (130). Patients are at increased risk of early and late dumping syndrome after bariatric surgery especially in patients who had RYGB (131). Bariatric surgery had been associated with macro and micro nutrient deficiencies including vitamin B1, B12 and D deficiencies, iron and folate (132).

Systematic review of 32 studies involving 148,643 patients showed patients are at higher risk of suicide/ self- harm attempt after bariatric surgery (133). Systematic review of 10 studies with three years follow up found increased risk of alcohol use disorders after bariatric surgery (134).

1.2.4.4 Guidelines and Recommendations

NICE guideline CG 189 (135) recommends considered bariatric surgery as a treatment option for people with obesity if all of the following criteria are fulfilled:

- They have a BMI of 40 kg/m^2 or more, or between 35 kg/m^2 and 40 kg/m^2 and other significant disease (for example, type 2 diabetes or high blood pressure) that could be improved if they lost weight.
- All appropriate non-surgical measures have been tried but the person has not achieved or maintained adequate, clinically beneficial weight loss.
- The person has been receiving or will receive intensive management in a tier 3 service.
- The person is generally fit for anaesthesia and surgery.
- The person commits to the need for long-term follow-up.

American Diabetes Association (ADA) 2011: recommends that "Bariatric surgery may be considered for adults with BMI ≥ 35 kg/m^2 and type 2 diabetes, especially if the diabetes or associated comorbidities are difficult to control with lifestyle and pharmacologic therapy."(136)

International Diabetes Federation (IDF) 2011: recommends "Bariatric surgery is an appropriate treatment for people with type 2 diabetes and obesity. Surgery should be an

accepted option in people who have type 2 diabetes and a BMI of ≥ 35 kg/m^2 or more. Surgery should be considered as an alternative treatment option in patients with a BMI between 30 kg/m^2 and 35 kg/m^2 when diabetes cannot be adequately controlled by optimal medical regimen, especially in the presence of other major cardiovascular disease risk factors."(137)

1.2.4.5 Diabetes remission and prediction model

Bariatric surgery had been found to have superior effect on diabetes glycaemic control, decreasing the number of anti- diabetes medications, but not all patients with type 2 diabetes achieve similar outcomes. Diabetes remission rates around 30-70% have been reported following bariatric surgery (138-142). The observed variation in the figures may be due to differences in definitions of diabetes remission (143), the population studied, the type of bariatric surgery and duration of follow-up. Identifying predictors and developing prediction model had got lots of attention in last one decade, but not widely used in clinical practice.

1.3 Rationale for my thesis projects:

Bariatric surgery is acknowledged as the most effective treatment for weight loss and remitting obesity related comorbidities, and metabolic syndrome. The clinical trials have repeatedly showed the superiority of bariatric surgery for weight management over routine clinical (non-surgical) treatment. Previous RCT by Mingrone et.al (108) , Ikramuddin et.al (144) and STAMPEDE study (145) showed reduction in cardiovascular risk factor like type 2 diabetes, hypertension, and hyperlipidaemia in surgical patients over five- year follow up, but no analysis was presented to compare the impact of bariatric surgery on incidence of cardiovascular disease. These studies also had small sample size and majority of bariatric procedures were RYGB.

Like any other intervention, follow-up and patient compliance can play a vital role in the outcome. Therefore, we need real world data to analyse the impact of bariatric surgery on incidence of cardiovascular and diabetes related microvascular complications which is currently limited.

SOS study showed reduction in incidence of cardiovascular disease which was defined as fatal or non- fatal cardiovascular events (myocardial infarction or stroke whichever comes first) over median follow up of 14.7 years. SOS study also showed reduction in incidence of macrovascular and microvascular complications. However, most of the procedures in the SOS were open surgery and >60% were vertical gastroplasty, which is not performed nowadays. SOS study was conducted in the era when use of medications like statin and ACE-I was limited. Now newer glucose lowering medications like GLP1A and SGLT2 I and newer bariatric procedures are being practiced.

Retrospective cohort study by Johnson et.al showed reduction in macrovascular complication defined as myocardial infarction, stroke or all- cause mortality and microvascular complication defined as diagnosis of blindness, laser eye treatment or retinal surgery, nontraumatic amputation, or new haemodialysis (113). None of the studies showed the impact of different type of bariatric procedures on incidence on vascular complications. The number of bariatric surgery being done UK is increasing (238 in 2000 to 2543 in 2007) and more laparoscopic procedures are being done compared open surgery (28% laparoscopic procedures in 2000 compared with 74.5% in 2007) (146).

With increasing prevalence of obesity in elderly and associated chronic health conditions and emerging safety evidence for bariatric surgery, number of patients undergoing bariatric surgery is gradually increasing (147) . However, impact of bariatric surgery on health outcome and all-cause mortality is not clear from current literature. A previous study from the United Kingdom National Bariatric Surgery Registry (NBSR) showed improvement/ remission in obesity-related complications following bariatric surgery (148), but the NBSR only included patients who had bariatric surgery and there was no control arm. Hence, I conducted series of matched control cohort studies examining the impact of bariatric surgery on incidence of vascular complications.

My hypothesis:

1) Bariatric surgery reduces the incidence of cardiovascular complications and mortality in patients with and without diabetes.
2) Bariatric surgery reduces the incidence of diabetes related microvascular complications (Diabetes related foot disease, Sight threatening diabetes retinopathy, and nephropathy) in patients with type 2 diabetes and obesity.

In addition, I undertook a systematic review to identify different diabetes remission prediction models and their relevance for clinical practice.

1.4 Layout of my chapters

This Section provides the outline of the following chapters of the thesis.

Chapter 2 is method section.

Chapter3, 4, 5 and 6 are results sections.

Chapter 3 covers Impact of bariatric surgery on cardiovascular disease and mortality in patients with and without type 2 diabetes.

Chapter 4 focusses on impact of bariatric surgery on cardiovascular disease and mortality in elderly population.

In chapter 5, impact of bariatric surgery on diabetes related microvascular complication in patients with type 2 diabetes and obesity has been presented.

Chapter 6 presents the impact of bariatric surgery on diabetes glycaemic status and glucose lowering medications.

Chapter 7 presents a systematic review on prediction models for diabetes remission in patients with type 2 diabetes who underwent bariatric surgery.

Chapter 8 is Discussion and future directions.

1.5 References:

1. Consultation W. Definition, Diagnosis and Classification of Diabetes Mellitus 1999 [Available from: https://www.staff.ncl.ac.uk/philip.home/who_dmc.htm.
2. PrentkiM, NolanCJ. Islet beta cell failure in type 2 diabetes. The Journal of clinical investigation. 2006;116(7).
3. Brownlee M. The Pathobiology of Diabetic Complications. 2005.
4. Kitada M, Zhang Z, Mima A, King GL. Molecular mechanisms of diabetic vascular complications. Journal of diabetes investigation. 1. J Diabetes Investig2010. p. 77-89.
5. WHO. Global Health Observatory (GHO) data 2014 [Available from: http://www.who.int/gho/ncd/risk_factors/overweight_text/en/.
6. IDF. IDF Diabetes Atlas | Tenth Edition. 2022.
7. England PH. <Adult_obesity_and_type_2_diabetes_.pdf> 31 July 2014 [Available from: https://www.gov.uk/government/publications/adult-obesity-and-type-2-diabetes.
8. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. Cardiovasc Diabetol. 172018.
9. E A, I R, S D-C, E D. Epidemiology and Economic Burden of Cardiovascular Disease in Patients with Type 2 Diabetes Mellitus in Spain: A Systematic Review. Diabetes therapy : research, treatment and education of diabetes and related disorders. 2021;12(6).
10. TR E, A A, C L, UH P. Economic Burden of Cardiovascular Disease in Type 2 Diabetes: A Systematic Review. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2018;21(7).
11. Prof Andrew JM Boulton FRCP a b, Loretta Vileikyte MD a, b, Gunnel Ragnarson-Tennvall PhD c, Jan Apelqvist MD. The global burden of diabetic foot disease - ScienceDirect. The Lancet. 2005.
12. Vickie R. Driver MD, FACFAS,a, Matteo Fabbi M, a Lawrence A. Lavery, DPM, MPH,b Gary Gibbons, MD,a Boston, Mass; and Georgetown, Tex. The costs of diabetic foot: The economic case for the limb salvage team ScienceDirect. 2017.
13. Noote CJMAaKYWaMHaCCbMScSLdFEv. Humanistic and economic burden of painful diabetic peripheral neuropathy in Europe: A review of the literature - ScienceDirect. Science Direct Volume 109, Issue 2. August 2015;109(2):215-25.
14. Cheung N, Mitchell P. Diabetic retinopathy. The Lancet. 2010;376(9735):124-36.
15. Petrović MA VB, Janicijević K, Vulović TS. Correlation between metabolic controls and changes in retina in patients having diabetes. 2014.
16. Chantelau E, Kohner EM. Why some cases of retinopathy worsen when diabetic control improves. 1997.
17. Dahl-Jørgensen K, Brinchmann-Hansen O, Hanssen KF, Sandvik L, Aagenaes O. Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin dependent diabetes mellitus: the Oslo study. 1985.
18. prevalence C. Chronic kidney disease (CKD) prevalence model briefing [Available from:

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/612303/ChronickidneydiseaseCKDprevalencemodelbriefing.pdf.
19. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C-y. Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization. http://dxdoiorg/101056/NEJMoa041031. 2009.
20. Timothy C. Evans M, PhD, and Peter Capell, MD Diabetic Nephropathy. Clinical Diabetes.18.
21. Ritz E, Koleganova N, Piecha G. Is there an obesity-metabolic syndrome related glomerulopathy? Curr Opin Nephrol Hypertens. 2011;20(1):44-9.
22. Debono M, Cachia E. The impact of diabetes on psychological well being and quality of life. The role of patient education. http://dxdoiorg/101080/13548500701235740. 2007.
23. Polonsky WH. Emotional and quality-of-life aspects of diabetes management | SpringerLink. 2002.
24. Panos Kanavos SvdAa. Diabetes expenditure, burden of disease and management in 5 EU countries 2012 [Available from: http://www.lse.ac.uk/LSEHealthAndSocialCare/research/LSEHealth/MTRG/LSEDiabetesReport26Jan2012.pdf.
25. WHO. Global report on Diabetes 2016 [Available from: http://apps.who.int/iris/bitstream/handle/10665/204871/9789241565257_eng.pdf jsessionid=2455A574B10C239EE9ED6E052717BFA3?sequence=1.
26. England PH. Health matters: preventing Type 2 Diabetes. 2018.
27. Chadt A, Scherneck S, Joost H-G, Al-Hasani H. Molecular links between Obesity and Diabetes: “Diabesity”. 2018.
28. Zierle-Ghosh A, Jan A. Physiology, Body Mass Index (BMI). 2018.
29. Lean MEJ, Han TS, Morrison CE. Waist circumference as a measure for indicating need for weight management. 1995.
30. National Heart L, and Blood Institute. Losing Weight, Body Mass Iindex: National Heart, Lung, and Blood Institute; 2018 [Available from: https://www.ncbi.nlm.nih.gov/pubmed/.
31. Conroy SM, Chai W, Lim U, Franke AA, Cooney RV, Maskarinec G. Leptin, adiponectin, and obesity among Caucasian and Asian women. Mediators of inflammation. 2011;2011:253580.
32. Sharma AM, Kushner RF. A proposed clinical staging system for obesity. International journal of obesity (2005). 2009;33(3):289-95.
33. Padwal RS, Pajewski NM, Allison DB, Sharma AM. Using the Edmonton obesity staging system to predict mortality in a population-representative cohort of people with overweight and obesity. 2011.
34. FrühbeckG, BusettoL, DickerD, YumukV, GH G, J H, et al. The ABCD of Obesity: An EASO Position Statement on a Diagnostic Term with Clinical and Scientific Implications. Obesity facts. 2019;12(2).
35. WHO. Tenfold increase in childhood and adolescent obesity in four decades: new study by Imperial College London and WHO 2018 [Available from: http://www.who.int/news-room/detail/11-10-2017-tenfold-increase-in-childhood-and-adolescent-obesity-in-four-decades-new-study-by-imperial-college-london-and-who.

36. center Hasci. Statistics on Obesity, Physical Activity and Diet The National Archives 2016 [Available from: http://content.digital.nhs.uk/catalogue/PUB20562/obes-phys-acti-diet-eng-2016-rep.pdf.
37. Kuk JL, Saunders TJ, Davidson LE, Ross R. Age-related changes in total and regional fat distribution. Ageing Res Rev. 2009;8(4):339-48.
38. Samper-Ternent R, Al Snih S. Obesity in Older Adults: Epidemiology and Implications for Disability and Disease. Rev Clin Gerontol. 2012;22(1):10-34.
39. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC public health. 2009;9:88.
40. Steven B. Heymsfield MD, and Thomas A. Wadden, Ph.D. . Mechanisms, pathophysiology and management of obesity. N Engl J. 2017(Med 2017;376:254-66.).
41. WilsonPW, D'AgostinoRB, SullivanL, PariseH, WB K. Overweight and Obesity as Determinants of Cardiovascular Risk: The Framingham Experience. Archives of internal medicine. 2002;162(16).
42. LassaleC, TzoulakiI, KGM M, M S, J B, L J, et al. Separate and combined associations of obesity and metabolic health with coronary heart disease: a pan-European case-cohort analysis. European heart journal. 2018;39(5).
43. Schwartz AR, Patil SP, Laffan AM, Polotsky V, Schneider H, Smith PL. Obesity and Obstructive Sleep Apnea: Pathogenic Mechanisms and Therapeutic Approaches. Proc Am Thorac Soc. 52008. p. 185-92.
44. Mary Forhan P, OT Reg(Ont) a,*, Simone V. Gill, PhD, OTR/L. Obesity, functional mobility and quality of life Best Practice & Research Clinical2013 [Available from: http://www.bu.edu/motordevlab/files/2012/08/2013_Obesity-functional-mobility-and-QoL.pdf.
45. Topsakal S, Erurker T, Akin F, Yaylali GF, Yerlikaya E, Kaptanoglu B. Heel Pain and Comorbid Conditions in Obese Patients. http://dxdoiorg/103109/105824522014883006. 2014.
46. Bolam KA, van Uffelen JG, Taaffe DR. The effect of physical exercise on bone density in middle-aged and older men: a systematic review. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2013;24(11):2749-62.
47. ZhengH, ChenC. Body mass index and risk of knee osteoarthritis: systematic review and meta-analysis of prospective studies. BMJ open. 2015;5(12).
48. Kopcakova J, Dankulincova Veselska Z, Madarasova Geckova A, van Dijk JP, Reijneveld SA. Is Being a Boy and Feeling Fat a Barrier for Physical Activity? The Association between Body Image, Gender and Physical Activity among Adolescents. Int J Environ Res Public Health. 112014. p. 11167-76.
49. Müller R. Psychische Folgeprobleme der Adipositas. 2013.
50. ChaputJP, FerraroZM, D Ph, SharmaAM. Widespread misconceptions about obesity. Canadian family physician Medecin de famille canadien. 2014;60(11).
51. NutterS, IrelandA, AlbergaAS, BrunI, LefebvreD, HaydenKA, et al. Weight Bias in Educational Settings: a Systematic Review. Current obesity reports. 2019;8(2).
52. Stuart W. Flint MC, Sonia C. Codreanu, Vanja Ivic, Colene Zomer and. Obesity Discrimination in the Recruitment Process: “You’re Not Hired!” | Psychology. 2016.

53. Puhl RM. The Stigma of Obesity: A Review and Update. Obesity2012.
54. Luppino FS, Wit LMd, Bouvy PF, Stijnen T, Cuijpers P, Penninx BWJH, et al. Overweight, Obesity, and Depression: A Systematic Review and Meta-analysis of Longitudinal Studies. Archives of General Psychiatry. 2018;67(3):220-9.
55. Ul-HaqZ, MackayDF, FenwickE, PellJP. Meta-analysis of the association between body mass index and health-related quality of life among adults, assessed by the SF-36. Obesity (Silver Spring, Md). 2013;21(3).
56. Peter Scarborough1 PB, Kremlin K. Wickramasinghe1, Steve Allender1,2,. The economic burden of ill health due to diet, physical inactivity, smoking, alcohol and obesity in the UK: an update to 2006-07 nhs costs: Journal of Public Health Advance Access published May 11, 2011; 2011 [Available from: http://www.ias.org.uk/uploads/pdf/Economic%20impacts%20docs/pubmed.fdr033.full.pdf.
57. Health matters: obesity and the food environment 2020 [Available from: https://www.gov.uk/government/publications/health-matters-obesity-and-the-food-environment/health-matters-obesity-and-the-food-environment--2.
58. Goettler A, Grosse A, Sonntag D. Productivity loss due to overweight and obesity: a systematic review of indirect costs. BMJ Open. 2017;7(10):e014632.
59. Harris RB. Contribution made by parabiosis to the understanding of energy balance regulation. Biochimica et biophysica acta. 2013;1832(9):1449-55.
60. van Vliet-Ostaptchouk JV, Hofker MH, van der Schouw YT, Wijmenga C, Onland-Moret NC. Genetic variation in the hypothalamic pathways and its role on obesity. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2009;10(6):593-609.
61. Ignatieva EV, Afonnikov DA, Saik OV, Rogaev EI, Kolchanov NA. A compendium of human genes regulating feeding behavior and body weight, its functional characterization and identification of GWAS genes involved in brain-specific PPI network. BMC Genetics. 17. BMC Genetics2016.
62. Thaker VV. GENETIC AND EPIGENETIC CAUSES OF OBESITY. Adolesc Med State Art Rev. 2017;28(2):379-405.
63. StunkardAJ, SørensenTI, HanisC, TeasdaleTW, ChakrabortyR, SchullWJ, et al. An adoption study of human obesity. The New England journal of medicine. 1986;314(4).
64. AllisonDB, KaprioJ, KorkeilaM, KoskenvuoM, NealeMC, HayakawaK. The Heritability of Body Mass Index Among an International Sample of Monozygotic Twins Reared Apart. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity. 1996;20(6).
65. Science GOf. Reducing obesity: obesity system map. 2007.
66. Gilbert-DiamondD, EmondJA, LansiganRK, RapuanoKM, KelleyWM, HeathertonTF, et al. Television food advertisement exposure and FTO rs9939609 genotype in relation to excess consumption in children. International journal of obesity (2005). 2017;41(1).
67. Qi Q, Chu AY, Kang JH, Jensen MK, Curhan GC, Pasquale LR, et al. Sugar-Sweetened Beverages and Genetic Risk of Obesity. http://dxdoiorg/101056/NEJMoa1203039. 2012.
68. ReynoldsRM, OsmondC, PhillipsDI, GodfreyKM. Maternal BMI, parity, and pregnancy weight gain: influences on offspring adiposity in young adulthood. The Journal of clinical endocrinology and metabolism. 2010;95(12).

69. Kushner RF. Weight Loss Strategies for Treatment of Obesity: Lifestyle Management and Pharmacotherapy. Prog Cardiovasc Dis (2018),. 2018;Prog Cardiovasc Dis (2018),
.
70. Gudzune KA, Doshi RS, Mehta AK, Chaudhry ZW, Jacobs DK, Vakil RM, et al. Efficacy of commercial weight loss programs: an updated systematic review. Ann Intern Med. 2015;162(7):501-12.
71. GROUP DPPR. Reduction in the incidence of Type 2 Diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346(6):393-403.
72. Pi-Sunyer X, Blackburn G, Brancati FL, Bray GA, Bright R, Clark JM, et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. Diabetes Care. 2007;30(6):1374-83.
73. UusitupaM, KhanTA, ViguilioukE, KahleovaH, RivelleseAA, HermansenK, et al. Prevention of Type 2 Diabetes by Lifestyle Changes: A Systematic Review and Meta-Analysis. Nutrients. 2019;11(11).
74. KnowlerWC, FowlerSE, HammanRF, ChristophiCA, HoffmanHJ, BrennemanAT, et al. 10-year Follow-Up of Diabetes Incidence and Weight Loss in the Diabetes Prevention Program Outcomes Study. Lancet (London, England). 2009;374(9702).
75. GreggEW, ChenH, WagenknechtLE, ClarkJM, DelahantyLM, BantleJ, et al. Association of an Intensive Lifestyle Intervention With Remission of Type 2 Diabetes. JAMA. 2012;308(23).
76. Wing RR, Espeland MA, Clark JM, Hazuda HP, Knowler WC, Pownall HJ, et al. Association of Weight Loss Maintenance and Weight Regain on 4-Year Changes in CVD Risk Factors: the Action for Health in Diabetes (Look AHEAD) Clinical Trial. Diabetes Care. 2016;39(8):1345-55.
77. Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet. 2018;391(10120):541-51.
78. Wadden TA, Webb VL, Moran CH, Bailer BA. Lifestyle Modification for Obesity. 2012.
79. Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. Lancet Diabetes Endocrinol. 2019;7(5):344-55.
80. Sharifi N, Mahdavi R, Ebrahimi-Mameghani M. Perceived Barriers to Weight loss Programs for Overweight or Obese Women. Health Promot Perspect. 2013;3(1):11-22.
81. SumithranP, PrendergastLA, DelbridgeE, PurcellK, ShulkesA, KriketosA, et al. Long-term Persistence of Hormonal Adaptations to Weight Loss. The New England journal of medicine. 2011;365(17).
82. Pucci A, Batterham RL. Mechanisms underlying the weight loss effects of RYGB and SG: similar, yet different. J Endocrinol Invest. 2019;42(2):117-28.
83. Rosa-GonçalvesP, MajerowiczD. Pharmacotherapy of Obesity: Limits and Perspectives. American journal of cardiovascular drugs : drugs, devices, and other interventions. 2019;19(4).
84. Keith JN. Pharmacotherapy in Treatment of Obesity. Gastroenterol Clin N Am 45 (2016) 663–672. 2016 december;45(4):663-72.

85. Kakkar AK, Dahiya N. Drug treatment of obesity: current status and future prospects. Eur J Intern Med. 2015;26(2):89-94.
86. NICE guideline T. Naltrexone–bupropion for managing overweight and obesity | Guidance and guidelines | NICE: NICE; 2017 [Available from: https://www.nice.org.uk/guidance/ta494/chapter/1-Recommendations.
87. DruckerDJ. Enhancing incretin action for the treatment of type 2 diabetes. Diabetes care. 2003;26(10).
88. K K, T Y. Neural effects of gut- and brain-derived glucagon-like peptide-1 and its receptor agonist. Journal of diabetes investigation. 2016;7 Suppl 1(Suppl 1).
89. Ladenheim EE. Liraglutide and obesity: a review of the data so far. Drug design, development and therapy. 2015;9:1867-75.
90. Davies MJ, Diabetes Research Centre UoL, Leicester, United Kingdom, Bergenstal R, International Diabetes Center PNHS, Minneapolis, Minnesota, Bode B, Atlanta Diabetes Associates A, Georgia, et al. Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes: The SCALE Diabetes Randomized Clinical Trial. JAMA. 2017;314(7):687-99.
91. WildingJPH, BatterhamRL, CalannaS, DaviesM, LF VG, I L, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. The New England journal of medicine. 2021;384(11).
92. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016;2016(375):311-22.
93. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016;375(19):1834-44.
94. RosenstockJ, WyshamC, FríasJP, KanekoS, LeeCJ, LandóL F, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. Lancet (London, England). 2021;398(10295).
95. Khera R, Murad MH, Chandar AK, Dulai PS, Wang Z, Prokop LJ, et al. Association of Pharmacological Treatments for Obesity With Weight Loss and Adverse Events: A Systematic Review and Meta-analysis. Jama. 2016;315(22):2424-34.
96. Zhou YH, Ma XQ, Wu C, Lu J, Zhang SS, Guo J, et al. Effect of anti-obesity drug on cardiovascular risk factors: a systematic review and meta-analysis of randomized controlled trials. PLoS One. 2012;7(6):e39062.
97. Buchwald H. Metabolic/Bariatric Surgery Worldwide 2011 | SpringerLink. 2013.
98. ASMBS. Estimate of Bariatric Surgery Numbers, 2011-2019 | American Society for Metabolic and Bariatric Surgery. 2021.
99. Alverdy JC, Prachand V, Flanagan B, Thistlethwaite WA, Siegler M, Garfinkel M, et al. Bariatric surgery: a history of empiricism, a future in science. J Gastrointest Surg. 2009;13(3):465-77.
100. LupoliR, LemboE, SaldalamacchiaG, AvolaCK, AngrisaniL, CapaldoB. Bariatric surgery and long-term nutritional issues. World journal of diabetes. 2017;8(11).
101. XuG, SongM. Recent advances in the mechanisms underlying the beneficial effects of bariatric and metabolic surgery. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2021;17(1).

102. Gloy VL, Briel M, Bhatt DL, Kashyap SR, Schauer PR, Mingrone G, et al. Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials. BMJ (Clinical research ed). 2013;347:f5934.
103. Golzarand M, Toolabi K, Farid R. The bariatric surgery and weight losing: a meta-analysis in the long- and very long-term effects of laparoscopic adjustable gastric banding, laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy on weight loss in adults. Surgical endoscopy. 2017;31(11):4331-45.
104. O'BrienPE, A H, L B, S S, P B, A S, et al. Long-Term Outcomes After Bariatric Surgery: A Systematic Review and Meta-analysis of Weight Loss at 10 or More Years for All Bariatric Procedures and a Single-Centre Review of 20-Year Outcomes After Adjustable Gastric Banding. Obesity surgery. 2019;29(1).
105. Sjostrom L, Peltonen M, Jacobson P, Sjostrom CD, Karason K, Wedel H, et al. Bariatric surgery and long-term cardiovascular events. Jama. 2012;307(1):56-65.
106. C. David Sjostrom LL, f Hans Wedel,$ and Lars Sjostrom. <Reduction in Incidence of Diabetes, Hypertension and Lipid Disturbances after Intentional Weight Loss Induced by Bariatric Surgery: the SOS Intervention Study
j.1550-8528.1999.tb00436.x.pdf>. Obesity research & clinical practice. 1999;Vol. 7 No. 5 Sept. 1999.
107. Cummings DE, Arterburn DE, Westbrook EO, Kuzma JN, Stewart SD, Chan CP, et al. Gastric bypass surgery vs intensive lifestyle and medical intervention for type 2 diabetes: the CROSSROADS randomised controlled trial. Diabetologia. 2016;59(5):945-53LID.
108. Mingrone G, Guidone C, Iaconelli A, Nanni G, Castagneto M, Panunzi S, et al. Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 Year follow-up of an open-label, single-centre, randomised controlled trial. The Lancet. 2015;386(9997):964-73.
109. Ikramuddin S BC, Lee WJ, Bantle JP, Thomas AJ, Connett JE, Leslie , DB IWr, Jeffery RW, Chong K, Chuang LM, Sarr MG, Jensen MD, Vella A, , Ahmed L BK, Schone JL, Olofson AE, Bainbridge HA, Laqua PS, Wang Q, Korner, J. Roux-en-Y gastric bypass for diabetes (the Diabetes Surgery Study): 2-year outcomes of a 5-year, randomised, controlled trial. . Lancet Diabetes Endocrinol
2015 Jun;3(6):413-422 2015.
110. Lee W-J, Chong K, Lin Y-H, Wei J-H, Chen S-C. Laparoscopic sleeve gastrectomy versus single anastomosis (mini-) gastric bypass for the treatment of type 2 diabetes mellitus: 5-year results of a randomized trial and study of incretin effect. Obesity surgery. 2014;24(9):1552-62.
111. Author not f, Schmid H, Goelzer N, Claudio F, Dias Lisiane S, Weston Antonio C, et al. Metabolic syndrome resolution by Roux-en-Y gastric bypass in a real world: a case control study. Revista da Associacao Medica Brasileira (1992). 2015;61(2):161-9.
112. Sjöström L, Peltonen M, Jacobson P, Ahlin S, Andersson-Assarsson J, Anveden Å, et al. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. JAMA. 2014;311(22):2297-304.
113. Johnson BL, Blackhurst DW, Latham BB, Cull DL, Bour ES, Oliver TL, et al. Bariatric surgery is associated with a reduction in major macrovascular and microvascular complications in moderately to severely obese patients with type 2 diabetes mellitus. J Am Coll Surg. 2013;216(4):545-56; discussion 56-8.

114. Sjostrom L, Peltonen M, Jacobson P, Ahlin S, Andersson-Assarsson J, Anveden A, et al. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. JAMA. 2014;311(22):2297-304LID.
115. LMS Carlsson1 SR, P Jacobson1, MA Burza1, C Maglio1, K Sjöholm1, P-A Svensson1, B Haraldsson1, M Peltonen2 and L Sjöström1. The incidence of albuminuria after bariatric surgery and usual care in SOS. International journal of obesity. 2015;39:169-75.
116. Sheng B, Truong K, Spitler H, Zhang L, Tong X, Chen L. The Long-Term Effects of Bariatric Surgery on Type 2 Diabetes Remission, Microvascular and Macrovascular Complications, and Mortality: a Systematic Review and Meta-Analysis. Obes Surg. 2017;27(10):2724-32.
117. Amin AM, Wharton H, Clarke M, Syed A, Dodson P, Tahrani AA. The impact of bariatric surgery on retinopathy in patients with type 2 diabetes: a retrospective cohort study. Surg Obes Relat Dis. 2016;12(3):606-12.
118. Mirajkar N BS, Ahmed M, Singhal R, Daskalakis M, Tahrani AA. The impact of bariatric surgery on estimated glomerular filtration rate in patients with type 2 diabetes: a retrospective cohort study. Surg Obes Relat Dis 2016 PubMed PMID: 27516220. 2016.
119. Cummings DE, Overduin J, Foster-Schubert KE, Carlson MJ. Role of the bypassed proximal intestine in the anti-diabetic effects of bariatric surgery. Surg Obes Relat Dis. 2007;3(2):109-15.
120. CM M, RJW M, ME P. Mechanisms of weight loss and improved metabolism following bariatric surgery. Annals of the New York Academy of Sciences. 2018;1411(1).
121. Doyle ME, Egan JM. Mechanisms of action of glucagon-like peptide 1 in the pancreas. Pharmacol Ther. 2007;Mar;113(3):546-93.
122. DJ P, A O, SC H, RP V, D M, P E, et al. Remission of type 2 diabetes after gastric bypass and banding: mechanisms and 2 year outcomes. Annals of surgery. 2010;252(6).
123. Rao RS. Bariatric surgery and the central nervous system. Obes Surg. 2012(2012 Jun;22(6)):967-78.
124. JP D, RL C, ND V, ID F, R L, DB W, et al. Decreased dopamine type 2 receptor availability after bariatric surgery: preliminary findings. Brain research. 2010;1350.
125. An Z, Wang H, Mokadem M. Role of the Autonomic Nervous System in Mechanism of Energy and Glucose Regulation Post Bariatric Surgery. Front Neuroscience. 2021.
126. LiuH, HuC, ZhangX, JiaW. Role of gut microbiota, bile acids and their cross-talk in the effects of bariatric surgery on obesity and type 2 diabetes. Journal of diabetes investigation. 2018;9(1).
127. ScholtzS, MirasAD, ChhinaN, PrechtlCG, SleethML, DaudNM, et al. Obese patients after gastric bypass surgery have lower brain-hedonic responses to food than after gastric banding. Gut. 2014;63(6).
128. KA C, RP V, AP B, RA S, SA A, AG P, et al. The effect of bariatric surgery on intestinal absorption and transit time. Obesity surgery. 2014;24(5).
129. Cardoso L, Rodrigues D, Gomes L, Carrilho F. Short- and long-term mortality after bariatric surgery: A systematic review and meta-analysis. Diabetes Obes Metab. 2017;19(9):1223-32.
130. LimR, BeekleyA, JohnsonDC, DavisKA. Early and late complications of bariatric operation. Trauma surgery & acute care open. 2018;3(1).

131. EmousM, WolffenbuttelBHR, DijkG v, TottéE, BeekAP v. Long-term self-reported symptom prevalence of early and late dumping in a patient population after sleeve gastrectomy, primary, and revisional gastric bypass surgery. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2018;14(8).
132. StrohC, MangerT, BenedixF. Metabolic surgery and nutritional deficiencies. Minerva chirurgica. 2017;72(5).
133. Castaneda D, Popov VB, Wander P, Thompson CC. Risk of Suicide and Self-harm Is Increased After Bariatric Surgery-a Systematic Review and Meta-analysis. Obes Surg. 2019;29(1):322-33.
134. AzamH, ShahrestaniS, PhanK. Alcohol use disorders before and after bariatric surgery: a systematic review and meta-analysis. Annals of translational medicine. 2018;6(8).
135. CG189 N. Obesity: identification, assessment and management | Guidance and guidelines | NICE. 2014.
136. ADA. STANDARDS OF MEDICAL CARE IN DIABETES—2020. The Journal of Clinical and Applied Research and Education. 2019;38(1).
137. DixonJB, ZimmetP, AlbertiKG, RubinoF, Prevention obotIDFToEa. Bariatric surgery: an IDF statement for obese Type 2 diabetes. 2011.
138. Hall TC, Pellen MGC, Sedman PC, Jain PK. Preoperative factors predicting remission of type 2 diabetes mellitus after Roux-en-Y Gastric bypass surgery for obesity. Obesity Surgery. 2010;20(9):1245-50.
139. Dicker D, Golan R, Aron-Wisnewsky J, Zucker JD, Sokolowska N, Comaneshter DS, et al. Prediction of Long-Term Diabetes Remission After RYGB, Sleeve Gastrectomy, and Adjustable Gastric Banding Using DiaRem and Advanced-DiaRem Scores. Obes Surg. 2019;29(3):796-804.
140. Badia AC, Gebelli JP, Ruiz De Gordejuela AG, Lopez JE, Sanmarti XD, Galvan ST, et al. T2DM: Evolution after bariatric surgery. Randomized controlled trial comparing sleeve gastrectomy, laparoscopic greater curvature plication and metabolic gastric bypass. 20th International Federation for the Surgery of Obesity and Metabolic Disorders World Congress, IFSO 2015 Vienna Austria. 2015;25(1 SUPPL. 1):S115.
141. Brethauer SA, Aminian A, Romero-Talamas H, Batayyah E, Mackey J, Kennedy L, et al. Can diabetes be surgically cured? Long-term metabolic effects of bariatric surgery in obese patients with type 2 diabetes mellitus. Annals of surgery. 2013;258(4):628-36; discussion 36.
142. Schauer PR, Mingrone G, Ikramuddin S, Wolfe B. Clinical Outcomes of Metabolic Surgery: Efficacy of Glycemic Control, Weight Loss, and Remission of Diabetes. Diabetes Care. 2016;39(6):902-11.
143. PournarasDJ, AasheimET, SøvikTT, AndrewsR, MahonD, WelbournR, et al. Effect of the definition of type II diabetes remission in the evaluation of bariatric surgery for metabolic disorders. The British journal of surgery. 2012;99(1).
144. Ikramuddin S, Billington CJ, Lee WJ, Bantle JP, Thomas AJ, Connett JE, et al. Roux-en-Y gastric bypass for diabetes (the Diabetes Surgery Study): 2-year outcomes of a 5-year, randomised, controlled trial. Lancet Diabetes Endocrinol. 2015;3(6):413-22.
145. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Aminian A, Brethauer SA, et al. Bariatric Surgery versus Intensive Medical Therapy for Diabetes - 5-Year Outcomes. N Engl J Med. 2017;376(7):641-51.

146. BurnsEM, NaseemH, BottleA, LazzarinoAI, AylinP, DarziA, et al. Introduction of laparoscopic bariatric surgery in England: observational population cohort study. BMJ (Clinical research ed). 2010;341.
147. GebhartA, YoungMT, NguyenNT. Bariatric surgery in the elderly: 2009-2013. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2015;11(2).
148. Miras AD, Kamocka A, Patel D, Dexter S, Finlay I, Hopkins JC, et al. Obesity surgery makes patients healthier and more functional: real world results from the United Kingdom National Bariatric Surgery Registry. Surg Obes Relat Dis. 2018;14(7):1033-40.

Chapter 2: Method

In this thesis I conducted five studies, four based on the IQVIA Medical Research Data (IMRD) database and one systematic review. In this chapter I have discussed aspects common to retrospective cohort studies performed using IQVIA Research (IMRD) database. Methods regarding specific aspects of each cohort study and the systematic review are detailed in the relevant chapter.

In the present UK NHS structure, primary care maintains a complete care record of the patients. The primary care staff enter patient information electronically using different clinical systems. Commonly used systems are TPP System One, EMIS Web, INPS Vision and Microtest Open volution. The information on these systems has been till recently being coded using READ codes.

Electronic health records are precious tool in field of medical research. They are electronically collected and digitally stored. It provides real world data and allows us to assess the impact of intervention on healthcare and patient from a different angle. In UK, General practice research database and IMRD database had been used consistently in research field (1, 2) and appraising NICE guidelines (3).

2.1 Ethical approval

The IMRD data acquisition was approved by the NHS South-East Multicentre Research Ethics Committee in 2003. In addition to this, a protocol specific to this piece of research was submitted to the Scientific Review committee and obtained approval in January 2018 (18THIN097).

2.2 Data source- IQVIA Medical Research Data (IMRD) – UK

I utilised IQVIA Medical Research Data (IMRD) (previously known as The Health Improvement Network, THIN) UK database as data source. IMRD database is a partnership between The In Practice System (INPS) who supply the Vision GP computer system and Cegedim strategic data (CSD) EPIC (4). The health care records are entered by the primary care staff on Vision computer system using Read codes (5). This patient data is collected from the Vision clinical system on regular basis and processed and validated by CSD EPIC Medical Research UK. They supply these data to IMRD database (6).

IMRD data contains de-personalised electronic medical record from 787 general practises It provides longitudinal patient record of 17 million patients (3.1 million patients are actively registered with GP practices which are participating in IMRD) (7, 8). Data from IMRD has been approved for observational research studies (9).

2.2.1 The IMRD structure and presentation

2.2.1.1 Information presentation

Information on patient demographics, health condition(s), treatment(s) etc are presented mainly under five files. These files are cross-referenced via patient identification code and practice identification code making the data pseudo-anonymised (Figure 1).

1. Practice file- Information about practice, location

2. Patient file – Gives information on patient's demographics, registration date.
3. Therapy file – Gives information on all prescriptions along with the date issued, formulation, strength, quantity, and dosing instructions, indication for treatment for all new prescriptions, and events leading to withdrawal of a drug or treatment.
4. Medical file (medical diagnosis)- Gives information on medical diagnoses, date of diagnosis, and referrals to hospitals and specialists.
5. Additional health data - vaccinations and prescription contraceptives; miscellaneous information such as smoking, height, weight, immunizations, pregnancy, birth, death, and laboratory results.

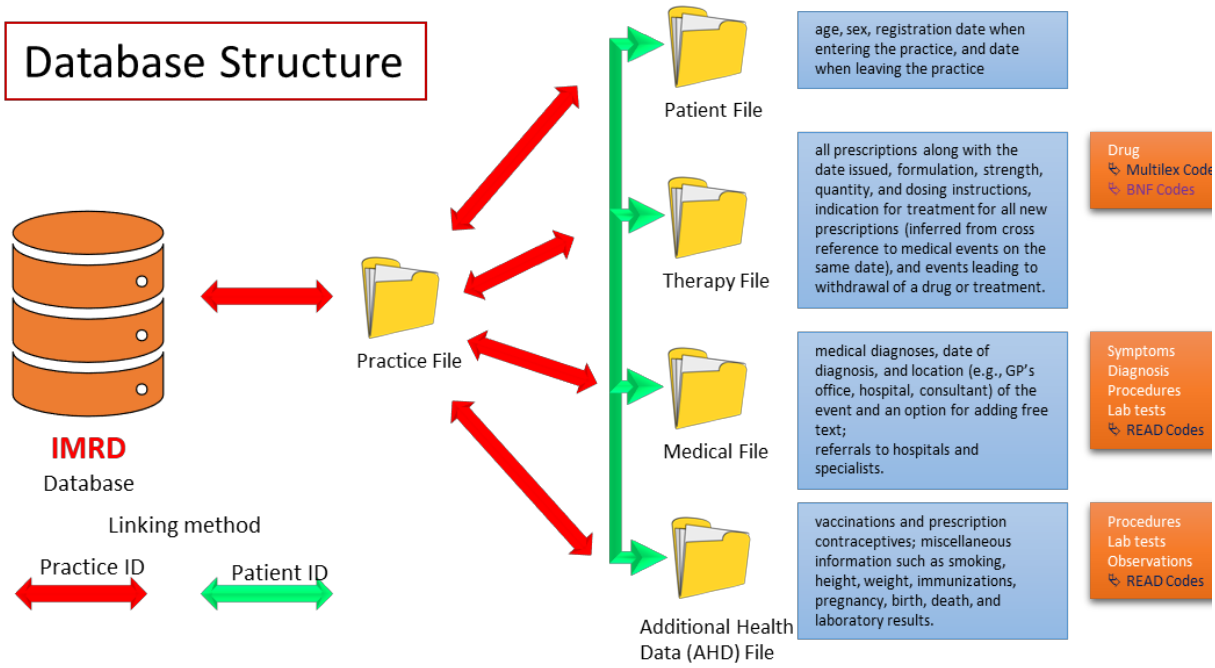


Figure 1: IMRD database layout

2.2.2 Selection of general practice and study participants-

To ensure the quality of data, strict criteria is used for selection of general practices and patients enrolled. The general practice should have acceptable computer usage standard and Acceptable Mortality Recording (AMR) for at least a year before contributing to data source. For acceptable computer usage, general practice should have been using the Vision system for at least a year, have at least a medical record, one additional health data and two prescriptions per patients. AMR is an indicator of practice data quality and is defined when practice declares its mortality rate like expected rate for their population by National statistics (10).

From the eligible GP practices, study participants must have been registered with their practice for at least a year before study entry to ascertain documentation of concomitant diseases and treatments.

2.2.3 READ codes

Read codes are alphanumeric code developed by Dr James Read, a general practitioner in Loughborough to help with the computerized system in GP surgeries. Initially, it had four alphanumeric character (4 byte) consisting upper case letters and numbers 0-9 which later on expanded to five characters (Read code version 2) and incorporated lower case letters (11). It was first published in BMJ in 1986. In 1988, RCGP and BMA decided to adopt the coding system nationally (5). It is being used widely by GPs in the UK for better health care

record, patient care and for research purposes. Read codes were further developed and lead to version 2 and 3

Read codes used are seven-character string variables arranged as hierarchy system. The first letter represents a group of condition. Subsequent letter or number add more specific information. eg C10..00 refers to diabetes mellitus, C10E.00 refers to type 1 diabetes and C10F.00 refers to type 2 diabetes.

Read codes are selected by two individuals independently. Key words or various synonyms for each variable of interest are identified and used to search Read codes in Read code database, Read code repositories and supplementary information of published articles that used similar condition read codes. Identified list of Read codes are discussed with all study team members, general practitioners, and speciality field experts.

For drugs codes, each drug including its synonyms and market name are searched in BNF and similar steps mentioned before are implemented to achieve the final list of Read code

For specific lists please refer to the relevant study chapter.

2.2.4 Important dates

Acceptable Mortality Reporting (AMR) as detailed in section 1.2.3 is has been calculated by CSD Medical Research UK from reviewing trends in death reporting for each individual practices.

Vision date is when the practice started using the Vision practice management software to record consultations.

Index date is defined as the documented date of bariatric surgery in the exposed group

Patients in control group were assigned same date as their expose patient to mitigate immortal bias.

Study end date- I defined our exit date as 31/01/2018.

Exit date- was defined as earliest of the following end points:

- Outcome of interest date under consideration
- Death date
- Date they leave the practice.
- Date the practice ceases contributing to the database.
- Study end date (31/01/2018 for our studies)

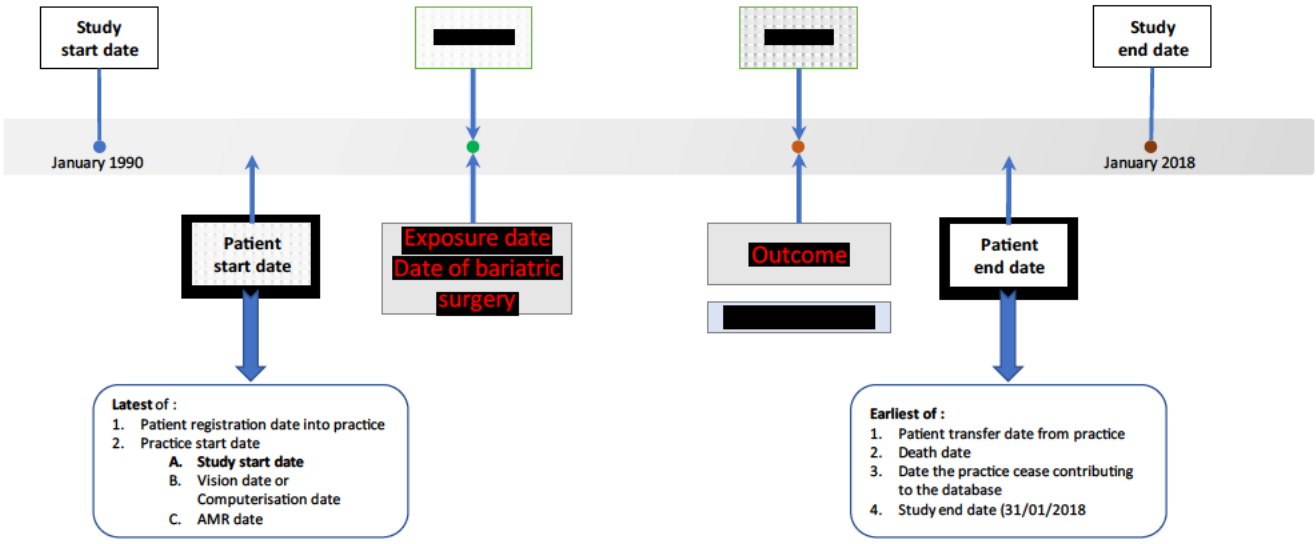


Figure 2: Important dates

2.2.5 Data Extraction for Epidemiological Research (DExtER)

DExtER software designed by PhD student K Gokhale and Prof. Nirantharakumar was used for data extraction (12). DExtER software uses three strep process- extraction of data from high quality patient based data system, transformation and loading the extracted data in target system (12). It has been widely used for epidemiological and observational studies (13, 14)

2.2.6 Validation of IMRD database

IMRD database is an established database for epidemiology- based research work and subjected to validation studies compared with established database including General practice Research database, direct questionnaire from health professional and NHS prescription service (15, 16). Vincent et al validated the Hepatitis C virus specific code and compared it with direct questionnaire from GP and found the code to be specific of predicting HCV infection (15). Another study compared the smoking cessation medication/ prescription data in IMRD database (THIN database) to NHS prescription service during January 2004 to December 2005 and found the data to be highly comparable supporting the use of IMRD for pharmacological study (2).

2.2.7 Strengths and Limitation of IMRD database:

The strength and limitations of each study has been discussed in chapter 3-6. IMRD database represents wide UK population, in term of demographics, prevalence of disease and mortality (9).

The quality of data from IMRD UK is very much dependent on the data uploaded by primary care team. The quality can be affected by what the GP considers to be important for the long-term care of individual patients. However, the outcomes of our study including diabetes, chronic kidney disease, atrial fibrillation, hypertension, heart failure, obesity, stroke are part of Quality Outcome Framework (incentive payment scheme) (17) ensuring consistency in definitions and mitigating against detection bias.

In this section, I have presented few limitations which is common to my chapter 3-6

1) Index date- The index date for patients in our study is the date bariatric surgery was offered. The date of surgical intervention may not be the exact date, it can be the date the information was put on the system.
2) Drug codes- Medications prescribed during inpatient stay are not recorded in GP record as it does not feature on discharge letters. Few medications given by specialist in hospital only may be missing. Medications like insulin type is mentioned, but not the exact dosing. Adherence to medication may not be picked up by this database if not mentioned in GP notes.
3) Right-censoring. I censored the patient as the incidence of the outcome of interest was observed (per criteria mentioned in 2.3.3). I could have missed event which happened before the index date or after the exit date.

2.3 Study design and study population

I conducted retrospective, matched controlled cohort studies using IMRD UK database. I defined my study period as 01-01-1990 to 31-01-2018. Two datasets were extracted for my thesis - project 1 (included patients with obesity, had bariatric surgery) and project 2 (patients with obesity and type 2 diabetes, had bariatric surgery).

2.3.1 Project 1- Patients with obesity and had bariatric surgery

In my first dataset, I defined exposed group as adult population (age 18-75 years), with body mass index (BMI) ≥30 kg/m^2 underwent bariatric surgery during study period 01 January 1990 to 31 January 2018

Every exposed patient was matched for two controls within the same general practice by age (± 2 years), sex, body mass index (BMI, ±2 kg/m^2) and diabetes status.

2.3.2 Project 2- Patients with obesity and type 2 diabetes and subsequently had bariatric surgery

Second data set included patients aged 18-75 years with BMI) ≥30 kg/m^2 and type 2 diabetes and subsequently had bariatric surgery during study period 01 January 1990 to 31 January 2018. Every exposed patient was matched for two controls within the same general practice by age (± 2 years), sex, body mass index (BMI, ±2 kg/m^2) and diabetes duration (± 3 years).

I used matched control as it makes sure that each patient in exposed group is paired on key variables which were age, sex and BMI of my study. I chose not to use propensity score matching for two reasons. Firstly, the index date for control group was selected in the absence of a intervention and secondly due to the computational difficulty of calculating multiple propensity scores for each unexposed participant when they are eligible to be controls for multiple exposed participants with different index dates (18).

2.4 Limitations of study design

My studies are retrospective matched control longitudinal cohort studies. Longitudinal cohort nature of my study allowed me to examine multiple outcomes with long latency period. However, observational nature of my studies have limitations. Firstly, data collected for participants and covariables were routinely collected data which lead to missing data on covariables. These covariables could be important confounding factors in outcome which could not be examined. In dataset, there were missing data on ethnicity and socio-economic status. Socio-economic status has been identified as independent risk factor for diabetes related foot disease in patients with type 2 diabetes (19). Socio-economic status could possibly cause referral bias to weight management service and accessing health care system which is a selection bias (20).I do not have data about dietary habit and physical activity which could have contributed to outcomes. Family history of cardiovascular disease has been identified as risk factor for cardiovascular disease. I do not have data on family history which could be important confounder for my outcomes.

Secondly, I presented the association of bariatric surgery and incidence of vascular complications. However due to lack of randomisation, we cannot account for the reason why

patients in control group did not have bariatric surgery. Study lacks the capacity to explain this association and causality (21).

2.5 Outcomes

2.5.1 Project 1

The outcomes were incidence of composite cardiovascular disease (CVD), atrial fibrillation, hypertension, and all- cause mortality in surgical group compared to routine care. I conducted this analysis in patients with and without diabetes. I also analysed the incidence CVD, atrial fibrillation and all- cause mortality in elderly population defined as aged 65-75 years. Results have been presented in chapter 3 & 4.

2.5.2 Project 2

The outcomes were incidence of diabetes related microvascular complications. I also examined impact of bariatric surgery on glycaemic status and glucose lowering medications. Results have been presented in chapter 5 & 6

2.6 Co-variates

Covariates that may impact the outcomes were selected based on biological plausibility and literature review. For our studies in project 1, common covariates of interest were age, gender, body mass index (BMI), ethnicity and social deprivation status. For studies in project

2, beside co-variables mentioned for project 1, we also adjusted for diabetes duration, baseline HbA1c, and baseline insulin user.

Age at baseline was categorised as ≤40 years, 41-60 years and >60 years, but included as continuous variable in regression analysis. BMI below 14 kg/m^2 and above 100 kg/m^2 was considered implausible. BMI was categorised as ≤35 kg/m^2, 35-39.9 kg/m^2 and ≥40 kg/m^2.

The Hba1c was standardised and expressed as percentage IFCC. Diabetes duration at baseline was calculated from the time of diagnosis of diabetes and index date and expressed in years.

In Cox regression analysis. I adjusted the result for above covariates and smoking status, alcohol consumption, socio-economic deprivation status and ethnicity. Smoking and alcohol consumption was categorised as non, active and ex group (eg non-smoker, smoker and ex-smoker).

Social deprivation status was expressed as Townsend quartile which is a measure of material deprivation within a population. It incorporates four variables- unemployment, non- car ownership, non- home ownership and household overcrowding.

Ethnicity was categorised as Caucasian, Black Afro-Caribbean, South Asian, Mixed race and other.

A missing category was used for missing data for BMI, Townsend quintile, smoking status, alcohol consumption and ethnicity.

I adjusted for morbidity index called Charlsons Comorbidity Index in adjusted model for mortality.

2.7 Analysis

I outline the general principles, but specific methods will be detailed in relevant chapters. STATA, version 15 was used to analyse the data. This is a statistical software for data science by StataCorp (22)

2.7.1 Baseline characteristics

Descriptive analysis of the baseline characteristics for patients in surgical and control group was performed and expressed in mean, standard deviation (SD), medians with interquartile range (IQR), and percentage.

Age was presented as mean (SD) and percentage in different category. Gender was presented as percentage of male and female in surgical and control group.

Number of patients were presented as percentage in different BMI (in kg/m^2), smoking and alcohol category and were included as categorical variable in analysis.

Townsend quintile and ethnicity were counted as categorised as categorical variable. 1^{st} quartile represents least deprived (<20%) and 5^{th} quartile represents most deprived (>80%). Missing category was used for missing data for BMI, Townsend quintile and ethnicity.

The STROBE (23) statements, stated that the reporting of p-values in baseline tables is not recommended, particularly for large database studies. P- values in such circumstances do not provide any clinically meaningful information. Hence, baseline patients' characteristics has been presented in line with the guidance and no p-value calculated to compare the baseline characteristics.

2.7.2 Survival analysis

Survival analysis is a method for analysis of longitudinal data who have time as an outcome variable (24). Time stands for the time until the event of interest happens. Survival analysis gives the probability of the even to happen in a group.

I used Cox Proportional hazard regression and Nelson- Aalen estimator graph.

2.7.2.1 Cox Proportional hazard regression

Cox proportional hazard regression is also called cox regression analysis. It is a semiparametric regression model. It allows us to examine the impact of different covariates on the rate of particular outcome of interest happening at a particular point in time (24).

The Cox proportional hazards model makes two assumptions: (1) survival curves for different group (intervention and control group) should have hazard functions that are proportional over the time (2) Each covariables have multiplicative effect in the hazard function that is linear and constant over time (25). The proportional hazards assumption was checked using the Schoenfeld residuals test.

2.7.2.2 Nelson–Aalen estimator graph

Nelson Aalen estimator graph gives a direct nonparametric estimate for the cumulative hazard function based on irregular time intervals (24).

The difference between the exposed and control group was expressed as a Hazard ratio with 95% confidence interval. P-value of less than 0.05 (5%) was considered statistically significant.

I analysed the impact of bariatric surgery on cardiovascular disease in surgical vs non-surgical group. I did subset analysis based on type of bariatric surgery. I also run the analysis in patients with and without diabetes. For subset analysis I compared the cohort who underwent a particular type of surgery and their matched control.

Similarly, I examined the impact of bariatric surgery on incidence microvascular complications in surgical vs non-surgical and further subset analysis based on type of bariatric surgery.

2.8 References:

1. James D. Lewis MD M, Rita Schinnar MPA. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. 2006.
2. Langley TE, Szatkowski L, Gibson J, Huang Y, McNeill A, Coleman T, et al. Validation of The Health Improvement Network (THIN) primary care database for monitoring prescriptions for smoking cessation medications. Pharmacoepidemiology and drug safety. 2010;19(6):586-90.
3. TP L, S R, C S. The use of UK primary care databases in health technology assessments carried out by the National Institute for health and care excellence (NICE). BMC health services research. 2020;20(1).
4. Sciences. tNCIsoCCaP. The Health Improvement Network (THIN) the National Cancer Institute'sDivision of Cancer Control and Population Sciences.2018 [Available from: https://epi.grants.cancer.gov/pharm/pharmacoepi_db/thin.html.
5. Tim Benson GG. Coding and Classification Schemes | SpringerLink. 2016.
6. Health TURDPCP. THIN Database 2018 [Available from: http://www.ucl.ac.uk/pcph/research/thin-database/database.
7. IQVIA Medical Research Data: @HRA_Latest; 2020 [Available from: https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/the-health-improvement-network-thin-database/.
8. THIN-HES Privacy Notice 2019 [Available from: https://www.iqvia.com/locations/united-kingdom/information-for-members-of-the-public/thin-hes-data.
9. Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. Informatics in primary care. 2011;19(4):251-5.
10. Maguire A, Blak BT, Thompson M. The importance of defining periods of complete mortality reporting for research using automated data from primary care. Pharmacoepidemiology and drug safety. 2009;18(1):76-83.
11. Benson T. The history of the Read Codes: the inaugural James Read Memorial Lecture 2011. Informatics in primary care. 19. England2011. p. 173-82.
12. KM G, JS C, K T, G G, P T, K N. Data extraction for epidemiological research (DExtER): a novel tool for automated clinical epidemiology studies. European journal of epidemiology. 2021;36(2).
13. Adderley NJ, Nirantharakumar K, Marshall T. Risk of stroke and transient ischaemic attack in patients with a diagnosis of resolved atrial fibrillation: retrospective cohort studies. BMJ (Clinical research ed). 2018;361:k1717.
14. Subramanian A, Adderley NJ, Tracy A, Taverner T, Hanif W, Toulis KA, et al. Risk of Incident Obstructive Sleep Apnea Among Patients With Type 2 Diabetes. Diabetes Care. 2019.
15. Vincent LR, K H, KA F, AR L, R S, JD L. Validity of The Health Improvement Network (THIN) for epidemiologic studies of hepatitis C virus infection. Pharmacoepidemiology and drug safety. 2009;18(9).

16. AV M, LA GR, S H-D. Positive predictive value of computerized medical records for uncomplicated and complicated upper gastrointestinal ulcer. Pharmacoepidemiology and drug safety. 2009;18(10).
17. Digital N. QOF Main findings - NHS Digital: @NHSDigital; 2021 [Available from: https://digital.nhs.uk/data-and-information/publications/statistical/quality-and-outcomes-framework-achievement-prevalence-and-exceptions-data/2020-21/main-findings.
18. N A, P S, AA T, K N. Author Response To: Comment On: Impact of Bariatric Surgery on Cardiovascular Outcomes and Mortality: A Population-Based Cohort Study. The British journal of surgery. 2020;107(7).
19. RileyJ, AntzaC, KempegowdaP, SubramanianA, ChandanJS, GokhaleK, et al. Social Deprivation and Incident Diabetes-Related Foot Disease in Patients With Type 2 Diabetes: A Population-Based Cohort Study. Diabetes care. 2021;44(3).
20. DJ M, O O, ML S. Socioeconomic Status and Access to Healthcare: Interrelated Drivers for Healthy Aging. Frontiers in public health. 2020;8.
21. EuserAM, ZoccaliC, JagerKJ, DekkerFW. Cohort studies: prospective versus retrospective. Nephron Clinical practice. 2009;113(3).
22. software S. Stata: Software for Statistics and Data Science 2019 [Available from: https://www.stata.com/.
23. Jan P Vandenbroucke, Erik von Elm, Douglas G Altman, Peter C Gøtzsche, Cynthia D Mulrow, Stuart J Pocock, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration. 2020.
24. Emmert-Streib F, Dehmer M. Introduction to Survival Analysis in Practice. Machine Learning and Knowledge Extraction. 2019;1(3):1013-38.
25. XueX, XieX, M G, TE R, S W-S, GY H, et al. Testing the proportional hazards assumption in case-cohort analysis. BMC medical research methodology. 2013;13.

Chapter 3: Impact of bariatric surgery on cardiovascular outcomes and mortality

3.1 Contents of chapter 3

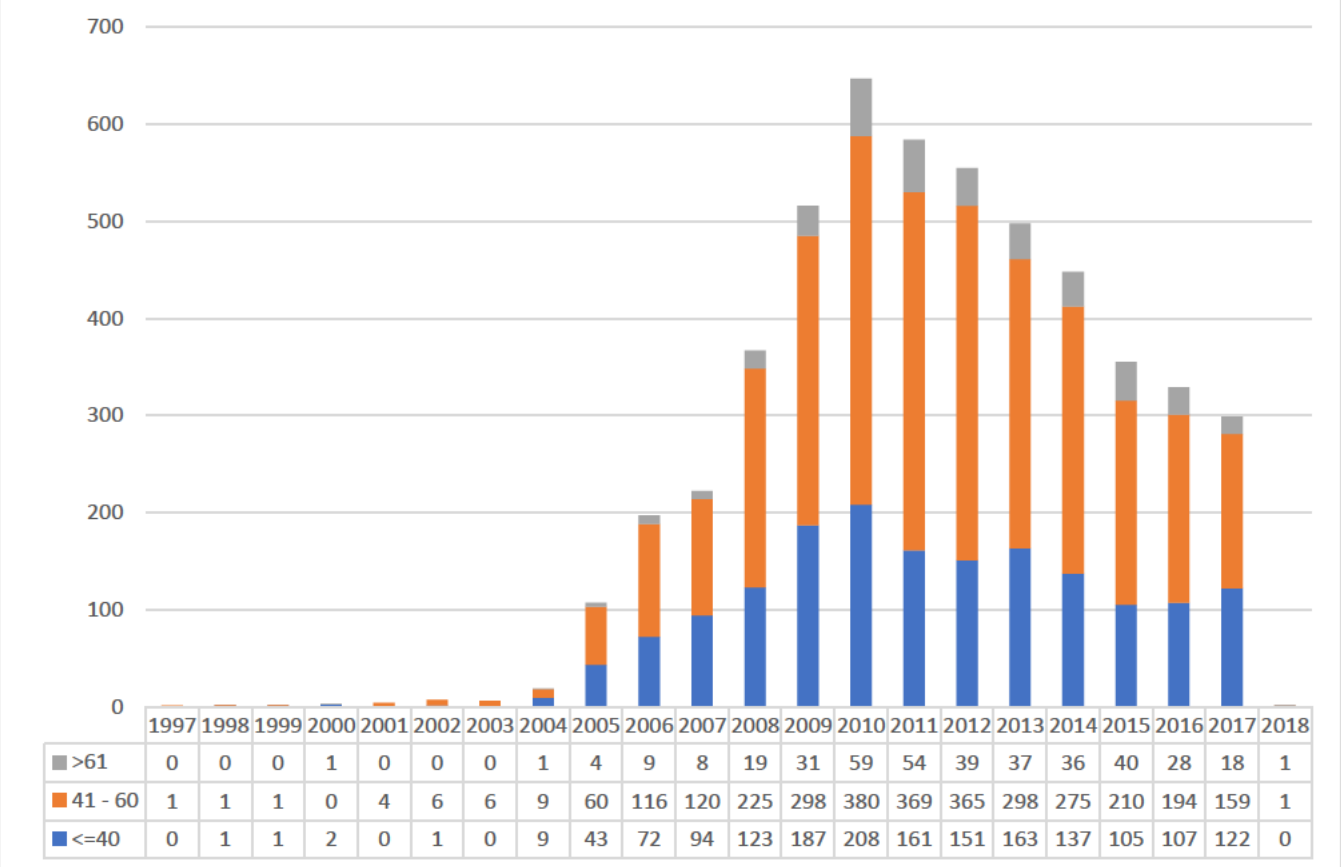
Cardiovascular disease (CVD) had been censured as a major cause of mortality worldwide (1). According to WHO estimate, 31% (17.9 million) of death in 2016 was from CVD and majority (85%) were caused by heart attack and stroke (1). In UK, it the second major cause of mortality (2). Obesity is a major risk factor for CVD and mortality and contributes to the pathogenesis of several CVD risk factors such as hypertension, hyperlipidaemia, and type 2 diabetes (3-5).

Weight loss, via lifestyle intervention or bariatric surgery, has been associated with significant improvements/remission of CVD risk factors (such hypertension, hyperlipidaemia, and type 2 diabetes) and mortality (6-10). Systematic review including 54 studies showed weight loss by dietary intervention with or without exercise was associated in reduction in mortality (11).

Bariatric surgery offers significant sustained weight loss in patients with obesity. Many studies including randomized control trial showed the positive impact of bariatric surgery on reduction in cardiovascular risk factor like diabetes, hypertension. and hyperlipidaemia, (7-10, 12) but the impact on cardiovascular event itself using real world data is limited. Outcome from real world data is available from US and Sweden. However, UK has unique National Health Service. In UK, patients referred to weight management service get two years close follow up in secondary/ tertiary care and then discharged to primary care for long term follow up.

In this chapter, I examined the impact of bariatric surgery on incidence of cardiovascular outcomes and mortality in patients with obesity, with and without type 2 diabetes. Subset analysis based on type of surgery was undertaken This chapter is presented in format of a published article.

With increasing prevalence of elderly population and increasing prevalence of obesity like all age groups, the number of patient eligible for bariatric surgery will rise. In my dataset, the number of patients who had bariatric surgery gradually increased over time (Fig 1). Analysis based on age of patient showed number of elderly patients (age ≥60 years) undergoing bariatric surgery is also increasing as expected. I have presented association of bariatric surgery and incidence CVD and mortality in chapter 4.



	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
>61	0	0	0	1	0	0	0	1	4	9	8	19	31	59	54	39	37	36	40	28	18	1
41 - 60	1	1	1	0	4	6	6	9	60	116	120	225	298	380	369	365	298	275	210	194	159	1
<=40	0	1	1	2	0	1	0	9	43	72	94	123	187	208	161	151	163	137	105	107	122	0

Figure 1 - Distribution of bariatric surgery in different age groups over time

3.2 References:

1. WHO. Cardiovascular diseases (CVDs) 2017 May [Available from: http://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).
2. Bhatnagar P, Wickramasinghe K, Williams J, Rayner M, Townsend N. The epidemiology of cardiovascular disease in the UK 2014. 2015.
3. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. Journal of the American College of Cardiology. 2009;53(21):1925-32.
4. Caleyachetty R, Thomas GN, Toulis KA, Mohammed N, Gokhale KM, Balachandran K, et al. Metabolically Healthy Obese and Incident Cardiovascular Disease Events Among 3.5 Million Men and Women. Journal of the American College of Cardiology. 2017;70(12):1429-37.
5. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC public health. 2009;9:88.
6. Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. Lancet Diabetes Endocrinol. 2019;7(5):344-55.
7. Sjostrom L, Peltonen M, Jacobson P, Sjostrom CD, Karason K, Wedel H, et al. Bariatric surgery and long-term cardiovascular events. Jama. 2012;307(1):56-65.
8. Major P, Kowalczuk A, Wysocki M, Osadnik S, Pedziwiatr M, Gluszewska A, et al. Effects of bariatric surgery on cardiovascular risk factors among morbidly obese patients. Pol Przegl Chir. 2017;89(1):41-9.
9. Ricci C, Gaeta M, Rausa E, Asti E, Bandera F, Bonavina L. Long-term effects of bariatric surgery on type II diabetes, hypertension and hyperlipidemia: a meta-analysis and meta-regression study with 5-year follow-up. Obes Surg. 2015;25(3):397-405.
10. Benotti PN, Wood GC, Carey DJ, Mehra VC, Mirshahi T, Lent MR, et al. Gastric Bypass Surgery Produces a Durable Reduction in Cardiovascular Disease Risk Factors and Reduces the Long-Term Risks of Congestive Heart Failure. Journal of the American Heart Association. 2017;6(5).
11. Ma C, Avenell A, Bolland M, Hudson J, Stewart F, Robertson C, et al. Effects of weight loss interventions for adults who are obese on mortality, cardiovascular disease, and cancer: systematic review and meta-analysis. BMJ (Clinical research ed). 2017;359:j4849.
12. Schiavon CA, Bersch-Ferreira AC, Santucci EV, Oliveira JD, Torreglosa CR, Bueno PT, et al. Effects of Bariatric Surgery in Obese Patients With Hypertension: The GATEWAY Randomized Trial (Gastric Bypass to Treat Obese Patients With Steady Hypertension). Circulation. 2018;137(11):1132-42.

3.3 Manuscript 1: Impact of bariatric surgery on cardiovascular outcomes and mortality

Singh P., Subramanian A., Adderley N., Gokhale K., Singhal R., Bellary S., Nirantharakumar K., Tahrani A.A. Impact of bariatric surgery on cardiovascular outcomes and mortality: a population-based cohort study. British Journal of Surgery, Volume 107, Issue 4, March 2020, Pages 432–442. (First published: 21 January 2020) https://doi.org/10.1002/bjs.11433

Original article

Impact of bariatric surgery on cardiovascular outcomes and mortality: a population-based cohort study

P. Singh[1,4], A. Subramanian[2], N. Adderley[2], K. Gokhale[2], R. Singhal[5], S. Bellary[3,4], K. Nirantharakumar[2,4,6,7] and A. A. Tahrani[1,4,5]

[1]Institute of Metabolism and Systems Research and [2]Institute of Applied Health Research, University of Birmingham, [3]School of Life and Health Sciences, Aston University, [4]Department of Endocrinology and Diabetes and [5]Department of Surgery, University Hospitals Birmingham NHS Foundation Trust, and [6]Centre for Endocrinology, Diabetes and Metabolism, Birmingham Health Partners, Birmingham, and [7]Health Data Research UK, London, UK

Correspondence to: Dr A. A. Tahrani, Department of Endocrinology and Diabetes, University Hospital Birmingham, Edgbaston, Birmingham B15 2WB, UK (e-mail: [redacted] @PushpaS0489754, @anuradhaa_s, @KrishnaGokhale, @singhalrishi1, @sribellary, @Nirantharakumar, @AbdTahrani)

Background: Cohort studies have shown that bariatric surgery may reduce the incidence of and mortality from cardiovascular disease (CVD), but studies using real-world data are limited. This study examined the impact of bariatric surgery on incident CVD, hypertension and atrial fibrillation, and all-cause mortality.

Methods: A retrospective, matched, controlled cohort study of The Health Improvement Network primary care database (from 1 January 1990 to 31 January 2018) was performed (approximately 6 per cent of the UK population). Adults with a BMI of 30 kg/m^2 or above who did not have gastric cancer were included as the exposed group. Each exposed patient, who had undergone bariatric surgery, was matched for age, sex, BMI and presence of type 2 diabetes mellitus (T2DM) with two controls who had not had bariatric surgery.

Results: A total of 5170 exposed and 9995 control participants were included; their mean(s.d.) age was 45·3(10·5) years and 21·5 per cent (3265 of 15 165 participants) had T2DM. Median follow-up was 3·9 (i.q.r. 1·8– 6·4) years. Mean(s.d.) percentage weight loss was 20·0(13·2) and 0·8(9·5) per cent in exposed and control groups respectively. Overall, bariatric surgery was not associated with a significantly lower CVD risk (adjusted hazard ratio (HR) 0·80; 95 per cent c.i. 0·62 to 1·02; $P = 0·074$). Only in the gastric bypass group was a significant impact on CVD observed (HR 0·53, 0·34 to 0·81; $P = 0·003$). Bariatric surgery was associated with significant reduction in all-cause mortality (adjusted HR 0·70, 0·55 to 0·89; $P = 0·004$), hypertension (adjusted HR 0·41, 0·34 to 0·50; $P < 0·001$) and heart failure (adjusted HR 0·57, 0·34 to 0·96; $P = 0·033$). Outcomes were similar in patients with and those without T2DM (exposed *versus* controls), except for incident atrial fibrillation, which was reduced in the T2DM group.

Conclusion: Bariatric surgery is associated with a reduced risk of hypertension, heart failure and mortality, compared with routine care. Gastric bypass was associated with reduced risk of CVD compared to routine care.

Presented in part to the European Congress on Obesity, Glasgow, UK, April 2019

Paper accepted 28 October 2019

Published online in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.11433

Introduction

Cardiovascular disease (CVD) is a leading cause of mortality worldwide[1–3]. Obesity is a major risk factor for CVD and mortality, and contributes to the pathogenesis of several CVD risk factors such as hypertension, hyperlipidaemia and type 2 diabetes mellitus (T2DM)[4–6]. Weight loss, via lifestyle intervention or bariatric surgery, has been associated with significant improvements/remission in CVD risk factors (hypertension, hyperlipidaemia and T2DM) as well as a reduction in CVD and mortality, although the impact on CVD and mortality is mainly from observational studies[7–10].

Several studies[11–14] (including RCTs) have established that bariatric surgery is associated with a reduction in CVD risk factors, but the impact on CVD is limited to a few observational studies[10,15–17]. In the UK, patients with a BMI of 35 kg/m^2 or above and obesity-related

© 2020 BJS Society Ltd
Published by John Wiley & Sons Ltd

complications, a BMI of 40 kg/m^2 or above without obesity-related complications, or a BMI of 30–35 kg/m^2 with recent-onset T2DM can be offered bariatric surgery according to National Institute for Health and Care Excellence guideline CG189[18]. Patients are usually followed up for 2 years after surgery by the bariatric multidisciplinary team if they were treated in the National Health Service, and then discharged to primary care[18]. A previous study[19] from the UK National Bariatric Surgery Registry (NBSR) showed improvement or remission in obesity-related complications following bariatric surgery, but the NBSR included only patients who had surgery and hence there was no control group. In addition, the NBSR study[19] did not report on the impact on CVD or mortality. Hence, there is interest in real-world outcomes of bariatric surgery in order to ascertain its place in the management paradigm of people with obesity.

The present hypothesis was that bariatric surgery is associated with a reduction in CVD, all-cause mortality and hypertension. A population-based study was devised with the primary aim of assessing the impact of bariatric surgery on incident combined CVD (ischaemic heart disease (IHD), heart failure (HF) and stroke and transient ischaemic attack (TIA)) and all-cause mortality. Secondary aims included assessing the impact of bariatric surgery on incident hypertension and atrial fibrillation (AF).

Methods

A retrospective, matched, controlled cohort study using a data set from The Health Improvement Network (THIN) database from 1 January 1990 to 31 January 2018 was performed. THIN contains anonymized electronic records from 787 general practices. It includes longitudinal records of 15 million patients (3·1 million active patients), covering 6·2 per cent of the UK population[20–22], and is representative of the UK general population in relation to age, sex, health conditions, major chronic illnesses and mortality rates[23]. THIN contains information on patient demographics, therapies, symptoms and medical diagnoses. It also includes additional health data such as smoking and alcohol status, height, weight, death, and laboratory and investigation results. Symptoms and diagnoses are recorded using Read codes[24]. The THIN database has been used previously by the authors' group and others to examine chronic non-communicable disease (such as diabetes, CVD, obesity and its related complications) and mortality[25–28].

Ethical approval for the study was granted by the Scientific Review Committee in January 2019 (SRC reference number 18THIN097).

Study population

Primary care practices were eligible for inclusion in the study if they had been using the Vision electronic records system (In Practice Systems Ltd, London, UK) for at least 1 year, and had acceptable mortality recording (an indicator of the practice data quality) for at least 1 year preceding study entry[29]. In addition, study participants must have been registered with an eligible practice for at least 1 year before study entry to ensure adequate documentation of concomitant diseases and treatments.

The exposed population was defined as patients who had undergone bariatric surgery (gastric banding, sleeve gastrectomy, Roux-en-Y gastric bypass (RYGB) or duodenal switch) between 1 January 1990 and 31 January 2018. Every patient in the exposed cohort was matched with two controls (who had not had bariatric surgery) by age (± 2 years), sex, BMI (± 2 kg/m^2) and presence of T2DM. Patients were excluded from the study if they met any of the following criteria: BMI below 30 kg/m^2, age above 75 years, a record of gastric cancer before the index date (study entry date), or had undergone gastric balloon or endobarrier, or revisional bariatric surgery.

Follow-up

For patients in the exposed group, the index date was defined as the first Read code documentation date of bariatric surgery; the same index date was assigned to the corresponding matched controls to mitigate immortal time bias[30]. Study participants were followed up from the index date to the first record of any of the following: occurrence of the outcome of interest; death; study participant left the practice; the practice ceased contributing to THIN database.

Outcome measures

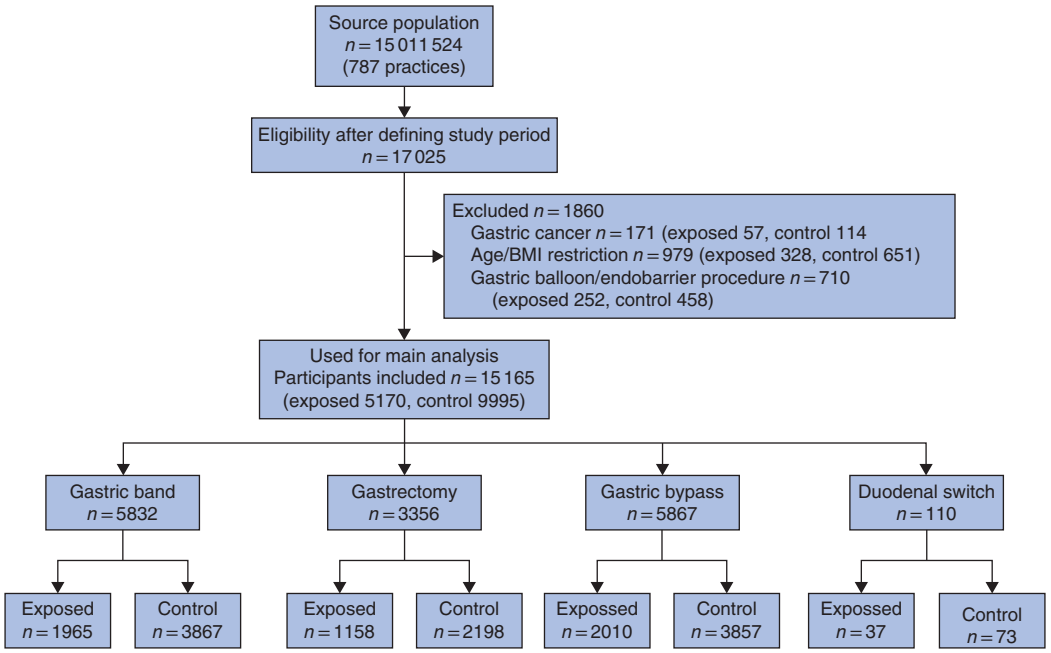
The incident composite CVD (IHD, HF, stroke and TIA), all-cause mortality, incident hypertension and AF were recorded. The individual components of the composite CVD outcome were examined separately.

Statistical analysis

Baseline characteristics are summarized as mean(s.d.) or median (i.q.r.) values for continuous variables, depending on data distribution, and as proportions for categorical variables. Cox proportional hazards regression was used to calculate crude and adjusted hazard ratios (HRs) and 95 per cent confidence intervals for the occurrence (incident) of each outcome of interest in the exposed and control groups.

© 2020 BJS Society Ltd
Published by John Wiley & Sons Ltd

Fig. 1 Flow diagram of participant selection



Each exposed patient who was excluded was removed from the study along with their matching controls.

Patients with the outcome of interest at baseline were excluded from the analysis; for example, when the outcome of interest was incident CVD, patients with baseline CVD were excluded. The proportional hazards assumption was checked using the Schoenfeld residuals test.

Co-variables in the adjusted multivariable model were selected based on biological plausibility; these included age, sex, BMI, smoking status, alcohol consumption, ethnicity and social deprivation status[31,32]. BMI was categorized as less than 35, 35–40 and more than 40 kg/m^2. Smoking and alcohol intake were categorized as user, non-user and ex-user. Social deprivation status was represented by the Townsend deprivation quintile[33], which is based on material deprivation within a population. Ethnicity was categorized as Caucasian, Afro-Caribbean, South Asian or mixed. Missing categories were used where values for BMI, smoking status, Townsend quintile or ethnicity were not recorded.

For composite CVD and AF outcomes, HRs were adjusted for all of the above-mentioned co-variables plus baseline hypertension and diabetes (model 1). For incident hypertension, the same co-variables were included, except for baseline hypertension. For mortality, an additional model was fitted, adjusting for the same variables included in model 1 plus the Charlson co-morbidity index[34] (model 2).

Preplanned subgroup analyses based on the type of bariatric surgery and baseline T2DM status were performed. Outcome was analysed in participants undergoing each type of surgery and their corresponding controls. Multivariable analysis was not performed in the duodenal switch subgroup, owing to small numbers. Based on T2DM status, outcomes in the participants with and without T2DM were analysed. In the T2DM subgroup analysis, duration of diabetes was included in the regression model (model 3) along with all co-variables included in model 1 (and model 2 in the case of mortality). A forest plot was used to represent graphically the impact of bariatric surgery based onT2DM status.

Percentage weight loss (%WL) was calculated as change in weight (postsurgery weight, defined as weight after the index date within 15 months minus baseline weight)/baseline weight × 100. For the control group who had no surgery, weight change was calculated using a similar formula. Independent-samples *t* tests were used to compare %WL in exposed and control groups.

Nelson–Aalen plots (non-parametric estimator) were used to display the cumulative hazard function for each outcome over a 10-year period. Two-tailed $P < 0{\cdot}050$ was considered statistically significant. All analyses were conducted using Stata® version 15 (StataCorp, College Station, Texas, USA).

© 2020 BJS Society Ltd
Published by John Wiley & Sons Ltd

Results

A total of 5170 participants who had undergone bariatric surgery over the study period were identified (exposed group) and 9995 matched controls (*Fig. 1*).

Baseline characteristics

Table 1 summarizes the baseline demographics of exposed and matched control participants. The mean(s.d.) age of the cohort was 45·3(10·5) years; 21·5 per cent had T2DM. The study population was mostly white European women with class III obesity. There was a high prevalence of mental health disorders, ranging from 24·1 to 46·1 per cent in the study population, which might reflect the underlying psychological impact and drivers of obesity. The rate of obstructive sleep apnoea was higher in the exposed group than in the control cohort (11·1 *versus* 3·4 per cent respectively), which probably reflects the active screening for this condition in a population undergoing bariatric surgery.

Weight changes

Some 4346 (84·1 per cent) of the 5170 exposed participants and 6957 (69·6 per cent) of the 9995 controls had weight measurement at baseline and at least once after bariatric surgery. Median follow-up for weight measurement was 1 (i.q.r. 0·6–12) years. The mean(s.d.) %WL was 20·0(13·2) per cent in the exposed group *versus* 0·8(9·5) per cent in controls. All surgical procedures resulted in greater mean(s.d.) %WL compared with that in matched controls (gastric band (1610 and 2789 participants respectively): 12·8(11·8) *versus* 0·3(9·8) per cent; sleeve gastrectomy (944 and 1338 participants): 22(12·1) *versus* 1·1(9·4) per cent; RYGB (1764 and 2781 participants): 26·1(11·8 *versus* 1·2(9·2) per cent; duodenal switch (28 and 49 participants): 23·4(12·3) *versus* −0·1(7·0) per cent).

Combined cardiovascular disease

After excluding 759 participants who had CVD at baseline, the study included 4922 exposed and 9484 control participants. Bariatric surgery was not significantly associated with a lower risk of composite CVD in the adjusted model (adjusted HR 0·80, 95 per cent c.i. 0·62 to 1·02; $P = 0·074$). Only RYGB had a statistically significant association with composite CVD (adjusted HR 0·53, 0·34 to 0·81; $P = 0·003$) (*Table 2*).

Ischaemic heart disease

After excluding 485 participants with a diagnosis of IHD at baseline, there were 5013 exposed and 9667 control

Table 1 Baseline characteristics of participants in exposed and control groups

	Exposed ($n = 5170$)	Control ($n = 9995$)
Age (years)		
< 40	1687 (32·6)	3192 (31·9)
41–60	3098 (59·9)	6040 (60·4)
> 60	385 (7·4)	763 (7·6)
Mean(s.d.)	45·2(10·6)	45·3(10·5)
Sex		
M	1012 (19·6)	1890 (18·9)
F	4158 (80·4)	8105 (81·1)
BMI (kg/m^2)		
< 35*	493 (9·5)	1077 (10·8)
35–39·9	950 (18·4)	1950 (19·5)
≥ 40	3634 (70·3)	6780 (67·8)
Missing	93 (1·8)	188 (1·9)
Smoking status		
Non-smoker	2866 (55·4)	5719 (57·2)
Smoker	700 (13·5)	1873 (18·7)
Ex-smoker	1579 (30·5)	2319 (23·2)
Missing	25 (0·5)	84 (0·8)
Alcohol status		
Non-drinker	1196 (23·1)	2316 (23·2)
Current drinker	3266 (63·2)	6427 (64·3)
Ex-drinker	205 (4·0)	313 (3·1)
Missing	503 (9·7)	939 (9·4)
Ethnicity		
Caucasian	2154 (41·7)	3759 (37·6)
Black Afro-Caribbean	92 (1·8)	177 (1·8)
South Asian	77 (1·5)	124 (1·2)
Mixed race	33 (0·6)	36 (0·4)
Other	32 (0·6)	33 (0·3)
Missing	2782 (53·8)	5866 (58·7)
Townsend quintile		
1 (least deprived)	955 (18·5)	1454 (14·5)
2	860 (16·6)	1531 (15·3)
3	952 (18·4)	1845 (18·5)
4	961 (18·6)	2057 (20·6)
5 (most deprived)	672 (13·0)	1662 (16·6)
Missing	770 (14·9)	1446 (14·5)
Baseline co-morbidity		
Mental health condition		
Anxiety	1469 (28·4)	2404 (24·1)
Depression	2381 (46·1)	3440 (34·4)
Cardiovascular disease		
Atrial fibrillation	83 (1·6)	137 (1·4)
Heart failure	43 (0·8)	76 (0·8)
Ischaemic heart disease	157 (3·0)	328 (3·3)
Hypertension	1603 (31·0)	2944 (29·5)
Stroke/TIA	76 (1·5)	159 (1·6)
Diabetes mellitus		
T1DM	17 (0·3)	47 (0·5)
T2DM	1176 (22·7)	2089 (20·9)
Obstructive sleep apnoea	572 (11·1)	335 (3·4)

Values in parentheses are percentages unless indicated otherwise. *BMI range 30–34·9 kg/m^2 in exposed group and 28–34·9 kg/m^2 in control group. TIA, transient ischaemic attack; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

© 2020 BJS Society Ltd
Published by John Wiley & Sons Ltd

Table 2 Impact of bariatric surgery on study outcomes across all surgical procedures and for individual procedures

	Hypertension		Atrial fibrillation		Combined cardiovascular event	
	Exposed	Control	Exposed	Control	Exposed	Control
Overall: all surgical procedures	3567	7051	5087	9858	4922	9484
Outcome events	118 (3·3)	567 (8·0)	59 (1·2)	130 (1·3)	87 (1·8)	230 (2·4)
Person-years	14 297·2	28 573·7	21 011·7	43 053·7	20 242·2	41 206·1
Crude incidence rate‡	8·25	19·84	2·81	3·02	4·30	5·58
Follow-up (years)*	3·5 (1·6–6·0)	3·6 (1·6–6·1)	3·6 (1·7–6·1)	4·0 (1·8–6·5)	3·6 (1·7–6·1)	4·0 (1·8–6·5)
Hazard ratio†						
Unadjusted	0·42 (0·34, 0·51); < 0·001		0·94 (0·69, 1·28); 0·708		0·78 (0·61, 1·00); 0·045	
Adjusted§	0·41 (0·34, 0·50); < 0·001		0·93 (0·68, 1·27); 0·661		0·80 (0·62, 1·02); 0·074	
Intervention: gastric band	1470	2902	1946	3834	1883	3716
Outcome events	72 (4·9)	278 (9·6)	31 (1·6)	51 (1·3)	45 (2·4)	92 (2·5)
Person-years	7439·7	14 342·6	10 274·7	20 780·2	9954·9	20 019·8
Crude incidence rate‡	9·68	19·38	3·02	2·45	4·52	4·60
Follow-up (years)*	4·9 (2·4–7·4)	4·7 (2·2–7·3)	5·1 (2·6–7·6)	5·4 (2·6–7·8)	5·2 (2·6–7·6)	5·4 (2·6–7·8)
Hazard ratio†						
Unadjusted	0·50 (0·39, 0·65); < 0·001		1·24 (0·80, 1·94); 0·340		0·99 (0·69, 1·41); 0·953	
Adjusted§	0·50 (0·38, 0·65); < 0·001		1·21 (0·77, 1·92); 0·406		1·07 (0·75, 1·54); 0·708	
Intervention: sleeve gastrectomy	768	1512	1135	2162	1101	2064
Outcome events	21 (2·7)	92 (6·1)	10 (0·9)	22 (1·0)	14 (1·3)	34 (1·6)
Person-years	2256·2	4538·8	3590·7	7075·4	3402·6	6706·9
Crude incidence rate‡	9·31	20·27	2·78	3·11	4·12	5·07
Follow-up (years)*	2·3 (1·0–4·1)	2·3 (1·0–4·4)	2·5 (1·2–4·6)	2·5 (1·1–4·8)	2·4 (1·1–4·4)	2·5 (1·1–4·8)
Hazard ratio†						
Unadjusted	0·45 (0·28, 0·73); 0·001		0·93 (0·44, 1·97); 0·852		0·83 (0·45, 1·55); 0·559	
Adjusted§	0·47 (0·29, 0·77); 0·002		0·98 (0·45, 2·16); 0·965		0·80 (0·42, 1·52); 0·494	
Intervention: gastric bypass	1305	2585	1971	3789	1903	3635
Outcome events	24 (1·8)	194 (7·5)	18 (0·9)	57 (1·5)	27 (1·4)	104 (2·9)
Person-years	4538·5	9543·3	7049·8	14 978·5	6787·3	14 261·8
Crude incidence rate‡	5·29	20·33	2·55	3·81	3·98	7·29
Follow-up (years)*	3·1 (1·4–5·1)	3·4 (1·5–5·5)	3·2 (1·5–5·3)	3·7 (1·7–5·8)	3·2 (1·4–5·2)	3·7 (1·7–5·8)
Hazard ratio†						
Unadjusted	0·26 (0·17, 0·40); < 0·001		0·68 (0·40, 1·15); 0·149		0·55 (0·36, 0·85); 0·006	
Adjusted§	0·25 (0·16, 0·38); < 0·001		0·65 (0·38, 1·11); 0·112		0·53 (0·34, 0·81); 0·003	
Intervention: duodenal switch	24	52	35	73	35	69
Outcome events	1 (4)	3 (6)	0 (0)	0 (0)	1 (3)	0 (0)
Person-years	62·7	148·9	96·5	219·5	97·34	217·53

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.); †values in parentheses are 95 per cent confidence intervals, followed by *P* value. Hazard ratio (HR) values are for exposed group with control group as reference (HR 1·00). ‡Rate per 1000 person-years. §Adjusted for age, sex, BMI, smoking status, alcohol consumption, Townsend deprivation quintile, ethnicity, baseline hypertension and type 2 diabetes mellitus.

participants. There was no difference in incident IHD between exposed and control cohorts (adjusted HR 0·85, 95 per cent c.i. 0·61 to 1·19; $P = 0·349$), and no significant reduction in incident IHD in the RYGB group *versus* controls (adjusted HR 0·57, 0·32 to 1·03; $P = 0·061$) (*Table 3*).

Heart failure

After excluding 119 participants with diagnosis of HF at baseline, 5127 exposed and 9919 control participants were included. There was a statistically significant reduction in incident HF in the exposed group (adjusted HR 0·57, 95 per cent c.i. 0·34 to 0·96; $P = 0·033$). Examination of the data based on the type of bariatric surgery showed a statistically significant decrease in incident HF in the RYGB group (adjusted HR 0·24, 0·08 to 0·68; $P = 0·007$), but not in the gastric band and sleeve gastrectomy cohorts (*Table 3*).

Stroke and transient ischaemic attack

After excluding 235 participants with a diagnosis of stroke and TIA at baseline, there were 5094 exposed and 9836

© 2020 BJS Society Ltd
Published by John Wiley & Sons Ltd

Table 3 Impact of bariatric surgery on separate cardiovascular events across all surgical procedures and in individual procedures

	Ischaemic heart disease		Heart failure		Stroke and transient ischaemic attack	
	Exposed	Control	Exposed	Control	Exposed	Control
Overall: all surgical procedures	5013	9667	5127	9919	5094	9836
Outcome events	49 (1·0)	123 (1·3)	19 (0·4)	72 (0·7)	37 (0·7)	83 (0·8)
Person-years	20 681·4	42 126·0	21 281·1	43 418·6	21 102·1	43 064·6
Crude incidence rate‡	2·37	2·92	0·89	1·66	1·75	1·93
Follow-up (years)*	3·6 (1·7–6·1)	4·0 (1·8–6·5)	3·6 (1·7–6·2)	4 (1·8–6·5)	3·6 (1·7–6·1)	4 (1·8–6·5)
Hazard ratio†						
Unadjusted	0·82 (0·59, 1·14); 0·233		0·55 (0·33, 0·90); 0·019		0·91 (0·62, 1·35); 0·649	
Adjusted§	0·85 (0·61, 1·19); 0·349		0·57 (0·34, 0·96); 0·033		0·98 (0·66, 1·45); 0·907	
Intervention: gastric band	1912	3772	1954	3845	1943	3820
Outcome events	25 (1·3)	54 (1·4)	9 (0·5)	23 (0·6)	21 (1·1)	29 (0·8)
Person-years	10 139·5	20 405·0	10 402·9	20 904·0	10 308·8	20 773·0
Crude incidence rate‡	2·47	2·65	0·87	1·1	2·04	1·40
Follow-up (years)*	5·2 (2·6–7·6)	5·4 (2·6–7·8)	5·2 (2·7–7·6)	5·4 (2·7–7·8)	5·2 (2·6–7·6)	5·4 (2·7–7·8)
Hazard ratio†						
Unadjusted	0·94 (0·59, 1·51); 0·800		0·79 (0·37, 1·71); 0·553		1·46 (0·83, 2·56); 0·186	
Adjusted§	1·02 (0·63, 1·65); 0·937		0·90 (0·41, 1·99); 0·795		1·67 (0·94, 2·96); 0·079	
Intervention: sleeve gastrectomy	1120	2111	1143	2177	1146	2157
Outcome events	8 (0·7)	15 (0·7)	6 (0·5)	15 (0·7)	5 (0·4)	14 (0·6)
Person-years	3479·1	6863·8	3608·2	7129·8	3619·1	7067·4
Crude incidence rate‡	2·30	2·19	1·66	2·10	1·38	1·98
Follow-up (years)*	2·4 (1·1–4·5)	2·5 (1·1–4·8)	2·5 (1·2–4·6)	2·5 (1·1–4·8)	2·5 (1·2–4·6)	2·5 (1·1–4·8)
Hazard ratio†						
Unadjusted	1·06 (0·45, 2·51); 0·887		0·81 (0·32, 2·10); 0·669		0·71 (0·25, 1·97); 0·509	
Adjusted§	1·05 (0·43, 2·54); 0·920		0·91 (0·34, 2·44); 0·854		0·68 (0·24, 1·95); 0·470	
Intervention: gastric bypass	1946	3713	1993	3825	1969	3787
Outcome events	15 (0·8)	54 (1·5)	4 (0·2)	34 (0·9)	11 (0·6)	40 (1·1)
Person-years	6965·5	14 638·0	7164·8	15 166·9	7069·2	15 005·0
Crude incidence rate‡	2·15	3·69	0·56	2·24	1·56	2·67
Follow-up (years)*	3·2 (1·5–5·3)	3·7 (1·7–5·8)	3·2 (1·5–5·2)	3·7 (1·7–5·8)	3·2 (1·5–5·2)	3·7 (1·7–5·8)
Hazard ratio†						
Unadjusted	0·59 (0·33, 1·05); 0·072		0·25 (0·09, 0·72); 0·009		0·59 (0·30, 1·15); 0·121	
Adjusted§	0·57 (0·32, 1·03); 0·061		0·24 (0·08, 0·68); 0·007		0·59 (0·30, 1·16); 0·128	
Intervention: duodenal switch	35	71	37	72	36	72
Outcome events	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Person-years	97·3	219·3	105·2	217·9	105·1	219·3

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.); †values in parentheses are 95 per cent confidence intervals, followed by *P* value. Hazard ratio (HR) values are for exposed group with control group as reference (HR 1·00). ‡Rate per 1000 person-years. §Adjusted for age, sex, BMI, smoking status, alcohol consumption, Townsend deprivation quintile, ethnicity, baseline hypertension and type 2 diabetes mellitus.

control participants. No association of bariatric surgery and incident stroke and TIA was found (adjusted HR 0·98, 95 per cent c.i. 0·66 to 1·45; $P = 0·907$).

All-cause mortality

Over a median follow-up of 3·9 (i.q.r. 1·8–6·4) years, 90 deaths in the exposed and 278 in the control group were recorded. Mortality was reduced in the exposed group (adjusted HR 0·70, 95 per cent 0·55 to 0·89; $P = 0·004$). Further adjustment for Charlson's co-morbidity index (model 2) gave a similar result (adjusted HR 0·70, 0·55 to 0·89; $P = 0·004$). There was also a significant reduction in mortality in the gastric band (adjusted HR 0·54, 0·35 to 0·84; $P = 0·007$) and RYGB (adjusted HR 0·66, 0·45 to 0·97; $P = 0·033$) groups (*Table 4*).

Incident hypertension

After excluding 4547 participants with hypertension at baseline, the study included 3567 and 7051 participants in exposed and control groups respectively. Bariatric surgery

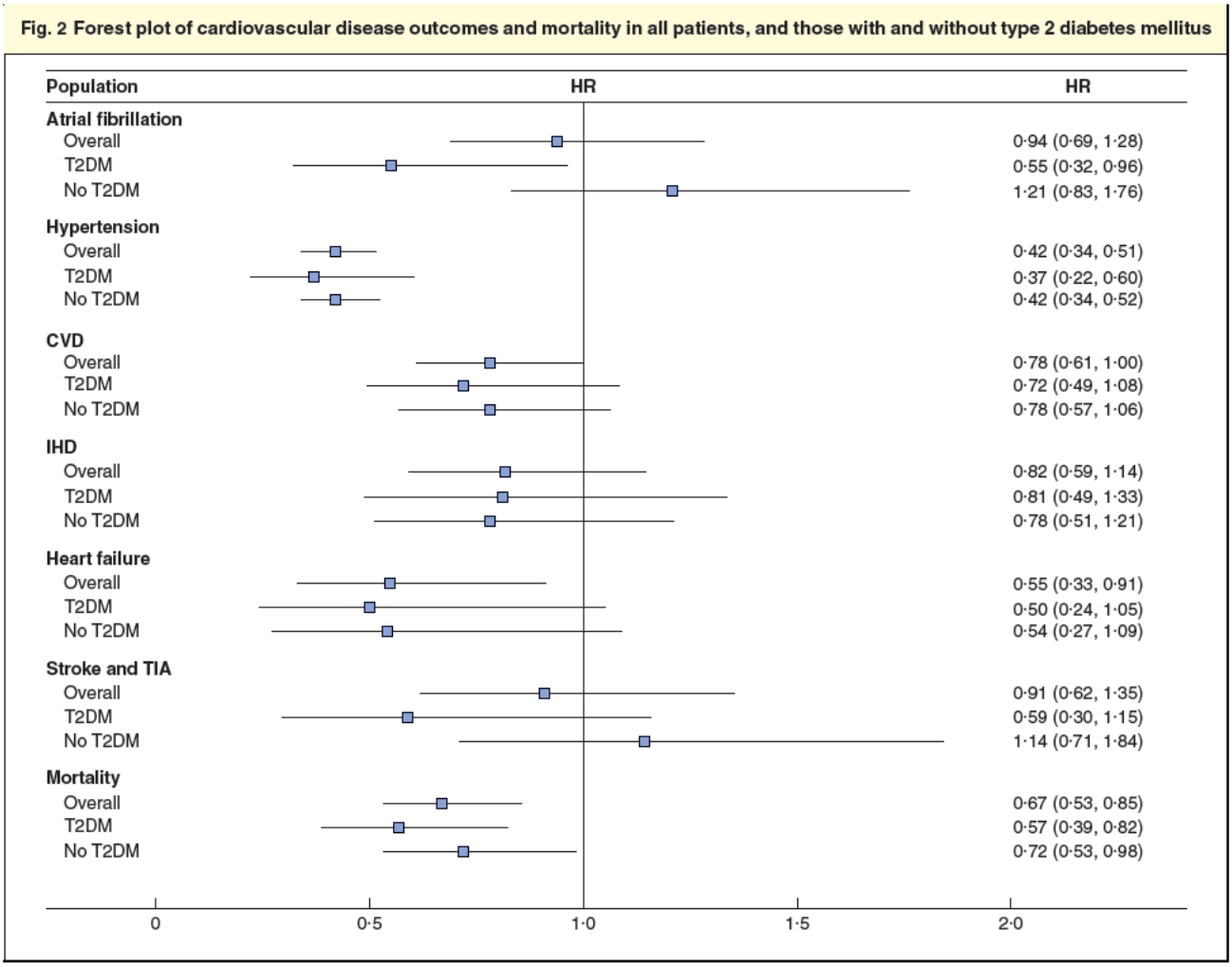
© 2020 BJS Society Ltd
Published by John Wiley & Sons Ltd

Table 4 Impact of bariatric surgery on mortality for all surgical procedures

	Overall		Gastric band		Sleeve gastrectomy		Gastric bypass	
	Exposed	Control	Exposed	Control	Exposed	Control	Exposed	Control
	5170	9995	1965	3867	1158	2198	2010	3857
Outcome events	90 (1·7)	278 (2·8)	25 (1·3)	103 (2·7)	27 (2·3)	61 (2·8)	37 (1·8)	113 (2·9)
Person-years	21 491·3	43 863·6	10 464·0	21 086·9	3671·0	7216·0	7251·1	15 341·2
Crude incidence rate‡	4·19	6·34	2·39	4·88	7·35	8·45	5·10	7·37
Follow-up (years)*	3·6 (1·7–6·2)	4·0 (1·8–6·5)	5·2 (2·7–7·6)	5·5 (2·7–7·8)	2·5 (1·2–4·6)	2·6 (1·1–4·8)	3·25 (1·49–5·26)	3·76 (1·76–5·86)
Hazard ratio†								
Unadjusted	0·67 (0·53, 0·85); 0·001		0·49 (0·32, 0·76); 0·001		0·89 (0·57, 1·40); 0·615		0·71 (0·49, 1·02); 0·067	
Adjusted model 1§	0·70 (0·55, 0·89); 0·004		0·53 (0·34, 0·83); 0·005		0·97 (0·61, 1·55); 0·901		0·69 (0·47, 1·01); 0·055	
Adjusted model 2¶	0·70 (0·55, 0·89); 0·004		0·54 (0·35, 0·84); 0·007		0·96 (0·60, 1·54); 0·874		0·66 (0·45, 0·97); 0·033	

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.); †values in parentheses are 95 per cent confidence intervals, followed by *P* value. Hazard ratio (HR) values are for exposed group with control group as reference (HR 1·00). ‡Rate per 1000 person-years. §Adjusted for age, sex, BMI, smoking status, alcohol consumption, Townsend deprivation quintile, ethnicity, baseline hypertension, and type 2 diabetes mellitus. ¶Adjusted for age, sex, BMI, smoking status, alcohol consumption, Townsend deprivation quintile, ethnicity, baseline hypertension and Charlson co-morbidity index.

Fig. 2 Forest plot of cardiovascular disease outcomes and mortality in all patients, and those with and without type 2 diabetes mellitus



Unadjusted hazard ratios (HRs) are shown with 95 per cent confidence intervals. CVD, cardiovascular disease; IHD, ischaemic heart disease; TIA, transient ischaemic attack.

© 2020 BJS Society Ltd
Published by John Wiley & Sons Ltd

was associated with a significant reduction in incident hypertension compared with the control group (adjusted HR 0·41, 95 per cent c.i. 0·34 to 0·50; $P < 0·001$). All bariatric procedures (except duodenal switch) were associated with a statistically significant reduction in incident hypertension compared with matched controls (*Table 2*).

Atrial fibrillation

After excluding 220 participants with AF at baseline, there were 5087 and 9858 participants in exposed and control groups respectively. There was no difference in incident AF between the two cohorts (adjusted HR 0·93, 95 per cent c.i. 0·68 to 1·27; $P = 0·661$). The increase in incident AF in the gastric band group *versus* controls was not significant (adjusted HR 1·21, 0·77 to 1·92; $P = 0·406$), and neither was the reduction in incident AF in the RYGB group (adjusted HR 0·65, 0·38 to 1·11; $P = 0·112$) (*Table 2*).

Nelson–Aalen cumulative hazard estimates for study outcomes

Fig. S1 (supporting information) shows the cumulative hazard estimates for the study outcomes over the 10-year interval. The association between bariatric surgery and the reduction in incident hypertension, CVD, HF and mortality started within the first 2 years of bariatric surgery, with the impact on hypertension and HF becoming apparent within the first year after surgery.

Impact of type 2 diabetes mellitus

Subgroup analyses were performed in participants with and without T2DM. There were 3265 participants (1176 exposed and 2089 controls) with and 11 900 without (3994 exposed and 7906 controls) T2DM.

Preoperative and postoperative weights were available for 1114 exposed and 1839 controls with T2DM, and for 3232 exposed and 5118 controls without T2DM. Over a median follow-up of 1 (i.q.r. 0·6–1·1) years, mean(s.d.) %WL was 22·0(12·3) per cent for exposed participants with T2DM and 1·6(6·7) per cent for controls. Similarly, over a median follow-up of 1 (0·6–1·3) years, mean(s.d.) %WL was 19·7(13·5) and 0·6(10·3) per cent in exposed and control participants without T2DM respectively.

The relationship between bariatric surgery and the outcomes examined was similar in those with and without T2DM, except that surgery was associated with lower likelihood of AF in patients with T2DM (adjusted HR 0·57, 95 per cent c.i. 0·32 to 1·01; $P = 0·053$), but a higher risk in patients without T2DM (adjusted HR 1·24, 0·85 to 1·81; $P = 0·271$). Findings for stroke and TIA were similar (*Fig. 2*; *Table S1*, supporting information).

The HR for mortality was reduced in the surgical compared with the control group in cohorts with and without T2DM (*Table S2*, supporting information).

Discussion

In this population-based study, bariatric surgery was associated with greater weight loss and reductions in incident hypertension, CVD and all-cause mortality compared with rates in matched obese patients who had not undergone bariatric surgery. These findings are consistent with the Swedish Obese Subjects (SOS) study[9,10], which observed lower incident CVD and mortality in patients who underwent bariatric surgery compared with matched controls over a median follow-up period of 14·7 years. However, unlike the present study, the SOS study also found a reduction in incident AF. This may be explained partly by the longer follow-up in the SOS study. However, most procedures in the SOS were open surgery and more than 60 per cent were vertical gastroplasties, which is also not performed nowadays. Furthermore, the present data showed that the benefits of bariatric surgery were evident at an even shorter follow-up duration (approximately 2 years) than in the SOS study, in which the impact of bariatric surgery on CVD started to become apparent approximately 6 years after surgery (based on Kaplan–Meier analysis)[10].

A systematic review[35] including eight controlled clinical studies (5 RYGB, 3 gastric band) with follow-up of 7·5(0·7) years found evidence of a mortality reduction (odds ratio 0·55, 95 per cent c.i. 0·49 to 0·63) after bariatric surgery. The present study has shown that mortality benefits start to occur relatively early following bariatric surgery. Similarly, the impact on HF, hypertension and CVD also started early during the follow-up, within the first 2 years. Consistent with the reduction in incident hypertension in the present study, bariatric surgery was also associated with a significant reduction in the risk of HF compared with the control group. A systematic review[36] summarizing the impact of bariatric surgery using data from seven studies found a reduction in incident HF in patients who had bariatric surgery, similar to the present study.

The present subgroup analysis based on the type of surgery showed a reduction in incident hypertension, irrespective of the type of intervention. This is not surprising considering the magnitude of weight loss observed for all bariatric procedures, given that a previous study[37] found that even a 5-kg weight loss over 18 months reduced incident hypertension over 7 years of follow-up. However, the observed reduction in incident combined CVD, IHD and HF was evident primarily in the RYGB group. The explanation for this difference is not clear, but could be due

© 2020 BJS Society Ltd
Published by John Wiley & Sons Ltd

to multiple factors. RYGB resulted in greater %WL than gastric banding and sleeve gastrectomy, and hence could have contributed to the favourable outcomes observed in the RYGB group[38]. In addition, unlike gastric banding, RYGB results in increased secretion of glucagon-like peptide (GLP) 1[39]. A recent cardiovascular outcome study[40] in patients with T2DM showed a favourable impact on CVD in those treated with GLP-1 receptor agonists.

The associations between bariatric surgery and CVD and hypertension were similar in patients with and without T2DM, except that patients with T2DM who underwent bariatric surgery had a non-significant reduction in the risk of AF and stroke and TIA compared with controls, whereas patients without T2DM had non-significant increased risk of AF and stroke and TIA after bariatric surgery. Most previous studies[41–44] analysing the impact of bariatric surgery in patients with T2DM focused on weight loss and glycaemic control, and had small sample sizes. A recent retrospective study[16] from the USA found a lower risk of composite cardiovascular outcome in participants with diabetes undergoing bariatric surgery. After analysing the outcomes separately, these authors[16] found a reduction in coronary artery disease, but a non-significant difference in CVD, as in the present study. A meta-analysis[45] including five cohort studies found a 48 per cent reduction in macrovascular complications during follow-up of 5–15 years, but no data were presented for individual components of macrovascular complications.

Given the observational nature of the present study, residual biases cannot be ruled out. The THIN database is a validated primary care data source and had been used previously by the authors and other researchers[25,46,47]. Immortal time bias was minimized by matching on the index date. Moreover, the large sample size allowed exploration of the relative effects of different bariatric procedures, compared with previous studies that included only one type of procedure.

Acknowledgements

A.A.T. and K.N. are joint senior authors and contributed equally to this manuscript.

A.A.T. is a clinician-scientist supported by the UK National Institute for Health Research (NIHR). The views expressed in this publication are those of the authors and not necessarily those of the National Health Service or the NIHR. A.A.T. and S.B. received funding from the project as PhD students from the Research and Development Department at University Hospitals Birmingham NHS Foundation Trust.

Disclosure: The authors declare no conflict of interest.

References

1 WHO. *Cardiovascular Diseases (CVDs)*; 2017. http://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) [accessed 8 October 2018].
2 Bhatnagar P, Wickramasinghe K, Williams J, Rayner M, Townsend N. The epidemiology of cardiovascular disease in the UK 2014. *Heart* 2015; **101**: 1182–1189.
3 Office for National Statistics. *Death Registrations Summary Tables – England and Wales*; 2018. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathregistrationssummarytablesenglandandwalesreferencetables [accessed 8 October 2018].
4 Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *J Am Coll Cardiol* 2009; **53**: 1925–1932.
5 Caleyachetty R, Thomas GN, Toulis KA, Mohammed N, Gokhale KM, Balachandran K *et al.* Metabolically healthy obese and incident cardiovascular disease events among 3·5 million men and women. *J Am Coll Cardiol* 2017; **70**: 1429–1437.
6 Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC Public Health* 2009; **9**: 88.
7 Wing RR, Lang W, Wadden TA, Safford M, Knowler WC, Bertoni AG *et al.* Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care* 2011; **34**: 1481–1486.
8 Heneghan HM, Meron-Eldar S, Brethauer SA, Schauer PR, Young JB. Effect of bariatric surgery on cardiovascular risk profile. *Am J Cardiol* 2011; **108**: 1499–1507.
9 Jamaly S, Carlsson L, Peltonen M, Jacobson P, Sjöström L, Karason K. Bariatric surgery and the risk of new-onset atrial fibrillation in Swedish obese subjects. *J Am Coll Cardiol* 2016; **68**: 2497–2504.
10 Sjostrom L, Peltonen M, Jacobson P, Sjostrom CD, Karason K, Wedel H *et al.* Bariatric surgery and long-term cardiovascular events. *JAMA* 2012; **307**: 56–65.
11 Major P, Kowalczuk A, Wysocki M, Osadnik S, Pedziwiatr M, Gluszewska A *et al.* Effects of bariatric surgery on cardiovascular risk factors among morbidly obese patients. *Pol Przegl Chir* 2017; **89**: 41–49.
12 Schiavon CA, Bersch-Ferreira AC, Santucci EV, Oliveira JD, Torreglosa CR, Bueno PT *et al.* Effects of bariatric surgery in obese patients with hypertension: the GATEWAY randomized trial (Gastric Bypass to Treat Obese Patients With Steady Hypertension). *Circulation* 2018; **137**: 1132–1142.
13 Ricci C, Gaeta M, Rausa E, Asti E, Bandera F, Bonavina L. Long-term effects of bariatric surgery on type II diabetes, hypertension and hyperlipidemia: a meta-analysis and

© 2020 BJS Society Ltd
Published by John Wiley & Sons Ltd

meta-regression study with 5-year follow-up. *Obes Surg* 2015; **25**: 397–405.
14 Benotti PN, Wood GC, Carey DJ, Mehra VC, Mirshahi T, Lent MR *et al.* Gastric bypass surgery produces a durable reduction in cardiovascular disease risk factors and reduces the long-term risks of congestive heart failure. *J Am Heart Assoc* 2017; **6**: pii: e005126.
15 Zhou X, Yu J, Li L, Gloy VL, Nordmann A, Tiboni M *et al.* Effects of bariatric surgery on mortality, cardiovascular events, and cancer outcomes in obese patients: systematic review and meta-analysis. *Obes Surg* 2016; **26**: 2590–2601.
16 Fisher DP, Johnson E, Haneuse S, Arterburn D, Coleman KJ, O'Connor PJ *et al.* Association between bariatric surgery and macrovascular disease outcomes in patients with type 2 diabetes and severe obesity. *JAMA* 2018; **320**: 1570–1582.
17 Scott JD, Johnson BL, Blackhurst DW, Bour ES. Does bariatric surgery reduce the risk of major cardiovascular events? A retrospective cohort study of morbidly obese surgical patients. *Surg Obes Relat Dis* 2013; **9**: 32–39.
18 National Institute for Health and Care Excellence (NICE). *Obesity: Identification, Assessment and Management. Clinical Guideline [CG189]*; 2014. https://www.nice.org.uk/guidance/cg189 [accessed 8 October 2018].
19 Miras AD, Kamocka A, Patel D, Dexter S, Finlay I, Hopkins JC *et al.* Obesity surgery makes patients healthier and more functional: real world results from the United Kingdom National Bariatric Surgery Registry. *Surg Obes Relat Dis* 2018; **14**: 1033–1040.
20 The Health Improvement Network. *THIN Data*. https://www.the-health-improvement-network.co.uk [accessed 3 December 2019].
21 *THIN HES Privacy Notice*. https://www.iqvia.com/locations/united-kingdom/information-for-members-of-the-public/thin-hes-data [accessed 3 December 2019].
22 UCL. *UCL – London's Global University*. https://www.ucl.ac.uk/epidemiology-health-care/node/7035/database [accessed 3 December 2019].
23 Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Inform Prim Care* 2011; **19**: 251–255.
24 Benson T, Grieve G. Coding and classification schemes. In *Principles of Health Interoperability*. London: Springer, 2016; 135–154.
25 Adderley NJ, Nirantharakumar K, Marshall T. Risk of stroke and transient ischaemic attack in patients with a diagnosis of resolved atrial fibrillation: retrospective cohort studies. *BMJ* 2018; **361**: k1717.
26 Daly B, Toulis KA, Thomas N, Gokhale K, Martin J, Webber J *et al.* Increased risk of ischemic heart disease, hypertension, and type 2 diabetes in women with previous gestational diabetes mellitus, a target group in general practice for preventive interventions: a population-based cohort study. *PLoS Med* 2018; **15**: e1002488.
27 Subramanian A, Adderley NJ, Tracy A, Taverner T, Hanif W, Toulis KA *et al.* Risk of incident obstructive sleep apnea among patients with type 2 diabetes. *Diabetes Care* 2019; **42**: 954–963.
28 Toulis KA, Willis BH, Marshall T, Kumarendran B, Gokhale K, Ghosh S *et al.* All-cause mortality in patients with diabetes under treatment with dapagliflozin: a population-based, open-cohort study in the health improvement network database. *J Clin Endocrinol Metab* 2017; **102**: 1719–1725.
29 Maguire A, Blak BT, Thompson M. The importance of defining periods of complete mortality reporting for research using automated data from primary care. *Pharmacoepidemiol Drug Saf* 2009; **18**: 76–83.
30 Suissa S. Immortal time bias in pharmaco-epidemiology. *Am J Epidemiol* 2008; **167**: 492–499.
31 Sheibani H, Esmaeili H, Tayefi M, Saberi-Karimian M, Darroudi S, Mouhebati M *et al.* A comparison of body mass index and percent body fat as predictors of cardiovascular risk factors. *Diabetes Metab Syndr* 2019; **13**: 570–575.
32 Burke GM, Genuardi M, Shappell H, D'Agostino RB Sr, Magnani JW. Temporal associations between smoking and cardiovascular disease, 1971 to 2006 (from the Framingham Heart Study). *Am J Cardiol* 2017; **120**: 1787–1791.
33 Townsend P, Phillimore P, Beattie A. *Health and Deprivation: Inequality and the North*. Croom Helm: Beckenham, 1988.
34 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**: 373–383.
35 Pontiroli AE, Morabito A. Long-term prevention of mortality in morbid obesity through bariatric surgery. A systematic review and meta-analysis of trials performed with gastric banding and gastric bypass. *Ann Surg* 2011; **253**: 484–487.
36 Berger S, Meyre P, Blum S, Aeschbacher S, Ruegg M, Briel M *et al.* Bariatric surgery among patients with heart failure: a systematic review and meta-analysis. *Open Heart* 2018; **5**: e000910.
37 He J, Whelton PK, Appel LJ, Charleston J, Klag MJ. Long-term effects of weight loss and dietary sodium reduction on incidence of hypertension. *Hypertension* 2000; **35**: 544–549.
38 Magkos F, Fraterrigo G, Yoshino J, Luecking C, Kirbach K, Kelly SC *et al.* Effects of moderate and subsequent progressive weight loss on metabolic function and adipose tissue biology in humans with obesity. *Cell Metab* 2016; **23**: 591–601.
39 le Roux CW, Aylwin SJ, Batterham RL, Borg CM, Coyle F, Prasad V *et al.* Gut hormone profiles following bariatric surgery favor an anorectic state, facilitate weight loss, and improve metabolic parameters. *Ann Surg* 2006; **243**: 108–114.
40 Bethel MA, Patel RA, Merrill P, Lokhnygina Y, Buse JB, Mentz RJ *et al.* Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2

© 2020 BJS Society Ltd
Published by John Wiley & Sons Ltd

diabetes: a meta-analysis. *Lancet Diabetes Endocrinol* 2018; **6**: 105–113.
41 Mingrone G, Guidone C, Iaconelli A, Nanni G, Castagneto M, Panunzi S *et al.* Bariatric-metabolic surgery *versus* conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. *Lancet* 2015; **386**: 964–973.
42 Schauer PR, Mingrone G, Ikramuddin S, Wolfe B. Clinical outcomes of metabolic surgery: efficacy of glycemic control, weight loss, and remission of diabetes. *Diabetes Care* 2016; **39**: 902–911.
43 Mohamed I. Mini gastric bypass is a safe and reliable procedure for type 2 diabetes remission/control in patients with BMI 31–40. Gastric bypass procedures including Roux-en-Y gastric bypass (RYGB) and one anastomosis gastric bypass (OAGB)/MGB. 22nd World Congress of the International Federation for the Surgery of Obesity and Metabolic Disorders, London, UK. *Obes Surg* 2017; **27**(Suppl 1): 581.
44 Dixon JB, O'Brien PE, Playfair J, Chapman L, Schachter LM, Skinner S *et al.* Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. *JAMA* 2008; **299**: 316–323.
45 Sheng B, Truong K, Spitler H, Zhang L, Tong X, Chen L. The long-term effects of bariatric surgery on type 2 diabetes remission, microvascular and macrovascular complications, and mortality: a systematic review and meta-analysis. *Obes Surg* 2017; **27**: 2724–2732.
46 Guest JF, Fuller GW, Vowden P. Diabetic foot ulcer management in clinical practice in the UK: costs and outcomes. *Int Wound J* 2018; **15**: 43–52.
47 Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study. *BMJ Open* 2016; **6**: e010210.

Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.

© 2020 BJS Society Ltd
Published by John Wiley & Sons Ltd

Chapter 4: Impact of Bariatric Surgery in Elderly Population

4.1 Abstract

Background: Bariatric surgery is the most effective treatment to produce sustained weight loss. Bariatric surgery has been associated with significant improvements in obesity-related complications and long-term reduction in cardiovascular disease (CVD) and mortality. However, whether bariatric surgery in older patients is beneficial or harmful has not been well examined, which is important considering the rising obesity prevalence and increasing life expectancy. Hence, we aimed to assess the impact of bariatric surgery on weight, incident CVD, hypertension, atrial fibrillation & mortality in older patients with obesity.

Methods: We conducted a retrospective cohort matched-controlled study of elderly population defined as age ≥ 65 years, who had bariatric surgery (Gastric band, sleeve gastrectomy, or gastric bypass) between 1/1/1990-31/1/2018. We used IQVIA Medical Research Data (IMRD), a validated & representative primary care electronic database. Each patient in surgical group was matched for up to 2 controls (no bariatric surgery) for age, gender, and baseline body mass index (BMI) and diabetes status. Adults with a BMI<30kg/m^2, age>75yrs and Gastric cancer in surgical group at baseline were excluded along with their controls. The study variables were identified using Read codes. CVD was defined as a composite of ischemic heart disease (IHD), heart failure (HF) & cerebrovascular accident (CVA).

Results: The analysis included 156 patients in surgical group & 299 patients in control group with mean (SD) age 67.3 (2.6) years, 65.05% were women & median (IQR) follow-up of 2.92 years (1.39-5.31).

The percentage total body weight loss (mean, CI) was greater in the surgical cohort (19.1%, CI 17.0% to 21.1%) compared to control group (1.0%, CI 0.2% to 1.6%). After adjusting for

gender, baseline BMI, diabetes, hypertension, smoking, alcohol intake, social deprivation & ethnicity, the HR for incident CVD in the exposed vs control cohorts was 0.54 (95%CI 0.22-1.34, p=0.181). On examining the individual components of the composite CVD showed non-significant increase in incident IHD, reduction in incident CVA and reduction in incident HF. Statistically non-significant increase in mortality was noted in surgical group compared to control group with adjusted Hr of 1.34 (0.68- 2.65, p= 0.404.

Conclusions: Bariatric surgery is effective weight loss intervention in older patients. We showed no major impact of surgery on incident CVD, hypertension, and mortality. But the points estimates were in favour of surgery in all outcomes except IHD and mortality. Larger studies are needed to examine the impact of bariatric surgery on metabolic, vascular, QOL and functionality outcomes in older patients are needed.

4.2 Introduction

The life expectancy has increased world-wide leading to increase in older population. Worldwide it had been estimated that the population over 60 years was 12% in 2015 will rise to 22% by 2050 (1). Obesity statistics for UK published early this year showed high prevalence of obesity in the age group 65-74 years, 75% were overweight or obese and 36% of this population were obese in 2019 (2).

High prevalence of obesity in older people will result in significant burden due to the well-established obesity-related complications such as type 2 diabetes, cardiovascular disease (CVD) musculoskeletal disorders and some cancers as well as functional disability and poor quality of life (3). Obesity in older population, is further complicated by reduction in muscle mass (sarcopenia). Sarcopenic obesity contribute to the increased morbidity (4).

Bariatric surgery is currently the most effective obesity treatment modality that results in sustained weight loss and long-term improvement in obesity-related complications (5, 6). We have shown in our previous study that bariatric surgery is associated with reduction in incidence of cardiovascular disease, diabetes-related microvascular complications, and mortality compared to standard care (7, 8).

There is no clear guideline on age limit for bariatric surgery. Systematic review including 13 studies found trend toward safety and better outcome after bariatric surgery in elderly population (9).This observation could be due to increasing laparoscopic procedures. In UK, 74.5% bariatric procedures are done laparoscopically in 2007 compared 28% in year 2000 (10). Studies has been conducted comparing the impact of bariatric surgery in elderly vs non elderly and found better mortality and morbidity remission in younger age group (11).

The outcomes of bariatric surgery in older patients compared to older patients with obesity who did not receive bariatric surgery is unknown.

Therefore, in this study we aimed to assess the impact of bariatric surgery on weight loss, incident cardiovascular disease (CVD), hypertension, atrial fibrillation, & mortality in older patients (≥65 years) with obesity.

4.3 Methods

4.3.1 Study design and data source

We conducted a retrospective, matched, controlled cohort study utilising a dataset from The IQVIA Medical Research Data (IMRD) database, from 1/1/1990 to 31/1/2018. IMRD contains electronic medical record from more than 787 general practices; it includes

longitudinal patient records of 15 million patients (3.1 million active patients) and covers around 6.2% of the UK population (12-14). IMRD contains information on patient demographics (e.g., age, sex), therapies (e.g., medications, dose), symptoms and medical diagnoses, and additional health data such as smoking and alcohol status, physiological measures, and test results. These information are recorded using Read codes (15). The IMRD database has been used previously used by our group and others to examine chronic non-communicable disease (such as diabetes, CVD, obesity, and its related complications) and mortality (16-19).

4.3.2 Population

Primary care practices were eligible for inclusion in the study at the later of the following dates: one year after beginning to use the Vision electronic records system, and one year after demonstrating Acceptable Mortality Recording (an indicator of the practice data quality) to ensure the quality of data (20). Study participants must have been registered with an eligible practice for at least one year before study entry to ensure adequate documentation of concomitant diseases and treatments.

Our population for this study was subset of the dataset used for previous study (7).

Our inclusion criteria for patients in surgical group were patients aged 65- 75 years who had bariatric surgery [gastric banding (GB), sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB), duodenal switch (DS)] between 1/1/1990 and 31/1/2018. Every patient in surgical (bariatric surgery) cohort was matched up to 2 controls who had not had bariatric surgery by age (± 2 years), sex and body mass index (BMI, ±2 kg/m^2) and diabetes status from same general practice. Patients were excluded from the surgical group if they met any of the following criteria had a BMI <30 kg/m^2, age > 75 years, had a record of gastric cancer before

the index date (study entry date), had gastric balloon or endo-barrier or had revisional bariatric surgery.

4.3.3 Follow-up

For patients in surgical group, study entry date (index date) was defined as the first Read code documentation date of bariatric surgery; the same index date was assigned to the corresponding matched controls to mitigate immortal time bias.

Study participants were followed-up from the index date until the earliest of the following: a) occurrence of the outcome of interest, b) death, c) study participant left the practice, d) the practice ceased contributing to IMRD.

4.3.4 Outcome

Primary outcomes were incident composite CVD [Ischaemic heart disease (IHD), cerebrovascular accident including stroke and transient ischaemic attack (CVA), or heart failure (HF)], and mortality. Secondary outcomes included the separate CVD outcomes (IHD, CVA, HF) hypertension, incident atrial fibrillation (AF).

4.3.5 Statistical analysis

We calculated crude and adjusted hazard ratios (HR) and 95% confidence intervals (CIs) for the occurrence (incident) of each outcome of interest in the exposed vs. control groups using Cox proportional hazards regression. The proportional hazards assumption was checked using the Schoenfeld residuals test.

Patients with the outcome of interest at baseline were excluded from the analysis; for example, when the outcome of interest was incident CVD, patients with baseline CVD were excluded.

Covariates in the adjusted/multivariable model were selected based on biological plausibility; these included age, sex, body mass index (BMI), smoking status, alcohol consumption, ethnicity, and social deprivation status (21, 22). BMI (in kg/m^2) was categorised as <35 kg/m^2, 35-40 kg/m^2 and > 40 kg/m^2. Smoking and alcohol intake were categorised as user, non-user and ex-user. Social deprivation status was represented by Townsend deprivation quintile which is based on material deprivation within a population. Ethnicity was categorised as Caucasian, Afro-Caribbean, south Asian, mixed. A missing category was used for missing data for BMI and Townsend quintile.

For Combined CVD, individual cardiovascular disease, hypertension and AF outcomes, the HRs were adjusted for all above-mentioned covariates, plus baseline hypertension and diabetes (model 1). For incident hypertension, the same covariates were included except for baseline hypertension. For mortality, an additional model was fitted adjusting for the same variables included in model 1 plus Charlson comorbidity index status (model 2).

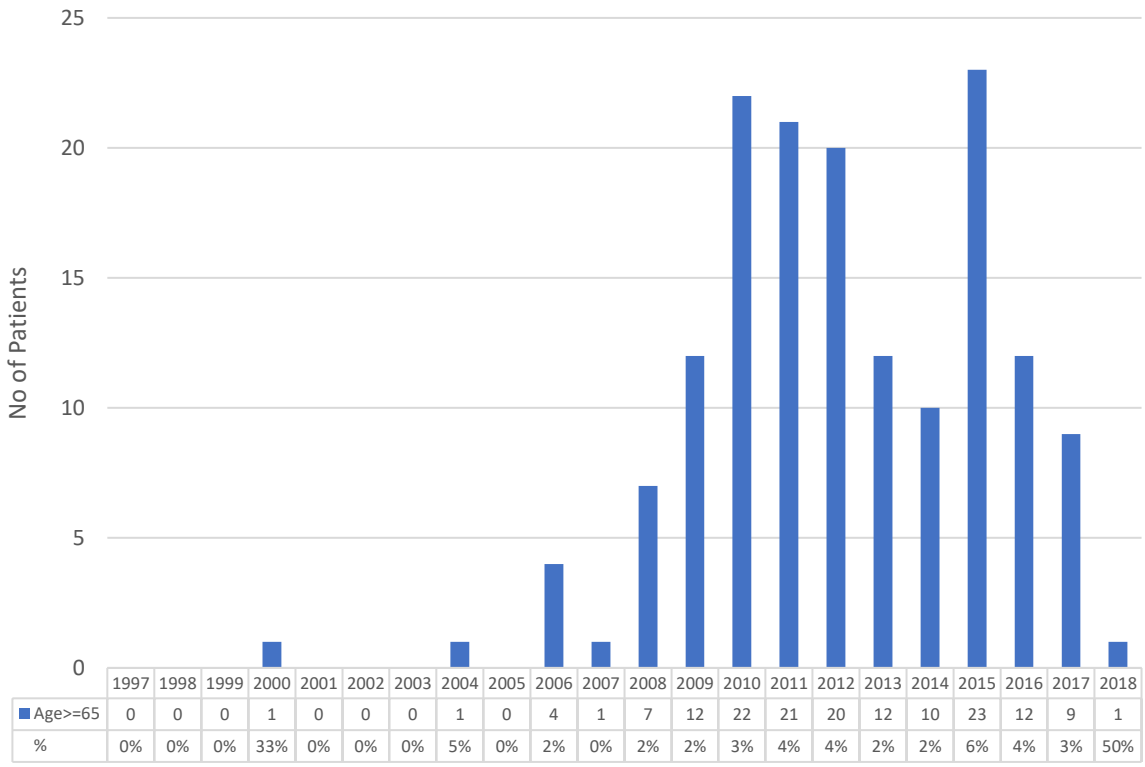
Percentage weight loss was calculated as change in weight (post-surgical weight - baseline weight) / baseline weight × 100. For control group who had no surgery, latest weight available after the index date was accounted equivalent to post -surgical weight. T-test was used to compare the percentage weight loss in surgical and control group.

A two-tailed p-value < 0.05 was considered statistically significant. All analyses were conducted using Stata version 15 (23).

4.4 Results

4.4.1 Baseline characteristics

From dataset of 15165 eligible participants, we identified cohort of 455 patients aged ≥65 years consisting of 156 patients in surgical and 299 patients in control group. The percentage of elderly patients (defined as aged 65-75 years) undergoing bariatric surgery has increased gradually, and noted to be 0% in year 2005 and 6% in year 2015 (Fig 1). This could be due to the introduction of laparoscopic surgery and increasing popularity of the intervention.



	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Age>=65	0	0	0	1	0	0	0	1	0	4	1	7	12	22	21	20	12	10	23	12	9	1
%	0%	0%	0%	33%	0%	0%	0%	5%	0%	2%	0%	2%	2%	3%	4%	4%	2%	2%	6%	4%	3%	50%

Figure 1: Number of elderly patients undergoing bariatric surgery from year 1997 to 2017

Mean age was 67.5 (±2.6) years, 65.1% were female. The prevalence of Type2 diabetes was 44.08% in exposed vs 45.82% in control group.

The prevalence of cardiovascular disease at baseline was higher in control group compared to exposed which could be due the selection process of candidates for bariatric surgery. The prevalence of obstructive sleep apnoea was four times higher in exposed group than control group which could be the result of screening processes before bariatric surgery.

In exposed group, 40 (25.64%) had gastric band, 57 (36.54%) had sleeve gastrectomy and the rest 59 (37.82%) had gastric bypass. No patients had duodenal switch.

Table 1: Baseline characteristics of surgical and control group

	Surgical **N= 156**	**Control** **N= 299**
Age Mean (SD)	67.46 (2.38)	67.18 (2.66)
Sex n (%)		
Male	55 (35.26%)	104 (34.78%)
Female	101 (64.74%)	195 (65.22%)
BMI		
BMI Categories		
28- 34.9	24 (15.38%)	53 (18.73%)
35- 39.9	39 (25%)	77 (25.75%)
>=40	91 (58.33%)	164 (54.85%)
Missing	2 (1.28%)	2 (0.67%)
Smoker categories		
Non-Smoker	72 (46.15%)	144 (48.16%)
Smoker	10 (6.41%)	27 (9.03%)
Ex-Smoker	74 (47.44%)	128 (42.81%)
Missing		
Drinker Categories		
Non-drinker	39 (25%)	82 (27.42%)
Drinker	99 (63.46%)	194 (64.88%)
Ex- Drinker	8 (5.13%)	10 (3.34%)
Missing	10 (6.41%)	13 (4.35%)

Ethnicity		
Caucasian	63 (40.38%)	129 (43.14%)
Blac Afro-Caribbean	2 (1.28%)	0
South Asian	1 (0.64%)	1 (0.33%)
Mixed	0	0
Other	2 (1.28	1 (0.33%)
Missing	88 (56.41%)	168 (56.19%)
Townsend		
<20%	32 (20.51%)	61 (20.40%)
20-40%	35 (22.44%)	59 (19.73%)
40-60%	22 (14.10%)	58 (19.40%)
60-80%	21 (13.46%)	53 (17.73%)
>80%	20 (12.82%)	36 (12.04%)
Missing	26 (16.67%)	32 (10.70%)
Baseline comorbidities		
Mental Health Conditions		
Anxiety	35 (22.44%)	74 (24.75%)
Depression	65 (41.67%)	78 (26.09%)
Cardiovascular Diseases		
Atrial Fibrillation	5 (3.21%)	25 (8.36%)
Hypertension	96 (61.54%)	203 (67.89%)
Heart Failure	6 (3.85%)	13 (4.35%)
Ischemic Heart Disease	12 (7.69%)	48 (16.05%)
Stroke/TIA	6 (3.85%)	16 (5.35%)
DM		
Type 2 DM	75 (48.08%)	137 (45.82%)
Type 1 DM	0	2 (0.67%)
OSA	22 (14.10%)	9 (3.01%)
Follow up	2.86 (1.39- 5.0)	3.05 (1.36- 5.37
Intervention		
Gastric Band	40 (25.64%)	77

Gastrectomy	57 (36.54%)	112
Gastric bypass	59 (37.82%)	110

4.4.2 Weight loss

Significant weight loss was noted in surgical group compared to control group. Data for weight before and after the index date was available for 135 (86.54%) exposed and 242 (80.94%) control participants. There was 19.05% (±11.9%) weight loss in exposed vs 0.93% (±5.4%) in control group over the median follow up period of 1 (IQR 0.6- 1.1) year.

4.4.3 Cardiovascular disease and mortality

After adjusting for gender, baseline BMI, diabetes, hypertension, smoking, alcohol intake, social deprivation & ethnicity, no association was noted between surgery and incident combined CVD (adj HR 0.53, 95%CI 0.21- 1.33, p= 0.178).

On examining the individual components of the composite CVD showed no statistically significant differences between surgical and control groups, but the point estimates for IHD was higher and for heart failure was lower in surgical group vs control (Table 2).

Analysing the impact of bariatric surgery on incidence of hypertension and atrial fibrillation showed no statistical difference. However, the point estimate for hypertension was lower (adj HR 0.35, 95% CI 0.08- 1.49, p= 0.156) and for atrial fibrillation was higher (adj HR 0.956, 95% CI 0.38- 2.41, p= 0.924) in surgical vs control group. Similarly, no statistically significant impact of bariatric surgery was noted on mortality, though point estimate was higher (adj HR 1.30, 95% CI 0.65- 2.60, 0.453) in surgical vs control group (Table 2).

Table 2: The impact of bariatric surgery on cardiovascular disease and all- cause mortality

	Exposed	Control	Exposed	Control	Exposed	Control
	Cardiovascular disease		**Hypertension**		**Atrial fibrillation**	
Number of patients	**136**	**232**	**N=60**	**N=96**	**N=151**	**N=274**
Outcome events, n (%)	7 (5.15%)	21 (9.05%)	3 (5%)	10 (10.42%)	8 (5.30%)	15 (5.47%)
Person-years	431.12	793.82	161.62	285.71	481.04	955.95
IRR	16.24	26.45	18.56	35	16.63	15.69
Follow-up years,	2.71 (1.23- 4.65)	2.85 (1.12- 5.16)	2.22 (1.19- 3.45)	2.51 (0.98- 4.37)	2.84 (1.3- 4.41)	2.9 (1.21- 5.04)
Unadj HRR (95% CI), p-value	0.62 (0.26- 1.48), 0.283		0.535 (0.147- 1.95), 0.343		1.038 (0.44- 2.45), 0.931	
Adj HRR (95% CI) , p-value	0.53 (0.21- 1.33), 0.178		0.35 (0.08- 1.49), 0.156		0.96 (0.38- 2.41), 0.924	
	Ischaemic heart disease		**Heart failure**		**Cardiovascular disease (stroke)**	
Number of patients	**144**	**251**	**150**	**286**	**150**	**283**
Outcome events, n (%)	6 (4.17%)	10 (3.98%)	1 (0.67%)	14 (4.90)	2 (1.33%)	7 (2.47%)
Person-years	460.71	889.75	489.55	1002.02	489.26	1007.14
IRR	13.02	11.24	2.043	13.97	4.09	6.95
Follow-up years,	2.79 (1.27- 4.65)	2.93 (1.18- 5.36)	2.86 (1.33- 4.76)	2.91 (1.29- 5.04)	2.84 (1.33- 4.98)	2.98 (1.31- 5.34)
Unadj HRR (95% CI), p-value	1.11 (0.403- 3.065), 0.838		0.14 (0.019- 1.099), 0.062		0.66 (0.13- 3.27), 0.609	
Adj HRR (95% CI) , p-value	1.36 (0.44- 4.22), 0.599		0.13 (0.02- 1.06), 0.056		0.42 (0.05- 3.34), 0.410	

		All- cause Mortality	
Number of patients		**156**	**299**
Outcome events, n (%)		16 (10.26%)	26 (8.70%)
Person-years		517.66	1087.86
IRR		30.91	23.9
Follow-up years,		2.86 (1.39- 5.0)	3.05 (1.36- 5.37)
Unadj HRR (95% CI), p-value		1.364 (0.727- 2.558), 0.334	
Adj HRR (95% CI) , p-value	Model 1	1.433 (0.72- 2.84), 0.303	
	Model 2	1.30 (0.65- 2.60), 0.453	

IRR= Crude Incidence Rate/1000-person years
Adjusted Model 1: Adjusted for age, sex, BMI, smoking status, alcohol consumption, Townsend deprivation quintile, ethnicity, baseline hypertension, Type2 diabetes.
Adjusted Model 2: Adjusted for age, sex, BMI, smoking status, alcohol consumption, Townsend deprivation quintile, ethnicity, baseline hypertension, Charlson comorbidity index.

4.5 Discussion

In this population based matched control cohort study, we have reported that bariatric surgery had beneficial effect on weight loss with no obvious impact on CVD or mortality outcomes when compared to routine care.in elderly population This lack of significant association could reflect the small sample size and the low number of events.

With increasing prevalence of elderly population and increasing prevalence of obesity like all age groups, the number of patient eligible for bariatric surgery is rising. The study from US showed that of all the bariatric procedures done, percentage of elderly patients (defined as aged >60 years) increased to 10.1% over study period of 2009 to 2013 compared to 2.7% in 1999- 2005 (24). Hence, we need strong evidence for the impact of bariatric surgery in elderly population.

The meta-analysis involving nine studies with studies conducted on patients who underwent gastric bypass found 4 times higher mortality,1.88 times morbidity and less weight loss, in elderly (defined as age ≥ 60 years) compared to younger population (25). The remission of hypertension recorded from 3 studies showed lower remission rate in older vs younger cohort. This systematic review also analysed 30 days mortality from 7 studies and found it to be higher in the elderly vs younger (25).

Another systematic review involving 26 studies conducted pooled analysis and found the weight loss, diabetes remission and hypertension remission and postoperative complications in older population are comparable to younger population (26). There had been wide

heterogeneity in these studies. The definition of elderly population itself had been different in these studies.

The studies focussed on the impact of bariatric surgery in elderly population found bariatric surgery to be safe and effective on weight management and CVD risk factor including diabetes, and hypertension (27, 28). The study based on NCQIOP database included 2010 elderly participants (≥65 years) underwent bariatric surgery noted increased mortality in the elderly compared younger (<65 years) especially in cohort undergoing LSG similar to our study (29).

BMI for weight measurement has been always criticised for not giving a complete picture of obesity. However, the things become more challenging in the elderly cohort. Sarcopenia is defined as loss of skeletal muscle mass and function and had been frequently associated with the older population (30). Obesity in the elderly population had led to a new concept of sarcopenic obesity (31). We do not have tool to measure the proportion of fat muscle mass and lean muscle mass lost resulting in weight loss in post bariatric participants. Loss in lean muscle mass can contribute to further increase in muscle weakness aggravating sarcopenic effect and a detrimental impact on mobility and mortality. It is important to examine the impact of bariatric surgery on body composition and not mere body weight.

The elderly population with obesity may have decreased physiological reserve and their bodies had been exposed to metabolic consequences of obesity for a long time. We know from the work of Barnette et al that the prevalence of comorbidity increases as the age increases and a steep rise in multimorbidity was noted by the age of 65 years (32). The paper from US found the increasing adverse event and mortality as the age increases and a sharp rise after the age of 65 years (33). Remission of comorbidities will be lower and mortality

higher in older population compared to younger population is expected. Hence, the more important questions are to compare older patients with obesity who had routine care or pharmacotherapy with bariatric surgery.

There has been new emerging glucose lowering medications like glucagon like peptide 1 agonist and analogue and sodium glucose cotransporter 2 inhibitor. Beside glucose lowering effect, these medications have been found to offer significant weight loss and cardiorenal benefit (34). The mean age of participants in these studies is <55 years. Studies are needed to examine the safety of weight loss by pharmacotherapy in elderly population especially from the perspective of muscle mass loss and impact of functionality.

Our study is a retrospective study with a small sample size but still bigger than most of the available studies in the literature. We had limited follow up. Study showed no association between bariatric surgery and mortality, but we could not identify if mortality noted in surgical group was secondary of surgery related or other. One of major limitation of our study was no data on mobility and quality of life. Reduced mobility with poor quality of life could be detrimental implication of obesity in elderly patients with obesity. Elderly population with obesity has been also reported to have poor recovery from other medical condition and more prone to institutionalization (35).

Studies are needed to examine impact of bariatric surgery on quality of life in elderly population. Focus of bariatric surgery in elderly population probably need to shift and should be based on safety and impact on mobility and quality of life rather than mortality and major adverse cardiac events.

However, to our knowledge, no previous studies analysed the impact of bariatric surgery on incident CVD as in our study comparing the elderly cohort who had surgery and who had routine care.

4.6 Conclusion

Bariatric surgery is an effective tool in the management of weight loss even in elderly population. No statistically benefit of bariatric surgery on incident cardiovascular disease and mortality was noted. Larger studies are needed to assess the impact of bariatric surgery on obesity related chronic health conditions and quality of life and functionality

4.7 References

1. WHO. Ageing and health. 2018 Feb.
2. Baker C. Obesity Statistics 2021 [Available from: https://commonslibrary.parliament.uk/research-briefings/sn03336/.
3. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC public health. 2009;9:88.
4. AJ C-J, JP B, JM B, Y B, T C, F L, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age and ageing. 2010;39(4).
5. Gloy VL, Briel M, Bhatt DL, Kashyap SR, Schauer PR, Mingrone G, et al. Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials. BMJ (Clinical research ed). 2013;347:f5934.
6. Chang SH, Stoll CR, Song J, Varela JE, Eagon CJ, Colditz GA. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003-2012. JAMA Surg. 2014;149(3):275-87.
7. SinghP, SubramaniaA, AdderleyN, GokhaleK, SinghalR, BellaryS, et al. Impact of Bariatric Surgery on Cardiovascular Outcomes and Mortality: A Population-Based Cohort Study. The British journal of surgery. 2020;107(4):432- 42.
8. Singh P, Adderley N, Subramanian A, Gokhale K, Singhal R, Toulis KA, et al. The Impact of Bariatric Surgery on Incident Microvascular Complications in Patients With Type 2 Diabetes: A Matched Controlled Population-Based Retrospective Cohort Study. Diabetes Care 2021. 2021;44 (1):116-24.
9. Cazzo E, Universidade Estadual de Campinas C, Brazil, Universidade Estadual de Campinas C, Brazil, Gestic MA, Unicamp C, Brazil, Unicamp C, Brazil, et al. Bariatric surgery in the elderly: A narrative review. Rev Assoc Med Bras. 2017;63(9):787-92.
10. BurnsEM, NaseemH, BottleA, LazzarinoAI, AylinP, DarziA, et al. Introduction of laparoscopic bariatric surgery in England: observational population cohort study. BMJ (Clinical research ed). 2010;341.
11. LynchJ, BelgaumkarA. Bariatric surgery is effective and safe in patients over 55: a systematic review and meta-analysis. Obesity surgery. 2012;22(9).
12. Sciences. tNCIsoCCaP. The Health Improvement Network (THIN) the National Cancer Institute'sDivision of Cancer Control and Population Sciences.2018 [Available from: https://epi.grants.cancer.gov/pharm/pharmacoepi_db/thin.html.
13. Health TURDPCP. THIN Database 2018 [Available from: http://www.ucl.ac.uk/pcph/research/thin-database/database.
14. Birmingham Uo. More about THIN - University of Birmingham, time and duration of consultation.. [Available from: https://www.birmingham.ac.uk/research/activity/mds/projects/HaPS/PCCS/THIN/more-about-thin/index.aspx.
15. Tim Benson GG. Coding and Classification Schemes | SpringerLink. 2016.

16. Adderley NJ, Nirantharakumar K, Marshall T. Risk of stroke and transient ischaemic attack in patients with a diagnosis of resolved atrial fibrillation: retrospective cohort studies. BMJ (Clinical research ed). 2018;361:k1717.
17. Daly B, Toulis KA, Thomas N, Gokhale K, Martin J, Webber J, et al. Increased risk of ischemic heart disease, hypertension, and type 2 diabetes in women with previous gestational diabetes mellitus, a target group in general practice for preventive interventions: A population-based cohort study. PLoS medicine. 2018;15(1):e1002488.
18. Subramanian A, Adderley NJ, Tracy A, Taverner T, Hanif W, Toulis KA, et al. Risk of Incident Obstructive Sleep Apnea Among Patients With Type 2 Diabetes. Diabetes Care. 2019.
19. Toulis KA, Willis BH, Marshall T, Kumarendran B, Gokhale K, Ghosh S, et al. All-Cause Mortality in Patients With Diabetes Under Treatment With Dapagliflozin: A Population-Based, Open-Cohort Study in The Health Improvement Network Database. J Clin Endocrinol Metab. 2017;102(5):1719-25.
20. Maguire A, Blak BT, Thompson M. The importance of defining periods of complete mortality reporting for research using automated data from primary care. Pharmacoepidemiology and drug safety. 2009;18(1):76-83.
21. Sheibani H, Esmaeili H, Tayefi M, Saberi-Karimian M, Darroudi S, Mouhebati M, et al. A comparison of body mass index and percent body fat as predictors of cardiovascular risk factors. Diabetes & metabolic syndrome. 2019;13(1):570-5.
22. Burke GM, Genuardi M, Shappell H, D'Agostino RB, Sr., Magnani JW. Temporal Associations Between Smoking and Cardiovascular Disease, 1971 to 2006 (from the Framingham Heart Study). The American journal of cardiology. 2017;120(10):1787-91.
23. software S. Stata: Software for Statistics and Data Science 2019 [Available from: https://www.stata.com/.
24. GebhartA, YoungMT, NguyenNT. Bariatric surgery in the elderly: 2009-2013. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2015;11(2).
25. Marczuk P, Kubisa MJ, Swiech M, Waledziak M, Kowalewski P, Major P, et al. Effectiveness and Safety of Roux-en-Y Gastric Bypass in Elderly Patients-Systematic Review and Meta-analysis. Obes Surg. 2019;29(2):361-8.
26. Giordano S, Victorzon M. Bariatric surgery in elderly patients: a systematic review. Clin Interv Aging. 2015;10:1627-35.
27. Danan M, Nedelcu A, Noel P, Zulian V, Carandina S, Nedelcu M. Operative morbidity of laparoscopic sleeve gastrectomy in subjects older than age 65. Surg Obes Relat Dis. 2019;15(1):8-11.
28. Elbahrawy A, Bougie A, Loiselle SE, Demyttenaere S, Court O, Andalib A. Medium to long-term outcomes of bariatric surgery in older adults with super obesity. Surg Obes Relat Dis. 2018;14(4):470-6.
29. Koh CY, Inaba CS, Sujatha-Bhaskar S, Nguyen NT. Outcomes of Laparoscopic Bariatric Surgery in the Elderly Population. Am Surg. 2018;84(10):1600-3.
30. Santilli V, Bernetti A, Mangone M, Paoloni M. Clinical definition of sarcopenia. Clin Cases Miner Bone Metab. 112014. p. 177-80.
31. Zamboni M, Mazzali G, Fantin F, Rossi A, Di Francesco V. Sarcopenic obesity: a new category of obesity in the elderly. Nutr Metab Cardiovasc Dis. 2008;18(5):388-95.

32. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet. 2012;380(9836):37-43.
33. Livingston EH, Langert J. The impact of age and Medicare status on bariatric surgical outcomes. Arch Surg. 2006;141(11):1115-20; discussion 21.
34. BrownE, HeerspinkHJL, CuthbertsonDJ, WildingJPH. SGLT2 inhibitors and GLP-1 receptor agonists: established and emerging indications. Lancet (London, England). 2021;398(10296).
35. Samper-Ternent R, Al Snih S. Obesity in Older Adults: Epidemiology and Implications for Disability and Disease. Rev Clin Gerontol. 2012;22(1):10-34.

Chapter 5: Impact of bariatric surgery on incident microvascular complications in patients with type 2 diabetes

5.1 Contents of chapter 5

Diabetes-related microvascular complications have significant negative impact on the health and health care economy. Diabetes-related foot disease (DFD) is the leading cause for non-traumatic lower limb amputation (1); sight threatening diabetic retinopathy (STDR) is a leading cause of blindness at younger age (2) and diabetic nephropathy is the leading cause of chronic kidney disease (CKD) and end-stage renal disease (3).

Diabetes causes high economic burden with large proportion coming from microvascular complications. The medical expenses of patients with diabetes is 2.3 times higher than the patients without diabetes (4). The recent ADA data has shown 26% rise in economic costs of diabetes (including direct and indirect costs) in 2017 compared to 2012 (4) and this is estimated to inflate further as per study from UK and world-wide (5, 6). Diabetes accounts for 10% of the NHS budget and 80% of this diabetes expense is spent in dealing with diabetes related complication mainly led by prolonged hospital stay, cardiovascular disease, kidney disease and neuropathy

Obesity is a major modifiable cause of type 2 diabetes. Obesity had been also found to an independent contributing factor for CKD (7) and associated with development and progression of DPN (8, 9).

Weight loss and bariatric surgery had been associated with good glycaemic control, blood pressure, hyperlipidaemia, and other vascular risk factor, which should lead to improvement in microvascular complications.

In this chapter, I examined the impact of bariatric surgery on incidence of microvascular complications in patients with obesity and type 2 diabetes. Subset analysis based on type of surgery was conducted This chapter is presented in format of a published article.

5.2 References

1. Prof Andrew JM Boulton FRCP a b, Loretta Vileikyte MD a, b, Gunnel Ragnarson-Tennvall PhD c, Jan Apelqvist MD. The global burden of diabetic foot disease - ScienceDirect. The Lancet. 2005.
2. Cheung N, Mitchell P. Diabetic retinopathy. The Lancet. 2010;376(9735):124-36.
3. Afkarian M, Leila R. Zelnick, Hall YN, Heagerty PJ, Tuttle K, Weiss NS, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. JAMA - Journal of the American Medical Association. 2016;316(6):602-10.
4. Association AD. Economic Costs of Diabetes in the U.S. in 2017. 2018.
5. A B, PK H, L M, CJ C. The Projected Health Care Burden of Type 2 Diabetes in the UK From 2000 to 2060. Diabetic medicine : a journal of the British Diabetic Association. 2002;19 Suppl 4.
6. C B, V S, E H, J M-G, R A, T B, et al. Global Economic Burden of Diabetes in Adults: Projections From 2015 to 2030. Diabetes care. 2018;41(5).
7. Hsu CY MC, Iribarren C et al. Body mass index and risk for end-stage renal disease. 2006.
8. Hozumi J, Sumitani M, Matsubayashi Y, Abe H, Oshima Y, Chikuda H, et al. Relationship between Neuropathic Pain and Obesity. Pain Research and Management. 2016;Hindawi.
9. Giacinta Miscio GG, Amelia Brunani, Alessandro Mauro. Obesity and peripheral neuropathy risk: a dangerous liaison. Journal of the Peripheral Nervous SystemNov 2005. p. 354-8.

5.3 Manuscript 2: Impact of bariatric surgery on incident microvascular complications in patients with type 2 diabetes

Singh P., Adderley N., Subramanian A., Gokhale K., Singhal R., Toulis K.A., Bellary S., Nirantharakumar K., Tahrani A.A. The Impact of Bariatric Surgery on Incident Microvascular Complications in Patients With Type 2 Diabetes: A Matched Controlled Population-Based Retrospective Cohort Study. Diabetes Care 2021 Jan; 44(1): 116-124. (First published 10 Nov 2020) https://doi.org/10.2337/dc20-0571

The Impact of Bariatric Surgery on Incident Microvascular Complications in Patients With Type 2 Diabetes: A Matched Controlled Population-Based Retrospective Cohort Study

Pushpa Singh,[1,2] Nicola Adderley,[3] Anuradhaa Subramanian,[3] Krishna Gokhale,[3] Rishi Singhal,[4] Konstantinos A. Toulis,[3,5] Srikanth Bellary,[2,6] Krishnarajah Nirantharakumar,[2,3,7,8] and Abd A. Tahrani[1,2,7]

https://doi.org/10.2337/dc20-0571

OBJECTIVE

To assess the impact of bariatric surgery (BS) on incident microvascular complications of diabetes-related foot disease (DFD), sight-threatening diabetic retinopathy (STDR), and chronic kidney disease (CKD) in patients with type 2 diabetes and obesity.

RESEARCH DESIGN AND METHODS

A retrospective matched, controlled population-based cohort study of adults with type 2 diabetes between 1 January 1990 and 31 January 2018 using IQVIA Medical Research Data (IMRD), a database of primary care electronic records. Each patient with type 2 diabetes who subsequently had BS (surgical group) was matched on the index date with up to two patients with type 2 diabetes did not have BS (nonsurgical group) within the same general practice by age, sex, preindex BMI, and diabetes duration.

RESULTS

Included were 1,126 surgical and 2,219 nonsurgical participants. In the study population 2,261 (68%) were women. Mean (SD) age was 49.87 (9.3) years vs. 50.12 (9.3) years and BMI was 46.76 (7.96) kg/m^2 vs. 46.14 (7.49) kg/m^2 in the surgical versus nonsurgical group, respectively. In the surgical group, 22.1%, 22.7%, 52.2%, and 1.1% patients had gastric band, sleeve gastrectomy, Roux-en-Y gastric bypass (RYGB), and duodenal switch, respectively. Over a median follow-up of 3.9 years (interquartile range 1.8–6.4), BS was associated with reduction in incident combined microvascular complications (adjusted hazard ratio 0.53, 95% CI 0.43–0.66, $P < 0.001$), DFD (0.61, 0.50–0.75, $P < 0.001$), STDR (0.66, 0.44–1.00, $P = 0.048$), and CKD (0.63, 0.51–0.78, $P < 0.001$). Analysis based on the type of surgery showed that all types of surgery were associated with a favorable impact on the incident of composite microvascular complications, with the greatest reduction for RYGB.

CONCLUSIONS

BS was associated with a significant reduction in incident diabetes-related microvascular complications.

[1]Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, U.K.
[2]Department of Diabetes and Endocrinology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, U.K.
[3]Institute of Applied Health Research, University of Birmingham, Birmingham, U.K.
[4]Department of Surgery, University Hospital Birmingham NHS Foundation Trust, Birmingham, U.K.
[5]Department of Endocrinology, 424 General Army Training Hospital, Thessaloniki, Greece
[6]School of Life and Health Sciences, Aston University, Birmingham, U.K.
[7]Centre for Endocrinology, Diabetes and Metabolism, Birmingham Health Partners, Birmingham, U.K.
[8]Midlands Health Data Research, Birmingham, U.K.

Corresponding author: Krishnarajah Nirantharakumar, [redacted]

Received 19 March 2020 and accepted 7 October 2020

This article contains supplementary material online at https://doi.org/10.2337/figshare.13075748.

K.N. and A.A.T. are joint senior authors and contributed equally to this manuscript.

© 2020 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at https://www.diabetesjournals.org/content/license.

The rising levels of obesity and type 2 diabetes are major global health challenges. Vascular complications (microvascular and macrovascular) are the major causes of morbidity and mortality in patients with type 2 diabetes (1,2).

Worldwide, the cost of health expenditures due to diabetes has increased from U.S. dollars (USD) 232 billion in 2007 to USD 727 billion in 2017 and is estimated to rise further to USD 825 billion by 2030. The major portion of direct cost in diabetes management is spent in managing diabetes-related complications and its consequences (2). The cost of diabetes management had been estimated to be 20 times more in patients with four or more diabetes-related complications compared with patients with diabetes with no complications (2). In the U.K., diabetes accounts for 10% of the National Health Service budget, and 80% of this expense is spent dealing with diabetes-related complications mainly due to prolonged hospital stay, cardiovascular disease (CVD), kidney disease, and neuropathy (3).

Despite improved clinical management of type 2 diabetes over the last two decades, including new classes of glucose-lowering medication (dipeptidyl peptidase 4 inhibitor, sodium–glucose cotransporter 2 [SGLT2] inhibitor, glucagon-like peptide 1 agonist), the reduction in microvascular complications is far less compared with the reductions observed in CVD (4). Diabetes-related foot disease (DFD) is the leading cause for nontraumatic lower limb amputation in the developed world (5), sight-threatening diabetic retinopathy (STDR) is a leading cause of blindness at younger age (6), and diabetic nephropathy is the leading cause of chronic kidney disease (CKD) and end-stage renal disease (7).

Obesity is an established risk factor for type 2 diabetes, hypertension, and hyperlipidemia (8). In addition, obesity is an independent risk factor for CKD (9), peripheral neuropathy (10–12), CVD (13), and mortality (14). A number of studies have shown that intentional weight loss is associated with improvements in glycemic control, blood pressure, hyperlipidemia, and other vascular risk factors (15,16). Among the several interventions for the treatment of obesity, bariatric surgery (BS) provides the most significant and sustainable weight loss and has a favorable impact on glycemic control and other vascular risk factors (17–19). We recently showed that BS in patients with and without type 2 diabetes was associated with a reduction in incident hypertension, CVD, and all-cause mortality compared with routine care (20). Hence, it would be expected that BS may also reduce the incidence of microvascular complications in patients with type 2 diabetes.

Currently, the impact of BS on diabetes-related microvascular complications remains unclear. A meta-analysis of 10 studies (3 randomized controlled trials and 7 controlled studies) involving 17,532 patients found an overall reduction in the incidences of retinopathy and nephropathy, but not neuropathy, in the surgical arm compared with the nonsurgical arm, but there was heterogeneity in findings and in the definition of microvascular outcomes between the studies (21). Hence, there is lack of large, population-based studies examining the impact of BS on individual diabetes-related microvascular outcomes.

Our hypothesis was that BS is associated with a reduction in the incidence of microvascular complications compared with routine care in people with type 2 diabetes and obesity. We therefore conducted a population-based matched controlled cohort study to assess the impact of BS on incident microvascular complications in patients with type 2 diabetes. We also examined the findings stratified by individual bariatric procedures.

RESEARCH DESIGN AND METHODS

Study Design and Data Source

A retrospective matched controlled cohort study using the IQVIA Medical Research Data (IMRD) database was conducted. IMRD is an electronic primary care database that includes longitudinal patient records of >15 million patients, of which 3.7 million are currently active (contributing data to the database). The database covers ~6.2% of the U.K. population and has been shown to be representative of the U.K. demographic structure (22). IMRD contains demographic information, clinical diagnoses, procedures, laboratory results, medications, lifestyle information, and every consultation episode with primary care. IMRD (previously referred as The Health Improvement Network [THIN] database) has previously been used for research related to diabetes and vascular outcomes (23–27) and to assess effectiveness of bariatric surgery (20,28).

Study Population

Primary care practices were eligible for inclusion in the study if they had been using the Vision electronic records system for at least 1 year and had Acceptable Mortality Reporting (an indicator of the practice data quality) for at last 1 year before study entry (29). In addition, study participants must have been registered with an eligible practice for at least 1 year before study entry. The above-mentioned criteria were to ensure data extracted was high quality, with adequate documentation of concomitant diseases and treatments. The surgical cohort was adult patients (≥18 years) with obesity (BMI ≥30 kg/m^2) who had type 2 diabetes and a subsequent record of a primary BS, comprising gastric banding (GB), sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB), or duodenal switch (DS). Each patient with type 2 diabetes who had BS (surgical group) was matched on the index date with up to two patients with type 2 diabetes who did not have BS (nonsurgical group) within the same general practice by age (±2 years), sex, preindex BMI (±2 kg/m^2), and diabetes duration (±3 years). Patients in the surgical group and their corresponding nonsurgical group were excluded from the study if they met any of the following criteria: had a BMI <30 kg/m^2, age >75 years, gastric balloon or endobarrier, or gastric cancer before BS or had been coded as type 1 diabetes (Supplementary Fig. 1).

Follow-up

The index date for the surgical cohort was the date of BS. For the nonsurgical population, the index date was assigned as the corresponding index date of their matched surgical patient to mitigate immortal time bias (30). Eligible participants were monitored from the index date until the earliest occurrence of the following end points: *1*) incidence of the outcome of interest; *2*) death; *3*) patient left the practice; *4*) the practice ceased contributing to the database; or *5*) study end date (31 January 2018).

Outcome Measures

The primary outcome measures were composite microvascular disease, DFD, STDR, and CKD. Outcomes were defined by a rigorous process of clinical Read code selection (31), reviewing them against existing literature, and ratifying through an expert panel of specialists in the field and primary care professionals.

DFD was defined as a composite of foot ulcer, gangrene, deformity, or amputation, moderate/high foot risk, peripheral vascular disease (PVD), or diabetes-related peripheral neuropathy (DPN) according to Read codes in the IMRD database, defined as DFD1. Moderate foot risk was defined as presence of DPN, deformity, or noncritical limb ischemia. High foot risk was defined as previous ulcer, amputation, more than two of the three parameters of DPN, deformity, or PVD (32,33). We considered alternative definitions for DFD in the analysis. DFD2 was defined as any of the components of DFD1, not including PVD/DPN codes. DFD3 was defined as any of the components of DFD2 without including moderate/high foot risk codes. In addition, we explored the risk of incident DPN and PVD separately as secondary outcomes.

STDR was defined as preproliferative retinopathy (R2), proliferative retinopathy (R3), or maculopathy (M1); retinopathy treatment (photocoagulation/vitreous injection); or vision loss (24). In a sensitivity analysis, we excluded vision loss from the outcome definition, because this may have been caused by pathologies other than diabetes such as macular degeneration or cataract.

CKD was defined as estimated glomerular filtration rage (eGFR) $<$60 mL/min/1.73 m^2 or albuminuria (albumin-to-creatinine ratio [ACR] $\geq$3 mg/mmol) (34). In addition, we looked at eGFR $<$30 mL/min/1.73 m^2 and macroalbuminuria (ACR $>$30 mg/mmol) separately. We used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to calculate the eGFR value from the creatinine value (35). In sensitivity analysis, we defined two consecutive values of eGFR $<$60 mL/min/1.73 m^2 and two consecutive ACR $\geq$3 mg/mmol as outcomes. In both analyses, patients who had the outcome measure of interest before the index date were excluded.

All outcomes defined above are assessed annually as part of the Quality and Outcomes Framework (QOF) scheme in primary care and are therefore likely to be accurate; this regular assessment also mitigates surveillance bias (36).

Statistical Analysis

Baseline characteristics are summarized as mean (SD) or median (interquartile range [IQR]) for continuous variables and proportions for categorical variables. Covariates in the adjusted/multivariable model were selected based on biological plausibility. These included age, sex, high BMI, smoking status, ethnicity, social deprivation status, hypertension status, diabetes duration, baseline HbA_{1c}, and medications, including ACE inhibitors, antilipid drugs, and insulin. BMI was categorized as $<$35 kg/m^2, 35–40 kg/m^2, and $>$40 kg/m^2. Smoking was categorized as smoker, nonsmoker, and former smoker. Social deprivation status was represented by the Townsend deprivation quintile, which is based on material deprivation within a population (31). Race/ethnicity was categorized as Caucasian, Afro-Caribbean, south Asian, or mixed. A missing category was used for missing data for BMI, Townsend quintile, smoking status, and race/ethnicity. Hypertension status and medications were handled as binomial variables and age, diabetes duration, and baseline HbA_{1c} as continuous variables.

We calculated crude and adjusted hazard ratios (adjHRs) and 95% CIs for the occurrence (incident) of each outcome of interest in the surgical versus nonsurgical groups using a Cox proportional hazards regression model. Participants with the outcome of interest in the surgical or nonsurgical group at baseline were excluded from the respective analysis. For CKD analysis, we also excluded the patients on renal replacement therapy, defined as a patient with renal transplant or on dialysis at baseline.

The proportional hazards assumption was checked using the Schoenfeld residuals test. We adjusted for biologically plausible confounders as mentioned above.

Stratifying by type of surgery, we analyzed the outcome in participants undergoing GB, SG, and RYGB and their corresponding nonsurgical control group. We did not perform this analysis in the DS subgroup due to small numbers.

We know that beneficial effects of BS on weight loss and glycemic control lessen over time, so we reported the latest weight and HbA_{1c} to avoid inflation of results in favor of surgery. Postsurgical weight was defined as latest weight available for the surgical or nonsurgical group after the index date and before the exit date. Percentage weight loss (%WL) was calculated as

$$\frac{post \quad surgical\ weight\ (latest\ available) \quad baseline\ weight}{baseline\ weight} \times 100$$

For the nonsurgical group who had no surgery, weight change was calculated using latest weight after the index date and baseline weight. Independent sample *t* test was used to compare the %WL in surgical and nonsurgical groups. HbA_{1c} was standardized as a percentage (Diabetes Control and Complications Trial [DCCT] unit). We calculated the change in HbA_{1c} (latest HbA_{1c} available after the index date minus baseline HbA_{1c}) and used the independent sample *t* test to compare the percentage difference between surgical and nonsurgical groups.

We used Nelson-Aalen plots (nonparametric estimator) to present the cumulative hazard function for each outcome over 10-year periods. A two-tailed *P* value $<$0.05 was considered statistically significant. All analyses were conducted using Stata 15 software.

RESULTS

Baseline Characteristics

We included 1,126 surgical and 2,219 nonsurgical participants. Baseline characteristics are summarized in Table 1. Mean (SD) age was 50 (9.3) years, and 2,261 (67.59%) participants were women. Mean (SD) BMI was 46.76 (7.96) kg/m^2 vs. 46.14 (7.49) kg/m^2, and mean (SD) HbA_{1c} was 7.78% (1.82) vs. 7.82% (1.69) for surgical versus nonsurgical participants, respectively. Median (IQR) diabetes duration was 4.72 (2.17–8.93) vs. 4.63 (1.91–8.19) years in surgical versus nonsurgical participants. Most of the study population (88.9% of the surgical and 82.1% of the nonsurgical) was not recorded as active smokers. Insulin was prescribed for 270 surgical (23.98%) versus 315 of the nonsurgical participants (14.20%). The prevalence of microvascular complications at baseline was similar in the surgical and nonsurgical groups.

Table 1—Baseline characteristics of participants in the surgical and nonsurgical groups

	Surgical	Nonsurgical
Population, *n*	1,126	2,219
Age		
Age categories, years, *n* (%)		
<41	171 (15.19)	329 (14.83)
41 60	803 (71.31)	1,568 (70.66)
61 max	152 (13.50)	322 (14.51)
Mean (SD)	49.87 (9.3)	50.12 (9.3)
Sex, *n* (%)		
Male	366 (32.50)	718 (32.36)
Female	760 (67.50)	1,501 (67.64)
BMI categories, kg/m^2, *n* (%)		
<35	57 (5.06)	121 (5.46)
35 39 9	165 (14.65)	344 (15.50)
≥40	901 (80.02)	1,748 (78.77)
Missing	3 (0.27)	6 (0.27)
Mean (SD)	46.76 (7.96)	46.14 (7.49)
Smoker categories, *n* (%)		
Nonsmoker	563 (50.00)	1,189 (53.58)
Smoker	125 (11.10)	395 (17.80)
Former smoker	438 (38.90)	633 (28.53)
Missing	0 (0)	2 (0.09)
Drinker categories, *n* (%)		
Nondrinker	315 (27.98)	625 (28.17)
Drinker	688 (61.10)	1,403 (63.23)
Former drinker	74 (6.57)	92 (4.15)
Missing	49 (4.35)	99 (4.46)
Race/ethnicity, *n* (%)		
Caucasian	620 (55.06)	1,094 (49.30)
Black Afro Caribbean	25 (2.22)	37 (1.67)
South Asian	32 (2.84)	56 (2.52)
Mixed race	7 (0.62)	10 (0.45)
Other	2 (0.18)	9 (0.41)
Missing	440 (39.08)	1,013 (45.65)
Townsend, *n* (%)		
1 (least deprivation <20%)	185 (16.43)	250 (11.27)
2	178 (15.81)	290 (13.07)
3	219 (19.45)	463 (20.87)
4	234 (20.78)	492 (22.17)
5 (most deprived >80%)	160 (14.21)	414 (18.66)
Missing	150 (13.32)	310 (13.97)
Baseline comorbidities		
Mental health conditions, *n* (%)		
Anxiety	310 (27.53)	526 (23.70)
Depression	616 (54.71)	1,001 (45.11)
Cardiovascular diseases, *n* (%)		
Hypertension	620 (55.06)	1,239 (55.84)
Atrial fibrillation	26 (2.31)	47 (2.12)
Heart failure	16 (1.42)	46 (2.07)
Ischemic heart disease	74 (6.57)	165 (7.44)
Stroke/transient ischemic attack	30 (2.66)	70 (3.15)
Obstructive sleep apnea	243 (21.58)	175 (7.89)
Diabetes duration, median (IQR)	4.72 (2.17 8.93)	4.63 (1 91 8.19)
Insulin user, *n* (%)	270 (23.98)	315 (14.20)
Baseline microvascular complications		
Any microvascular complication (DFD3/STDR/CKD)	649 (57.64)	1,220 (54.98)
DFD1	350 (31.08)	633 (28.53)
DFD2	212 (18.83)	371 (16.72)
DFD3	61 (5.42)	106 (4.78)
DPN	155 (13.77)	291 (13.11)
PVD	126 (11.19)	226 (10.18)
STDR	57 (5.06)	151 (6.80)
CKD	481 (42.72)	865 (38.98)

CKD, eGFR <60 mL/min/1.73 m^2 or ACR ≥3; DFD1, ulcer or gangrene or deformity or amputation or moderate/high foot risk or DPN/PVD; DFD2, ulcer or gangrene or deformity or amputation or moderate/high foot risk; DFD3, ulcer or gangrene or deformity or amputation.

Of the 1,126 participants in the surgical group, 249 (22.1%), 255 (22.7%), 610 (52.2%), and 12 (1.1%) patients had GB, SG, RYGB, and DS, respectively.

Weight Change

Data on weight before and after the index date were available for 1,067 surgical (94.8%) and 1,943 nonsurgical (87.6%) participants. Over the median (IQR) follow-up of 2.8 years (1.2–4.9) in the surgical group and 3.4 years (1.5–5.6) in the nonsurgical group, the surgical group achieved a greater mean (SD) %WL of 21.6% (13%) compared with 4.6% (9.7%) in the nonsurgical group.

Participants who underwent surgery lost more weight compared with their matched nonsurgical participants for all surgical procedures: GB, 14.6% (13.9%) vs. 4.6% (10.3%), $P < 0.001$; SG, 20.6% (11.5%) vs. 4.2% (10.1%), $P < 0.001$; RYGB, 25.0% (12.0%) vs. 4.8% (9.1%), $P < 0.001$; and DS, 21.2% (10.8%) vs. 1.7% (9.3%), $P < 0.001$.

Glycemic Control

HbA_{1c} values before and after the index date were available for 1,043 surgical (93%) and 1,958 nonsurgical (88%) participants. Over the median (IQR) follow-up period of 2.6 years (1–4.9) in the surgical group versus 3.1 years (1.2–5.5) in the nonsurgical group, participants in the surgical group achieved a mean reduction in HbA_{1c} of 1.3% (95% CI 1.2–1.5) (14.2 mmol/mol [13.1–16.4]), while in the nonsurgical group, HbA_{1c} increased by 0.2% (95% CI 0.1–0.3) (2.2 mmol/mol [1.1–3.3]). The mean HbA_{1c} reduction difference between the surgical and nonsurgical cohorts was 1.5% (95% CI 1.4–1.7) (16.4 mmol/mol [15.3–18.5]). Participants receiving any of the surgical procedures achieved greater HbA_{1c} reductions compared with the nonsurgical group, with a mean reduction difference of 1% (95% CI 0.7–1.3) (10.9 mmol/mol [7.6–14.2]) in GB, 1.4% (1.1–1.7) (15.3 mmol/mol [12.0–18.5]) in SG, 1.8% (1.6–2.0) (19.6 mmol/mol [17.4–21.8]) in RYGB, and 2.4% (0.8–4.0) (26.2 mmol/mol [8.7–43.6]) in DS.

Composite Microvascular Disease

BS was associated with 47% reduction in the hazard of developing composite microvascular complications versus nonsurgical (adjHR 0.53; 95% CI 0.43–0.66) over the median follow-up period of 2.2 years (IQR 1–4.4).

Analysis based on the type of surgery showed that all types of surgery were associated with favorable impact on the incidence of composite microvascular complications. The adjHRs and follow-up duration in each surgical procedure can be found in Table 2.

Diabetes-Related Foot Disease, Peripheral Neuropathy, and PVD

BS was associated with reduction in the hazards of incidence DFD1 by 39% ($P <$ 0.001). Analysis based on the type of surgery showed that all types of surgery were associated with favorable impact on the incident of DFD1; however, this reached statistical significance only in the RYGB and GB groups but not in the SG group (Table 2). BS was associated with reduction in incidence DFD2 by 37% ($P <$ 0.001) and DPN by 28% (P 0.037). There was nonsignificant reduction in hazards of DFD3 and PVD in the surgical group versus the nonsurgical group in adjusted analysis (Table 3).

STDR

Over the median follow-up of 3.5 years (IQR 1.6–5.7), BS was associated with a 34% reduction in incidence of STDR (P 0.048). In a sensitivity analysis excluding low vision/blindness in the outcome definition, we found a 42% reduction in incidence of STDR in the surgical group compared with the nonsurgical group, (P 0.021) (Table 2). Stratifying by the type of BS showed that there was a statistically significant decrease in incident STDR in the GB cohort versus their nonsurgical counterparts, but no association was observed in the SG or RYGB groups (Table 2).

CKD

Over the median follow-up of 2.7 years (IQR 1.1–4.9), there was a 37% reduction in incident CKD in the surgical group compared with the nonsurgical group ($P <$ 0.001) (Table 2). An examination of the data based on the type of BS showed that all types of surgery were associated with favorable impact on incident CKD, but this was statistically significant in RYGB and SG but not in GB (Table 2).

No significant association was observed between BS and incident eGFR $<$60 mL/min/1.73 m^2 or $<$30 mL/min/1.73 m^2 (Table 4).

Table 2—Incidence of composite microvascular complications and DFD, STDR, and nephropathy in total population and subgroup analyses

	Composite microvascular complications		DFD1		STDR		CKD	
	Surgical	Nonsurgical	Surgical	Nonsurgical	Surgical	Nonsurgical	Surgical	Nonsurgical
Population, *n*	477	999	776	1,586	1,069	2,068	645	1,354
Outcome events, *n* (%)	116 (24.3)	420 (42.0)	125 (16.1)	396 (25.0)	34 (3.2)	96 (4.6)	113 (17.5)	385 (28.4)
Person years	1,478.6	2,768.3	2,681.7	5,271.4	4,014.3	8,205.3	2,108.4	4,378.2
Crude IRR	78.45	151.72	46.61	75.12	8.47	11.7	53.6	87.94
Follow up	2.4 (1 4.4)	2.1 (1 4.3)	3.0 (1.3 5.2)	2.8 (1.3 5.0)	3.3 (1.5 5.5)	3.6 (1.5 5.9)	2.7 (1.1 4.9)	2.7 (1.1 5.0)
Crude HR (95% CI), *P* value	0.52 (0.42 0.64), <0.001		0.62 (0.51 0.76), <0.001		0.72 (0.49 1.07), 0.105		0.61 (0.49 0.75), <0.001	
AdjHR (95% CI), *P* value	0.53 (0.43 0.66), <0.001		0.61 (0.50 0.75), <0.001		0.66 (0.44 1.00), 0.048		0.63 (0.51 0.78), <0.001	
Gastric banding								
Population, *n*	133	240	188	366	240	465	165	308
Outcome events, *n* (%)	49 (36.8)	127 (52.9)	39 (20.7)	119 (32.5)	12 (5.0)	36 (7.7)	51 (30.9)	121 (39.3)
Person years	514.4	845.9	895.3	1,521.9	1,223.4	2,399.5	692.5	1,287.2
Crude IRR	95.25	150.13	43.56	78.19	9.81	15	73.65	94
Follow up	3.5 (1 6.2)	2.7 (1.3 5.6)	4.3 (2 7.2)	3.8 (1.8 6.3)	4.9 (2.3 7.5)	5.2 (2.6 7.5)	4.1 (1.4 6.5)	3.7 (1.8 6.4)
Crude HR (95% CI), *P* value	0.64 (0.46 0.89), 0.008		0.55 (0.39 0.80), 0.001		0.65 (0.34 1.25), 0.194		0.77 (0.55 1.06), 0.112	
AdjHR (95% CI), *P* value	0.65 (0.46 0.91), 0.013		0.53 (0.36 0.78), 0.001		0.49 (0.24 0.99), 0.048		0.77 (0.55 1.09), 0.144	
Sleeve gastrectomy								
Population, *n*	104	206	165	335	241	456	147	283
Outcome events, *n* (%)	21 (20.2)	73 (35.4)	27 (16.4)	76 (22.7)	6 (2.5)	12 (2.6)	17 (11.6)	65 (23)
Person years	299.07	439.21	484.73	926.2	782.32	1,521.87	425.9	756.58
Crude IRR	70.22	166.21	55.7	82.06	7.67	7.89	39.92	85.91
Follow up	2.3 (1 4.0)	1.6 (0.7 3.6)	2.4 (0.9 4.3)	2.3 (1 4.1)	2.8 (1.3 5)	2.8 (1.2 4.9)	2.2 (1 4.2)	2 (0.9 4.0)
Crude HR (95% CI), *P* value	0.45 (0.27 0.73), 0.001		0.69 (0.44 1.07), 0.098		1 (0.376 2.69, 0.989		0.47 (0.27 0.80), 0.005	
AdjHR (95% CI), *P* value	0.49 (0.29 0.83), 0.008		0.70 (0.44 1.11), 0.13		1.41 (0.49 3.99), 0.523		0.52 (0.29 0.91), 0.023	
Gastric bypass								
Population, *n*	236	542	413	869	577	1,123	329	748
Outcome events, *n* (%)	44 (18.6)	220 (40.6)	57 (13.8)	201 (23.1)	16 (2.8)	48 (4.3)	44 (13.4)	197 (26.3)
Person years	656.1	1,446.46	1,277.87	2,775.225	1,978.4	4,206.25	979.26	2,288.854
Crude IRR	67.06	152.1	44.61	72.43	8.087	11.41	44.93	86.07
Follow up	2.2 (1 4.2)	1.9 (0.9 4.1)	2.6 (1.3 4.4)	2.8 (1.3 4.8)	3.0 (1.5 5.0)	3.5 (1.6 5.6)	2.5 (1 4.4)	2.5 (1 4.8)
Crude HR (95% CI), *P* value	0.44 (0.32 0.61), <0.001		0.61 (0.46 0.82), 0.001		0.72 (0.41 1.27), 0.255		0.52 (0.38 0.72), <0.001	
AdjHR (95% CI), *P* value	0.42 (0.30 0.59), <0.001		0.58 (0.43 0.79), 0.001		0.63 (0.35 1.16), 0.137		0.51 (0.36 0.71), <0.001	

AdjHR, adjusted for age, sex, smoking status, baseline BMI category, ethnicity, Townsend quantile, hypertension, diabetes duration, baseline HbA_{1c}, and medications, including ACE inhibitors, antilipid drugs, and insulin. Crude HR, unadjusted HR. DFD1, ulcer/gangrene/deformity/amputation/moderate or high foot risk/peripheral neuropathy/PVD; IRR, incidence rate ratio/1,000 person years.

Table 3—Incidence of DFD2 and DFD3, peripheral neuropathy, and PVD

	DFD2		DFD3		DPN		PVD	
	Surgical	Nonsurgical	Surgical	Nonsurgical	Surgical	Nonsurgical	Surgical	Nonsurgical
Population, *n*	914	1,848	1,065	2,113	971	1,928	1,000	1,993
Outcome events, *n* (%)	147 (16.1)	453 (24.5)	29 (2.7)	64 (3.0)	58 (6.0)	157 (8.1)	29 (3.0)	81 (4.1)
Person years	3,314.8	6,488.0	4,028.9	8,457.09	3,590.71	7,308.73	3,642.73	7,667.25
Crude IRR	44.35	69.82	7.2	7.57	16.15	21.48	7.96	10.56
Follow up	3.3 (1.5 5.4)	3.0 (1.4 5.3)	3.3 (1.6 5.5)	3.6 (1.6 6.0)	3.2 (1.5 5.4)	3.4 (1.5 5.7)	3.2 (1.5 5.4)	3.5 (1.6 5.6)
Crude HR (95% CI), *P* value	0.63 (0.53 0.76), <0.001		0.96 (0.62 1.48), 0.841		0.75 (0.55 1.01), 0.06		0.75 (0.49 1.15), 0.185	
AdjHR (95% CI), *P* value	0.63 (0.52 0.76), <0.001		0.87 (0.55 1.37), 0.538		0.72 (0.52 0.98), 0.037		0.70 (0.45 1.09), 0.113	

AdjHR, adjusted for age, sex, smoking status, baseline BMI category, ethnicity, Townsend quantile, hypertension, diabetes duration, baseline HbA_{1c} and medications, including ACE inhibitors, antilipid drugs and insulin. Crude HR, unadjusted HR. DFD2, amputation/ulcer/gangrene/deformity/moderate/high foot risk; DFD3, amputation/ulcer/gangrene/deformity; IRR, incidence rate ratio/1,000 person years.

There was a 40% reduction in incident albuminuria in the surgical group compared with the nonsurgical group ($P <$ 0.001) and a 64% reduction in macroalbuminuria (P 0.009) (Table 4).

In a sensitivity analysis, the observed association of BS with reduction in incidence microalbuminuria, defined with two consecutive measurements, ACR ≥3 mg/mmol persisted with an adjHR of 0.52 (95% CI 0.37–0.72). But no association of BS and incidence eGFR <60 mL/min/1.73 m^2 (two consecutive results) was found.

Nelson-Aalen Cumulative Hazard Estimates for Study Outcomes

The cumulative hazard estimates for the study outcomes over a 10-year period can be found in Supplementary Fig. 2. The figure illustrates the association between BS and the reduction in incident composite microvascular complications, DFD1, STDR, and CKD. The impact of BS on incident DFD1 and CKD was apparent within the first 2–3 years postsurgery, whereas the impact on STDR took longer to become apparent (5–6 years).

Table 4—Incidence of eGFR <60 mL/min per 1.73 m^2, eGFR <30 mL/min per 1.73 m^2, ACR ≥3 mg/mmol, and ACR >30 mg/mmol and sensitivity analysis

	eGFR		ACR	
	Surgical	Nonsurgical	Surgical	Nonsurgical
Population, *n*	963	1,931	737	1,510
	eGFR <60		ACR ≥3	
Outcome events, *n* (%)	67 (6.96)	174 (9.01)	109 (14.79)	372 (24.64)
Person years	3,482.7	7,405.5	2,525.8	5,001.2
Crude IRR	19.24	23.5	43.16	74.38
Follow up	3.4 (1.5 5.5)	3.5 (1.5 5.6)	2.9 (1.3 5.5)	2.8 (1.1 5.1)
Crude HR (95% CI), *P* value	0.82 (0.62 1.1), 0.181		0.58 (0.47 0.72), <0.001	
AdjHR (95% CI), *P* value	0.81 (0.62 1.11), 0.21		0.60 (0.48 0.75), <0.001	
	eGFR <30		ACR >30	
Outcome events, *n* (%)	8 (0.8)	28 (1.5)	8 (1.1)	48 (3.2)
Person years	3,693.9	7,826.8	2,907.4	6,200.2
Crude IRR	18.14	22.23	2.75	7.74
Follow up	3.7 (1.7 6.0)	3.7 (1.7 6.0)	3.5 (1.6 5.7)	3.8 (1.6 6.1)
Crude HR (95% CI), *P* value	0.63 (0.29 1.37), 0.242		0.36 (0.17 0.76), 0.007	
AdjHR (95% CI), *P* value	0.74 (0.32 1.70), 0.48		0.36 (0.17 0.77), 0.009	
Sensitivity analysis	Two consecutive eGFR <60		Two consecutive ACR ≥3	
Population, *n*	963	1,931	924	1,795
Outcome events, *n* (%)	67 (7.0)	174 (9.0)	46 (5.0)	168 (9.4)
Person years	3,482.7	7,405.5	3,419.7	6,675.1
Crude IRR	19.24	23.50	13.45	25.17
Follow up	3.2 (1.5 5.3)	3.5 (1.4 5.6)	3.3 (1.5 5.4)	3.3 (1.4 5.6)
Crude HR (95% CI), *P* value	0.83 (0.62 1.09), 0.181		0.53 (0.39 0.74), <0.001	
AdjHR (95% CI), *P* value	0.83 (0.62 1.11), 0.21		0.52 (0.37 0.72), <0.001	

AdjHR, adjusted for age, sex, smoking status, baseline BMI category, ethnicity, Townsend quantile, hypertension, diabetes duration, baseline HbA_{1c} and medications, including ACE inhibitors, antilipid drugs and insulin; Crude HR, unadjusted HR; IRR, incidence rate ratio/1,000 person years.

CONCLUSIONS

Our study provides real-world population-based data showing that BS was associated with significant reduction in incident composite microvascular complications, DFD, STDR, CKD, and DPN, in patients with type 2 diabetes compared with routine care, after accounting for many potential confounders. The association between BS and the reduction in incident STDR took longer to become apparent compared with the other microvascular complications (Supplementary Fig. 2). In addition, BS was associated with greater reductions in weight and HbA_{1c} compared with routine care during the follow-up, with the greatest reductions observed in the RYGB and DS groups.

Our results are similar to other published findings but add novel aspects. Our group previously showed in single-center matched controlled studies that over 3 years, BS was associated with less eGFR decline (37) and incident maculopathy (38) compared with routine care; but these studies were of a small sample size, from a single center, and with a limited number of patients.

Sheng et al. (39) also showed that BS was associated with lower risk of incident composite microvascular complications in a systematic review, but unlike our study, there were no results based on individual microvascular complications.

The Swedish Obese Subject (SOS) study, a prospective matched controlled intervention study, showed a reduction in the incidence rate of composite microvascular complications in patients who had undergone BS (*n* 343) compared with controls (*n* 260) (18). However, there were limitations in that the majority surgical procedure performed was vertical gastroplasty, mean (±SD) diabetes duration in surgical group was short (2.9 ± 4.7 years), and there was no assessment of individual microvascular outcomes. In addition, the SOS study started before many of the current type 2 diabetes interventions were established (such as the use of statins and ACE inhibitors/angiotensin receptor blockers).

Another study from the U.S., with a design similar to our study, based on four integrated health systems, found that BS was associated with reduction in incident retinopathy, nephropathy, and neuropathy (40). This study did not examine the impact of BS on STDR, and the impact on nephropathy was measured only using eGFR and not albuminuria.

After BS, patients show a decrease in fat mass as well as a loss of lean mass, including muscle mass (41,42). Therefore, it is difficult to differentiate whether change in creatinine level and creatinine-based eGFR is indicative of true improvement in renal function. However, in our study, the association between surgery and reduction in incident CKD was mainly driven by a reduction in albuminuria, which is not affected by loss of muscle mass.

In another study of similar design from Denmark, RYGB was associated with a reduction in the incidence of microvascular complications (CKD, retinopathy, and neuropathy), similar to what we observed in our study (HR 0.53, 95% CI 0.38–0.73) (43). But in that study, they did not report the outcomes of individual microvascular complications, and our study adjusted for more variables in the Cox regression analysis (such as the Townsend social deprivation index).

The Longitudinal Assessment of Bariatric Surgery (LABS) Study examined the impact of RYGB and GB over a follow-up period of up to 7 years and found beneficial effect on weight loss, diabetes, and hypertension status (44). While this was a study conducted in general population with obesity, our study was specifically focused on people with type 2 diabetes and reported on comprehensive outcomes of multiple vascular complications.

The Teen-LABS study specifically reported the impact of BS on CKD in adolescents with type 2 diabetes with a sample size of 30. No other microvascular complications were analyzed (45). Our study was specific in adults, included multiple bariatric procedures, had a larger sample size, and reported on DFD and STDR.

We recently used the IMRD database to show that BS was associated with a reduction in incident CVD, hypertension, and mortality in patients with and without diabetes (20). Taken together with the findings of this study, this suggests that BS can play an important role in reducing the burden of type 2 diabetes by reducing the incidence of hypertension, CVD, microvascular disease, and mortality as well as resulting in significant improvements in weight and glycemic control. These benefits were observed despite that more patients in the surgical group had insulin treatment at baseline. Furthermore, in addition to reducing the personal burden of type 2 diabetes, the observed potential benefits are likely to have significant savings in health care costs considering the high cost of diabetes-related macro- and microvascular complications (3). Despite these potential benefits in people with type 2 diabetes, access to BS is limited in most Western health care systems, and improving access to BS in patients with type 2 diabetes might therefore have positive implications for diabetes care (46).

There are several plausible mechanisms for the observed beneficial effects of BS on incident microvascular complications. It is likely that BS exerts its beneficial effects by improving the established risk factors for microvascular complications, including weight, HbA_{1c}, blood pressure, lipids, and CVD (19,47,48). In addition, recent data suggest that BS can result in SGLT2 inhibition (49), and several studies previously showed that BS is associated with increased incretin and GLP-1 responses (50). These could contribute to the improved vascular outcomes after BS considering the latest cardiovascular outcomes trials in type 2 diabetes showing that GLP-1 receptor agonists and SGLT2 inhibitors can reduce CVD and CKD (51–53).

We managed to conduct subgroup analysis by type of procedure, which added novelty to our study. We showed that all types of surgery included in this study were associated with a reduction in the incidence of composite microvascular complications versus the nonsurgical arm. However, there was some variation in the relationship between the type of surgery and individual microvascular outcomes. GB had a favorable impact on DFD and STDR but not CKD, SG had a favorable impact on CKD only, and RYGB had a favorable impact on CKD and DFD but not STDR. These observations are not fully understood as yet and require further evaluation.

We could not find any studies comparing the impact of different bariatric procedures on microvascular diseases as we did in our study. The systematic review by Billeter et al. (21) showed that only three studies included all types of surgery in same study (18,38,54). However, none of these articles reported the outcomes based on type of surgery, and only the Johnson et al. (54) article reported individual microvascular complications, and again, no subgroup analysis by types of surgery was reported.

Limitations and Strengths

The main limitation of our study is its observational nature, and hence, causation cannot be proven. However, we used matching and extensive adjustments to account for confounding. Participants with the outcome of interest at baseline were excluded from the analysis due to methodological considerations. Therefore, any effect of BS in patients who already have microvascular complications requires future research. C-peptide data were not available in our study data set because it is not yet a routine care test in the U.K.; however, we included the information on diabetes duration and baseline insulin use and adjusted our outcomes for these variable. We had a short follow-up period duration.

Our study has several strengths: we used a validated primary care data source (the IMRD database) and used previously by our team (23–27) and other researchers to explore similar outcomes (55,56). Using IMRD allowed us to include a large sample size, matched with a nonsurgical sample, and adjust for several covariates, improving the generalizability of our findings. Furthermore, the outcomes

of our study were measured as part of the QOF annually, ensuring consistency in definitions and militating against detection bias.

Conclusion

BS was associated with a reduction in microvascular complications, including DFD, STDR, CKD, and DPN, in patients with type 2 diabetes and obesity. Improving access to BS could reduce the burden of type 2 diabetes, and access to surgery needs to be improved.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.
Author Contributions. P.S. designed and performed the analysis. P.S. wrote the first draft of the paper. P.S., A.S., K.N., and A.A.T. contributed to the data analysis and interpretation. P.S. and K.N. had full access to all the data in the study. P.S., K.N., and A.A.T. had the original idea for the study. P.S., K.N., and A.A.T. designed the study. P.S., K.N., and A.A.T. affirm that the manuscript is an honest, accurate, and transparent account of the study being reported. N.A., A.S., and K.N. reviewed the analysis. N.A., K.G., R.S., K.A.T., S.B., K.N., and A.A.T. revised and edited the first draft of the paper. K.G. undertook data extraction. P.S. and K.N. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Prior Presentation. Parts of this study were presented as oral presentation at the NeuroDiab conference at the 55th Annual Meeting of the European Association for the Study of Diabetes, Barcelona, 16 20 September 2019. A part was also presented in the EASD virtual meeting, 22 25th September 2020.
Ethics. Use of IMRD is approved by the UK Research Ethics Committee (reference number: 18/LO/0441). In accordance with this approval, the study protocol was reviewed and approved by an independent Scientific Review Committee (SRC) (in January 2019, reference number: 18THIN097). IMRD incorporates data from The Health Improvement Network (THIN), a Cegedim Database. Reference made to THIN is intended to be descriptive of the data asset licensed by IQVIA. This work used deidentified data provided by patients as a part of their routine primary care.
Copyright Statement. THIN is a registered trademark of Cegedim SA in the U.K. and other countries. Reference made to the THIN database is intended to be descriptive of the data asset licensed by IQVIA.

References

1. Fowler MJ. Microvascular and macrovascular complications of diabetes. Clin Diabetes 2008;26: 77 82
2. International Diabetes Federation. IDF Diabetes Atlas, 9th edition, 2019. Accessed 16 July 2020. Available from https://www.diabetesatlas.org/en/resources/
3. Diabetes UK. The Cost of Diabetes, 2014. Accessed 19 March 2020. Available from https://www.diabetes.org.uk/resources s3/2017 11/diabetes% 20uk%20cost%20of%20diabetes%20report.pdf
4. Gregg EW, Li Y, Wang J, et al. Changes in diabetes related complications in the United States, 1990 2010. N Engl J Med 2014;370: 1514 1523
5. Boulton AJM, Vileikyte L, Ragnarson Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet 2005;366:1719 1724
6. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet 2010;376:124 136
7. Afkarian M, Zelnick LR, Hall YN, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988 2014. JAMA 2016; 316:602 610
8. Wild SH, Byrne CD. Risk factors for diabetes and coronary heart disease. *BMJ* 2006;333: 1009 1011
9. Hsu C y, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass index and risk for end stage renal disease. Ann Intern Med 2006;144:21 28
10. Hozumi J, Sumitani M, Matsubayashi Y, et al. Relationship between neuropathic pain and obesity. Pain Res Manag 2016;2016:2487924
11. Miscio G, Guastamacchia G, Brunani A, Priano L, Baudo S, Mauro A. Obesity and peripheral neuropathy risk: a dangerous liaison. J Peripher Nerv Syst 2005;10:354 358
12. Tesfaye S, Selvarajah D. The Eurodiab study: what has this taught us about diabetic peripheral neuropathy? Curr Diab Rep 2009;9:432 434
13. Poirier P, Giles TD, Bray GA, et al.; American Heart Association; Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation 2006;113: 898 918
14. Abdelaal M, le Roux CW, Docherty NG. Morbidity and mortality associated with obesity. Ann Transl Med 2017;5:161
15. Ryan DH, Yockey SR. Weight loss and improvement in comorbidity: differences at 5%, 10%, 15%, and over. Curr Obes Rep 2017;6:187 194
16. Wing RR, Espeland MA, Clark JM, et al.; Action for Health in Diabetes (Look AHEAD) Study Group. Association of weight loss maintenance and weight regain on 4 year changes in CVD risk factors: the Action for Health in Diabetes (Look AHEAD) clinical trial. Diabetes Care 2016;39: 1345 1355
17. Schauer PR, Mingrone G, Ikramuddin S, Wolfe B. Clinical outcomes of metabolic surgery: efficacy of glycemic control, weight loss, and remission of diabetes. Diabetes Care 2016;39: 902 911
18. Sjöstrom L, Peltonen M, Jacobson P, et al. Association of bariatric surgery with long term remission of type 2 diabetes and with microvascular and macrovascular complications. JAMA 2014;311:2297 2304
19. Ricci C, Gaeta M, Rausa E, Asti E, Bandera F, Bonavina L. Long term effects of bariatric surgery on type II diabetes, hypertension and hyperlipidemia: a meta analysis and meta regression study with 5 year follow up. Obes Surg 2015; 25:397 405
20. Singh P, Subramanian A, Adderley N, et al. Impact of bariatric surgery on cardiovascular outcomes and mortality: a population based cohort study. Br J Surg 2020;107:432 442
21. Billeter AT, Scheurlen KM, Probst P, et al. Meta analysis of metabolic surgery versus medical treatment for microvascular complications in patients with type 2 diabetes mellitus. Br J Surg 2018;105:168 181
22. THIN HES Privacy Notice, 2019. Accessed 19 March 2020. Available from https://www.hra.nhs.uk/planning and improving research/application summaries/research summaries/the health improvement network thin database/
23. Hall GC, McMahon AD, Carroll D, Home PD. Observational study of the association of first insulin type in uncontrolled type 2 diabetes with macrovascular and microvascular disease. PLoS One 2012;7:e49908
24. Subramanian A, Adderley NJ, Tracy A, et al. Risk of incident obstructive sleep apnea among patients with type 2 diabetes. Diabetes Care 2019;42:954 963
25. Toulis KA, Willis BH, Marshall T, et al. All cause mortality in patients with diabetes under treatment with dapagliflozin: a population based, open cohort study in The Health Improvement Network Database. J Clin Endocrinol Metab 2017;102:1719 1725
26. Daly B, Toulis KA, Thomas N, et al. Increased risk of ischemic heart disease, hypertension, and type 2 diabetes in women with previous gestational diabetes mellitus, a target group in general practice for preventive interventions: a population based cohort study [published correction appears in PLoS Med 2019;16:e1002881]. PLoS Med 2018;15: e1002488
27. Toulis KA, Hanif W, Saravanan P, et al. All cause mortality in patients with diabetes under glucagon like peptide 1 agonists: a population based, open cohort study. Diabetes Metab 2017; 43:211 216
28. Alkharaiji M, Anyanwagu U, Donnelly R, Idris I. Effect of bariatric surgery on cardiovascular events and metabolic outcomes in obese patients with insulin treated type 2 diabetes: a retrospective cohort study. Obes Surg 2019;29: 3154 3164
29. Maguire A, Blak BT, Thompson M. The importance of defining periods of complete mortality reporting for research using automated data from primary care. Pharmacoepidemiol Drug Saf 2009;18:76 83
30. Suissa S. Immortal time bias in pharmacoepidemiology. Am J Epidemiol 2008;167:492 499
31. NHS Digital. Read Codes NHS Digital, Retirement of Read Version 2 and Clinical Terms Version 3, 2018. Accessed 19 March 2020. Available from https://digital.nhs.uk/services/terminology and classifications/read codes
32. Internal Clinical Guidelines Team. *Diabetic Foot Problems: Prevention and Management*. London, U.K., National Institute for Health and Care Excellence, 2015
33. Leese G, Schofield C, McMurray B, et al. Scottish foot ulcer risk score predicts foot ulcer healing in a regional specialist foot clinic. Diabetes Care 2007;30:2064 2069
34. NICE C. Chronic kidney disease NICE CKS 2019. Accessed 9 February 2020. Available from:

https://cks.nice.org.uk/topics/chronic kidney disease/
35. CKD EPI Adults (Conventional Units) | NIDDK 2019 Accessed 9 February 2020. Available from: https://www.niddk.nih.gov/health information/professionals/clinical tools patient management/kidney disease/laboratory evaluation/glomerular filtration rate calculators/ckd epi adults conventional units
36. National Institute for Health and Care Excellence. Quality and Outcomes Framework Indicators: Standards and Indicators, 2019. Accessed 19 March 2020. Available from https://www.nice.org.uk/standards and indicators/qofindicators?categories &page 2
37. Mirajkar N, Bellary S, Ahmed M, Singhal R, Daskalakis M, Tahrani AA. The impact of bariatric surgery on estimated glomerular filtration rate in patients with type 2 diabetes: a retrospective cohort study. Surg Obes Relat Dis 2016;12:1883 1889
38. Amin AM, Wharton H, Clarke M, Syed A, Dodson P, Tahrani AA. The impact of bariatric surgery on retinopathy in patients with type 2 diabetes: a retrospective cohort study. Surg Obes Relat Dis 2016;12:606 612
39. Sheng B, Truong K, Spitler H, Zhang L, Tong X, Chen L. The long term effects of bariatric surgery on type 2 diabetes remission, microvascular and macrovascular complications, and mortality: a systematic review and meta analysis. Obes Surg 2017;27:2724 2732
40. O'Brien R, Johnson E, Haneuse S, et al. Microvascular outcomes in patients with diabetes after bariatric surgery versus usual care: a matched cohort study. Ann Intern Med 2018;169:300 310
41. Zalesin KC, Franklin BA, Lillystone MA, et al. Differential loss of fat and lean mass in the morbidly obese after bariatric surgery. Metab Syndr Relat Disord 2010;8:15 20
42. Carey DG, Pliego GJ, Raymond RL. Body composition and metabolic changes following bariatric surgery: effects on fat mass, lean mass and basal metabolic rate: six months to one year follow up. Obes Surg 2006;16:1602 1608
43. Madsen LR, Baggesen LM, Richelsen B, Thomsen RW. Effect of Roux en Y gastric bypass surgery on diabetes remission and complications in individuals with type 2 diabetes: a Danish population based matched cohort study. Diabetologia 2019;62:611 620
44. Courcoulas AP, King WC, Belle SH, et al. Seven year weight trajectories and health outcomes in the Longitudinal Assessment of Bariatric Surgery (LABS) study. JAMA Surg 2018;153:427 434
45. Bjornstad P, Hughan K, Kelsey MM, et al. Effect of surgical versus medical therapy on diabetic kidney disease over 5 years in severely obese adolescents with type 2 diabetes. Diabetes Care 2020;43:187 195
46. Borisenko O, Colpan Z, Dillemans B, Funch Jensen P, Hedenbro J, Ahmed AR. Clinical indications, utilization, and funding of bariatric surgery in Europe. Obes Surg 2015;25:1408 1416
47. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta analysis [published correction appears 2in JAMA 2005;293:1728]. JAMA 2004;292:1724 1737
48. Brix JM, Herz CT, Kopp HP, et al. Albuminuria in patients with morbid obesity and the effect of weight loss following bariatric surgery. Obes Surg 2019;29:3581 3588
49. Akalestou E, Noriega LL, Chabosseau PL, Leclerc I, Rutter GA. 161 LB: Inhibition of kidney SGLT2 expression following bariatric surgery in mice (Abstract). Diabetes 2019;68(Suppl. 1)
50. Cummings DE, Overduin J, Shannon MH, Foster Schubert KE; 2004 ABS Consensus Conference. Hormonal mechanisms of weight loss and diabetes resolution after bariatric surgery. Surg Obes Relat Dis 2005;1:358 368
51. Marso SP, Bain SC, Consoli A, et al.; SUSTAIN 6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834 1844
52. Marso SP, Daniels GH, Brown Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311 322
53. Zinman B, Wanner C, Lachin JM, et al.; EMPA REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117 2128
54. Johnson BL, Blackhurst DW, Latham BB, et al. Bariatric surgery is associated with a reduction in major macrovascular and microvascular complications in moderately to severely obese patients with type 2 diabetes mellitus. J Am Coll Surg 2013;216:545 556; discussion 556 558
55. Guest JF, Fuller GW, Vowden P. Diabetic foot ulcer management in clinical practice in the UK: costs and outcomes. Int Wound J 2018;15:43 52
56. Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study [published correction appears in BMJ Open 2016;6:e010210corr1]. BMJ Open 2016;6:e010210

Chapter 6: Glycaemic outcomes in patients with type 2 diabetes following bariatric surgery

6.1 Contents of chapter 6

Despite the development of several new classes of glucose lowering pharmacotherapy like sodium-glucose transport-2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) agonists), only half of patients achieve HbA1c targets of < 7.0%.(1)

Weight loss had been associated with increased insulin sensitivity and improved glycaemic control in patients with obesity and type 2 diabetes. There is now good evidence to show that therapeutic approaches targeting weight loss have a beneficial effect on glycaemic control. The DiRECT trial showed that at 1 year after dietary intervention, 45.6% patients achieved diabetes remission (defined as HbA1c ≤ 6.5%, off glucose lowering medication) (2). Bariatric surgery offering significant and sustained weight loss has shown superior effect over medical treatment for achieving good glycaemic control, reduction in insulin requirements and glucose lowering treatments and diabetes remission (3-6).

The International Diabetes Federation (IDF) has acknowledged bariatric surgery as safe, effective and appropriate treatment option in patients with type 2 diabetes and obesity (7). Bariatric surgery had been accepted as a management option in patients with obesity and poorly controlled diabetes in national and international guidelines (8, 9). In this chapter, I have presented the impact of bariatric surgery on glycaemic status and glucose lowering medications from real-world data.

6.2 References

1. Edelman SV, Polonsky WH. Type 2 Diabetes in the Real World: The Elusive Nature of Glycemic Control. 2017.
2. Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet. 2018;391(10120):541-51.
3. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Aminian A, Brethauer SA, et al. Bariatric Surgery versus Intensive Medical Therapy for Diabetes - 5-Year Outcomes. N Engl J Med. 2017;376(7):641-51.
4. Mingrone G, Guidone C, Iaconelli A, Nanni G, Castagneto M, Panunzi S, et al. Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 Year follow-up of an open-label, single-centre, randomised controlled trial. The Lancet. 2015;386(9997):964-73.
5. SinghP, SubramaniaA, AdderleyN, GokhaleK, SinghalR, BellaryS, et al. Impact of Bariatric Surgery on Cardiovascular Outcomes and Mortality: A Population-Based Cohort Study. The British journal of surgery. 2020;107(4):432- 42.
6. Courcoulas Anita P, Belle Steven H, Neiberg Rebecca H, Pierson Sheila K, Eagleton Jessie K, Kalarchian Melissa A, et al. Three-Year Outcomes of Bariatric Surgery vs Lifestyle Intervention for Type 2 Diabetes Mellitus Treatment: A Randomized Clinical Trial. JAMA surgery. 2015;150(10):931-40.
7. JB D, P Z, KG A, F R, Baker IDI Heart and Diabetes Institute CR, Melbourne, Victoria, Australia., Dixon JB, et al. Bariatric surgery: an IDF statement for obese Type 2 diabetes. 2011.
8. ADA. STANDARDS OF MEDICAL CARE IN DIABETES—2020. The Journal of Clinical and Applied Research and Education. 2019;38(1).
9. 189 NgC. Obesity: identification, assessment and management | Guidance and guidelines | NICE. 2014.

6.3 Manuscript 3: Glycaemic outcomes in patients with type 2 diabetes following bariatric surgery

Singh P, Adderley N.J., Subramanian A., Gokhale K., Hazlehurst J, Singhal R., Bellary S., Tahrani A.A., Nirantharakumar K. Glycaemic outcomes in patients with type 2 diabetes following bariatric surgery: a population-based real-world UK cohort study

under peer review

6.3.1 Abstract

Background: Clinical trials have shown that bariatric surgery resulted in greater glycaemic control and diabetes remission in patients with type 2 diabetes compared to routine medical treatment. However, real-world studies are limited. We conducted a population-based study examining the impact of bariatric surgery on glycaemic control and medication use in patients with type 2 diabetes.

Methods: A retrospective matched, controlled cohort study between 1/1/1990 and 31/1/2018 using the IQVIA Medical Research Data (IMRD-UK) primary care electronic records database. Adults with a BMI ≥ 30 kg/m^2 and type 2 diabetes who had bariatric surgery (exposure) were matched for age, sex, body mass index (BMI) and diabetes duration to two controls with type 2 diabetes who had not had bariatric surgery.

Results: 1126 patients in the surgical and 2219 patients in the control group were analysed. For study cohort, mean (SD) age was 50.0 (9.3) years, 67.6% were women, and median (IQR) follow-up was 3.6 (1.7- 5.9) years. The median diabetes duration was 4.7 (2.2- 8.9) years vs 4.6 (1.9- 8.2) years and glycated haemoglobin (HbA1c) was 7.78% (1.82) and 7.82% (1.69) in the surgical and control groups, respectively.

A significantly higher proportion of patients in the surgical group achieved HbA1c of ≤ 6.0% than the control group (65.8% vs 22.8%). The surgical group showed a decrease in mean HbA1c of 1.5% (95% CI 1.4 to 1.7), 1.4% (95% CI 1.2 to 1.5) and 1.3% (95% CI 1.1 to 1.5) between baseline and 1-, 2- and 3-years' follow-up, respectively, while mean HbA1c increased between baseline and each year of follow-up in the control group. The proportion

of patients receiving glucose lowering medications decreased from baseline to study end in the surgical group (92.2% to 66.5%) but increased in the control group (85.3% to 90.2%). Conclusions: Bariatric surgery is associated with a significant improvement in glycaemic control, greater achievement of normal HbA1c and reduced need for glucose lowering therapy in patients with type 2 diabetes in a real-world setting.

6.3.2 Backgrounds

Improving glycaemic control and achieving diabetes remission are important treatment aims in patients with type 2 diabetes. Long term intensive glycaemic control to reduce diabetes-related complications has been the cornerstone of diabetes management. Epidemiological studies have shown that a 1% reduction in HbA1c is associated with a 21% decrease in deaths related to diabetes, a 14% decrease in myocardial infarction and a 37% decrease in risk of microvascular complications over a median of 10 years' follow-up (1). Reduction in HbA1c has also been associated with a 24% decrease in annual average healthcare cost in the first year and a 17% decrease in the second year compared to patients who did not achieve HbA1c reduction (2).

Despite the development of several new classes of glucose lowering pharmacotherapy, only half of patients with type 2 diabetes achieve HbA1c targets of < 7.0% (53mmol/mol) and 64% are estimated to be achieving individualised glycaemic targets (3). From the annual National Diabetes Audit (NADIA) in the UK, the percentage of patients achieving HbA1c ≤ 7.5% (58 mmol/mol) was 65.8% in 2011-12 and 66.8% in 2017-18 (4). Hence, further treatment strategies to improve the achievement of glycaemic targets are needed. Weight loss is an important treatment strategy that can have a significant impact on glycaemic control, as

shown by the DiRECT and LookAHEAD trials that utilised very low energy diet and intensive lifestyle interventions respectively (5, 6).

Bariatric surgery is the most successful weight loss treatment in the short and long term (7, 8). Several RCTs have also shown that bariatric surgery in people with type 2 diabetes is associated with significant improvements in glycaemic control, reduction in insulin requirements and glucose lowering treatments, and diabetes remission. (9-11). However, the uptake and accessibility of bariatric surgery in patients with type 2 diabetes remains low; in Europe, the number of bariatric surgeries per one million population was only 72 in Germany and 117 in England (12, 13). Hence, it is important to examine the impact of bariatric surgery on glycaemic outcomes in a real world setting, especially given that real world studies have shown bariatric surgery was associated with a reduction in incident cardiovascular disease, microvascular complications, and mortality in patients with and without type 2 diabetes (14, 15).

Here we aimed to assess the impact of bariatric surgery on glycaemic control and the use of glucose lowering medications in patients with obesity and type 2 diabetes who underwent bariatric surgery compared to routine care in a real-world UK setting.

6.3.3 Methods

6.3.3.1 Study design and data source

We conducted a retrospective cohort study between 1/1/1990 and 31/1/2018 utilising the IQVIA Medical Research Data (IMRD-UK) database. The IMRD database uses de-identified data of over 15 million patients collected as a part of their routine primary care, covering

nearly 6% of the UK population at a given time point (16). It contains information on patient demographics, treatments, physical measurements, laboratory results, symptoms, and medical diagnoses. This database is specifically suitable for research relevant to conditions that are part of the Quality and Outcomes Framework (QOF), including type 2 diabetes, as the QOF scheme incentivizes primary care physicians for identification and management of these conditions, and so they are well recorded (17).

Practices were eligible for inclusion from a year after installation of electronic medical records software and achieving acceptable mortality reporting, a measure of data quality (18). Patients registered with an eligible practice for at least one year were eligible for inclusion to ensure completeness of data.

6.3.3.2 Study population

We included patients aged 18 to 75 years with type 2 diabetes. The surgical cohort was defined as patients with type 2 diabetes who underwent primary bariatric surgery [gastric banding (GB), sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB), or duodenal switch (DS)] during the study period. Every patient in the exposed cohort was matched with up to 2 control patients (type 2 diabetes but who did not undergo bariatric surgery) within the same general practice for age (± 2 years), sex, body mass index (BMI, ±2 kg/m^2) and diabetes duration (±3 years).

The date of bariatric surgery was assigned as the index date for exposed patients and the same date was assigned as index date to their matched control patients in order to minimise immortal time bias (19).

Patients in the surgical group along with their controls were excluded from the study if they met any of the following criteria at baseline: BMI < 30 kg/m^2, age > 75 years, prior record of gastric cancer, prior record of gastric balloon/endo-barrier/revisional bariatric surgery. Eligible participants were followed up from the index date until the earliest occurrence of the following end points: a) record of target HbA1c (outcome (2) as defined below); b) death; c) patient left the practice; d) the practice ceased contributing to the database; and e) study end date (31/1/2018).

6.3.3.3 Outcome measures

The main outcomes of our study were: (1) mean change in HbA1c from baseline (yearly for up to 3 years); (2) attainment or maintaining of glycaemic targets, defined as HbA1c ≤ 6.0% (42mmol/mol), ≤ 6.5% (48mmol/mol) and ≤ 7% (53mmol/mol) (9, 20), irrespective of their baseline HbA1c and use of glucose lowering medication; and (3) number and type of glucose lowering medications being used after bariatric surgery. We also assessed percentage weight loss in surgical and control group.

6.3.3.4 Statistical analysis

For outcome (1), HbA1c is expressed as a percentage (Diabetes Control and Complications Trial, DCCT unit). Change in HbA1c was defined as the difference between latest available HbA1c in each year after the index date (up to 3 years) and the baseline HbA1c. We disregarded HbA1c readings available within 28 days of index date as HbA1c measurements within 28 days of surgery may be the result of short-term effects of surgery. We used the independent sample t-test to compare change in HbA1c in the surgical and control groups.

For the analysis of outcome (2), achieving target HbA1c, we used Cox proportional hazards regression analysis and calculated unadjusted and adjusted hazard ratios (HR) among patients who underwent bariatric surgery compared to their matched controls for each of the 3 glycaemic targets. For our study, we assessed achieving or maintaining glycaemic targets of ≤7% (53 mmol/mol), ≤ 6.5% (48mmol/mol) and ≤6 % (42 mmol/mol) based on earliest date after index date irrespective of baseline HbA1c and glucose lowering medications, as per the recommendations by ADA, NICE and studies examining diabetes remission after bariatric surgery (9, 20, 21). The proportional hazards assumption was checked using the Schoenfeld residuals test. The analysis was repeated in subsets of patients based on their insulin use status at baseline and the type of bariatric surgery they underwent.

For outcome (3), glucose lowering medications included metformin, sulphonylurea, glinides, acarbose, thiazolidinediones, dipeptidyl peptidase 4 (DPP4) inhibitors, sodium-glucose transport-2 (SGLT2) inhibitors, glucagon-like peptide 1 (GLP-1) agonists, and insulin. The proportion of patients who were prescribed each of these drugs at any time point before and after index date (pre- and post-surgery in the surgical group) are presented graphically drugs.

We also assessed the number of glucose-lowering medications pre- and post-bariatric surgery in the surgical and control groups. The number of glucose-lowering medications was categorised as no medication, monotherapy (one medication), dual therapy (two medications) and polypharmacy (≥ 3 medications).

Percentage weight loss (%WL) was calculated as change in weight (post-surgical weight defined as the latest available data after the index date - baseline weight) / baseline weight

× 100. For the control group who had no surgery, weight change was calculated using a similar formula.

A two-tailed p-value <0.05 was considered statistically significant. All analyses were conducted using Stata version 15.

Covariates in the adjusted/multivariable model were selected based on biological plausibility and these included: age, sex, baseline BMI, ethnicity, social deprivation status, baseline HbA1c, diabetes duration and insulin use. BMI was categorised as < 35 kg/m^2, 35-40 kg/m^2 and > 40 kg/m^2. Social deprivation status was represented by Townsend deprivation quintile which is based on material deprivation within a population. Ethnicity was categorised as White, Afro-Caribbean, South Asian and mixed. A missing category was used for missing data for BMI, Townsend quintile and ethnicity. Baseline HbA1c and diabetes duration were treated as continuous variables and insulin use as a binary variable.

6.3.4 Results

6.3.4.1 Baseline characteristics

The baseline characteristics of the 3345 participants included are summarised in Table 1. For the whole cohort, the mean age was 50 (9.3) years. Two thirds of the participants in the study (67.59%) were female. Baseline HbA1c was available for 1117 (99.2%) patients in surgical and 2184 (98.4%) in control group. The mean baseline HbA1c was similar in both groups (7.8%), but more participants in the surgical group were prescribed insulin compared to the control group (270 (23.98%) vs 315 (14.20%)). The median follow-up was 3.4 years (1.6- 5.6) years in the surgical group and 3.7 (1.7- 6.1) years in the control group. Out of 1126

participants in surgical group, 249 (22.1%), 255 (22.7%), 610 (52.2%) and 12 (1.1%) of patients had GB, SG, RYGB and DS, respectively.

Table 1: Baseline characteristics of participants in surgical and non-surgical groups

	Exposed	Unexposed
Population, n	1126	2219
Age, years, Mean (SD)	49.87 (9.3)	50.12 (9.3)
Age Categories, years, n (%)		
<41	171 (15.19)	329 (14.83)
41-60	803 (71.31)	1568 (70.66)
61-max	152 (13.50)	322 (14.51)
Sex, n (%)		
Male	366 (32.50)	718 (32.36)
Female	760 (67.50)	1501 (67.64)
BMI, kg/ m^2, Mean (SD)	46.76 (7.96)	46.14 (7.49)
BMI Categories, kg/m^2, n (%)		
30-34.9	57 (5.06)	121 (5.46)
35-39.9	165 (14.65)	344 (15.50)
≥40	901 (80.02)	1748 (78.77)
Missing	3 (0.27)	6 (0.27)
Ethnicity, n (%)		
White Caucasian	620 (55.06)	1094 (49.30)
Black Afro-Caribbean	25 (2.22)	37 (1.67)
South Asian	32 (2.84)	56 (2.52)
Mixed Race	7 (0.62)	10 (0.45)
Other	2 (0.18)	9 (0.41)
Missing	440 (39.08)	1013 (45.65)
Townsend quintile, n (%)		
1 (Least deprived)	185 (16.43)	250 (11.27)
2	178 (15.81)	290 (13.07)
3	219 (19.45)	463 (20.87)
4	234 (20.78)	492 (22.17)
5 (Most deprived)	160 (14.21)	414 (18.66)
Missing	150 (13.32)	310 (13.97)
Diabetes Status		
Diabetes duration (years), Median (IQR)	4.7 (2.1- 8.9)	4.6 (1.9- 8.1)
Mean HbA1c, Mean (SD)	7.8 (1.8)	7.8 (1.7)
Insulin user n (%)	270 (23.98)	315 (14.20)
No glucose lowering medication n (%)	88 (7.82)	326 (14.69)

6.3.4.2 Mean HbA1c and change in glycaemic status

At 1 year after index date, mean (SD) HbA1c for the surgical (n=699) and control (n=1444) groups was 6.3% (1.3) vs 7.9% (1.8), respectively. Mean of reduction in HbA1c was 1.5% (95% CI 1.7 to 1.4) in surgical group compared to an increase of HbA1c in the control group (0.1% (95% CI 0.0 to 0.2)) which equates to difference in mean change of 1.7 (95% CI 1.5 to 1.8).

Participants receiving any of the surgical procedures achieved greater HbA1c reductions compared to their matched controls, with a difference in mean HbA1c change of 1.0% (95% CI 0.7 to 1.3) in GB, 1.6% (1.3 to 1.9) in SG, 2.0% (1.7 to 2.2) in RYGB, and 3.2% (0.8 to 5.6) in DS.

At 2 years, mean (SD) HbA1c for the surgical (n=571) and control (n=1245) groups was 6.4% (1.4) vs 8.0% (1.8). Participants in the surgical group achieved a mean reduction in HbA1c of 1.4% (95% CI 1.2 to 1.5), while mean HbA1c in the control group increased by 0.2% (95% CI 0.1 to 0.3).

Similarly, at 3 years, mean (SD) HbA1c for the surgical (n=442) and control (n=1024) groups was 6.6% (1.5) vs 8.1% (1.9). Participants in the surgical group achieved a mean reduction in HbA1c of 1.3% (95% CI 1.1 to 1.5), while mean HbA1c in the control group increased by 0.3% (95% CI 0.2 to 0.4). The above is summarised in Figure 1 a) and b).

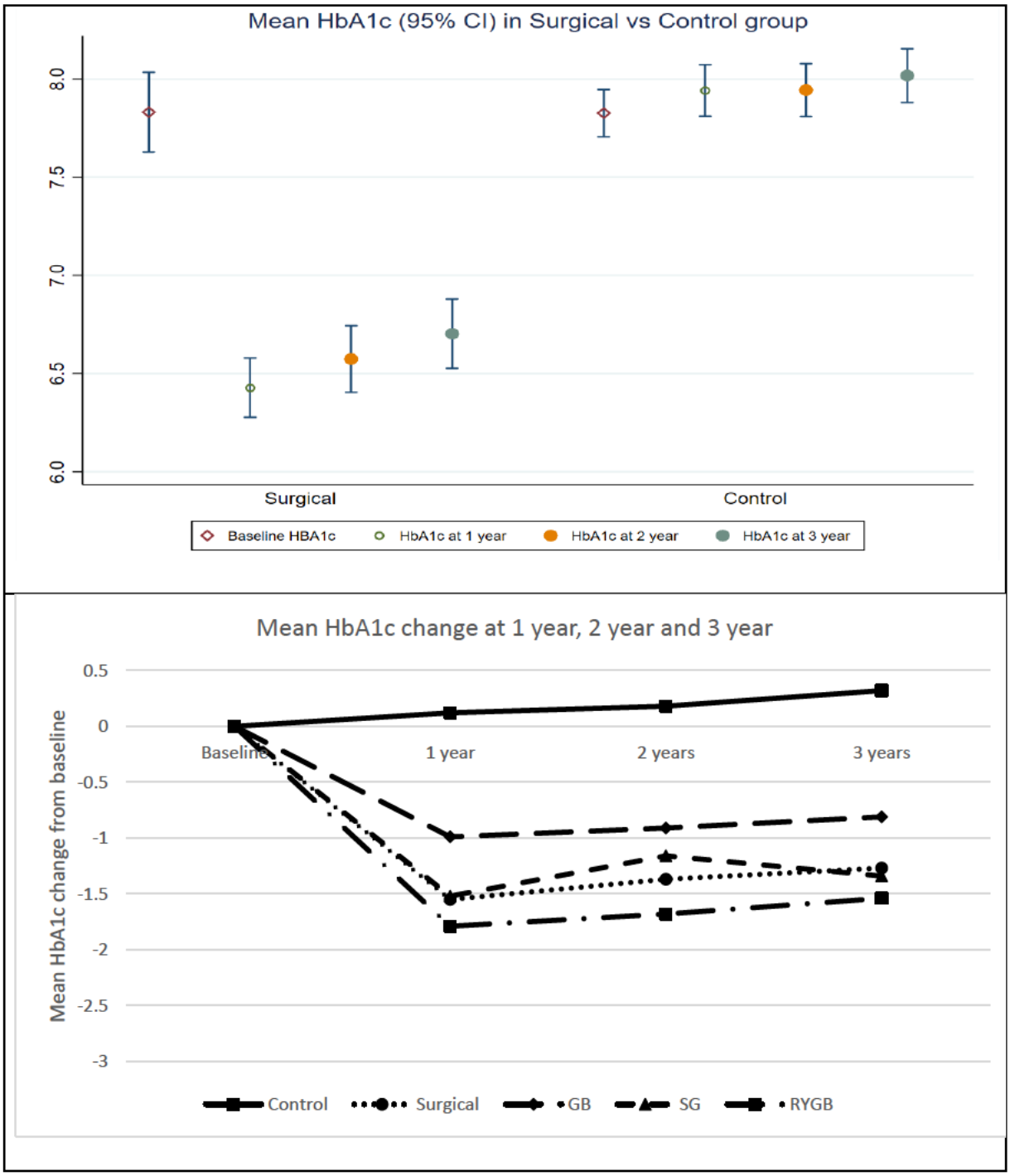


Figure 1: a) Mean (SD) HbA1c in surgical vs control groups. b) Mean HbA1c change from baseline in surgical vs control groups; GB= Gastric band, SG= Sleeve gastrectomy, RYGB= Gastric bypass

6.3.4.3 Achieving glycaemic targets

At baseline, 132 (11.72%) patients in the surgical group and 219 (9.87%) patients in the control group had HbA1c ≤ 6.0% (42 mmol/mol). Over the median (IQR) follow-up of 1.8 (0.6- 4.3) years, 741 (65.8%) vs 506 (22.8%) patients achieved a HbA1c ≤ 6.0% in the surgical vs control group. Achieving and maintaining HbA1c ≤ 6% was significantly more likely in the surgical vs control groups (adjusted HR 5.86 (95% CI 5.19 to 6.60), p<0.001) (Table 2).

All surgical procedures were associated with achieving target HbA1c ≤ 6.0% (42 mmol/mol) (Table 1). Analysing by insulin status showed similar results.

Before index date, 328 (29.13%) patients in the surgical and 540 (24.34%) in the control group had HbA1c ≤ 6.5%, and 483 (42.9%) patients in the surgical and 861 (38.81%) patients in the control group had HbA1c ≤ 7.0%. Achieving or maintaining target HbA1c of ≤ 6.5% and ≤ 7.0% was greater in the surgical group irrespective of type of surgery and baseline insulin use (Table 2).

Table 2: Achieving targeted HbA1c in surgical and control groups

		HBA1c ≤ 6		**HBA1c ≤ 6.5**		**HBA1c ≤ 7.0**	
		Surgical	Control	Surgical	Control	Surgical	Control
Total Population		**1126**	**2219**	**1126**	**2219**	**1126**	**2219**
Outcome events, n (%)		741 (65.81)	506 (22.80)	897 (79.66)	946 (42.63)	980 (87.03)	1283 (57.82)
Person-years		1179.55	7421.33	1227.48	58883.31	908.79	4469.07
Crude Incidence Rate*		416.39	68.18	730.77	160.69	1078.36	287.08
Follow-up years, Median (IQR)		0.7 (0.3- 1.9)	2.7 (1.1- 5.1)	0.5 (0.3- 1.1)	1.8 (0.6- 4.0)	0.4 (0.2- 0.8)	1.1 (0.4- 3.0)
HR (95% CI), p-value	Unadjusted	4.90 (4.36- 5.49), <0.001		3.52 (3.21- 3.87), <0.001		2.85 (2.62- 3.11), <0.001	
	Adjusted	5.86 (5.19- 6.60), <0.001		3.94 (3.57- 4.34), <0.001		2.98 (2.73- 3.26), <0.001	
On Insulin		270	315	270	315	270	315
Outcome events, n (%)		115 (42.59)	50 (15.87)	172(62.70)	84 (26.67)	211 (78.15)	123 (39.05)
Person-years		640.38	1067.41	475.13	952.24	342.60	796.95
Crude Incidence Rate*		179.58	46.84	362	88.21	615.89	154.34
Follow-up years, Median (IQR)		1.3 (0.5- 3.7)	3.1 (1.1-5.4)	0.8 (0.3- 2.5)	2.5 (0.9- 4.7)	0.5 (0.3- 1.3)	1.6 (0.6- 4.0)
HR (95% CI), p-value	Unadjusted	3.48 (2.50- 4.86), <0.001		3.54 (2.72- 4.6), <0.001		3.35 (2.68- 4.20), <0.001	
	Adjusted	3.98 (2.83- 5.60), <0.001		3.75 (2.87- 4.90), <0.001		3.55 (2.82- 4.46), <0.001	
Not on Insulin		856	1904	856	1904	856	1904
Outcome events, n (%)		626 (73.13)	459 (23.95)	725 (84.70)	862 (45.27)	769 (89.84)	1160 (60.92)
Person-years		1139.18	6353.92	752.34	4931.07	566.19	3672.12
Crude Incidence Rate*		549.52	71.77	963.66	174.81	1358.2	315.89
Follow-up years, Median (IQR)		0.6 (0.3- 1.4)	2.7 (1.1- 5.1)	0.4 (0.2- 0.8)	1.7 (0.6- 3.8)	0.4 (0.2- 0.7)	1 (0.4- 2.7)
HR (95% CI), p-value	Unadjusted	5.88 (5.19- 6.66), <0.001		4.07 (3.67- 4.51), <0.001		3.09 (2.81- 3.40), <0.001	
	Adjusted	6.21 (5.46- 7.06), <0.001		3.99 (3.59- 4.43), <0.001		2.92 (2.64- 3.22), <0.001	
Gastric Band		249	492	249	492	249	492
Outcome events, n (%)		143 (57.43)	140 (28.46)	186 (74.70)	235 (47.76)	211 (84.74)	308 (62.60)
Person-years		652.74	2075.4	450.23	1644.53	303.48	1221.87
Crude Incidence Rate*		219.08	67.46	413.12	142.9	695.27	252.07
Follow-up years, Median (IQR)		1.5 (0.6- 4.1)	3.6 (1.4- 6.5)	0.8 (0.4- 2.1)	2.5 (0.7- 5.6)	0.6 (0.3- 1.2)	1.2 (0.5- 3.8)
HR (95% CI), p-value	Unadjusted	2.87 (2.26- 3.62), <0.001		2.38 (1.96- 2.89), <0.001		2.12 (1.77- 2.53), <0.001	
	Adjusted	3.50 (2.72- 4.49), <0.001		2.59 (2.11- 3.18), <0.001		2.27 (1.89- 2.72), <0.001	
Sleeve Gastrectomy		255	497	255	497	255	497
Outcome events, n (%)		173 (67.84)	93 (18.71)	209 (81.96)	195 (39.24)	220 (86.27)	279 (56.14)
Person-years		316.27	1435.30	212.16	1135.16	172.05	869.38
Crude Incidence Rate*		546.99	64.79	985.12	171.8	1278.68	320.92
Follow-up years, Median (IQR)		0.6 (0.3- 1.2)	2.3 (1.0- 4.4)	0.5 (0.2- 0.9)	1.6 (0.6- 3.3)	0.4 (0.2- 0.7)	1 (0.4- 2.4)
HR (95% CI), p-value	Unadjusted	6.55 (5.06- 8.47), <0.001		4.35 (3.56- 5.33), <0.001		3.04 (2.53- 3.65), <0.001	
	Adjusted	8.29 (6.29- 10.92), <0.001		4.77 (3.84- 5.922), <0.001		3.12 (2.56- 3.78), <0.001	
Gastric bypass		610	1206	610	1206	610	1206
Outcome events, n (%)		418 (68.52)	267 (22.14)	494 (80.98)	505 (41.87)	538 (88.20)	680 (56.38)
Person-years		797.77	3850.68	553.68	3058.41	423.93	2345.38
Crude Incidence Rate*		523.96	69.34	892.21	1165.12	1269.07	289.93
Follow-up years, Median (IQR)		0.6 (0.3- 1.5)	2.7 (1.7- 4.9)	0.4 (0.2- 0.9)	1.7 (0.6- 3.9)	0.4 (0.2- 0.7)	1.1 (0.4- 2.9)
HR (95% CI), p-value	Unadjusted	5.71 (4.88- 6.68), <0.001		4.04 (3.55- 4.60), <0.001		3.25 (2.89- 3.66), <0.001	
	Adjusted	7.32 (6.19- 8.66), <0.001		4.98 (4.33- 5.73), <0.001		3.69 (3.26- 4.19), <0.001	

IRR = Crude Incidence Rate/1000 person-years

Adjusted for age, sex, baseline BMI, ethnicity, Townsend quintile, baseline HbA1c, diabetes duration and insulin use.

6.3.4.4 Change in medications

At baseline, the use of glucose lowering medications was similar in the surgical and control groups except that the percentage of patients on insulin (24.0% vs 14.2%) and GLP-1 agonists (25.6% vs 12.2%) which was higher in the surgical group compared to the control group. This observation could be reflection of closer follow up provided to patients under weight management service. There were 88 (7.8%) patients in the surgical vs 326 (14.7%) in the control group without pharmacotherapy prescriptions (Table 3).

Over the study period, the proportion of patients on glucose lowering medications decreased in the surgical group (92.2% at baseline to 66.5%), while it increased in the control group (85.3% at baseline to 90.2%).

In the surgical group, the percentage of patients taking metformin, sulphonylurea, DPP4 inhibitors, GLP-1 agonists and insulin decreased after the intervention compared to baseline.

In the control group, the percentage of patients taking metformin, sulphonylurea, and insulin increased, with a significant increase in DPP4 inhibitor and GLP-1 agonists.

There was a reduction in thiazolidinediones, glinides and acarbose, and an increase in SGLT2 inhibitors in both groups during the study period.

Table 3: Change in glucose lowering medications before and after index date in surgical and control groups.

	Surgical		Control	
	Before N (%)	After N (%)	Before N (%)	After N (%)
Metformin	1024 (90.94)	683 (60.66)	1863 (83.96)	1881 (84.77)
Glitazones	332 (29.48)	67 (5.95)	547 (24.65)	373 (16.81)
Glinides	26 (2.31)	4 (0.36)	38 (1.71)	8 (0.36)
Sulphonylurea	475 (42.18)	160 (14.21)	852 (38.40)	904 (40.74)
Acarbose	31 (2.75)	8 (0.71)	32 (1.44)	14 (0.63)
DPP4 inhibitor	178 (15.81)	102 (9.06)	325 (14.65)	641 (28.89)
SGLT2 inhibitor	53 (4.71)	71 (6.31)	70 (3.15)	352 (15.86)
GLP-1 agonist	288 (25.58)	109 (9.68)	270 (12.17)	512 (23.07)
Insulin	270 (23.98)	136 (12.08)	315 (14.20)	429 (19.33)
No treatment	88 (7.82)	388 (34.46)	326 (14.69)	217 (9.78)

The percentage of patients on no medication, monotherapy, dual therapy and polytherapy was similar in the surgical and control groups at baseline. After surgery/index date, the percentage of patients on no medication increased from 7.8 to 34.5% and there was a significant reduction in the proportion of patients on dual and polytherapy. In the control group, the percentage of patients on no therapy and monotherapy decreased after index date, and a significant increase in polytherapy was noted (31.9 % to 42.9%) (Figure 2).

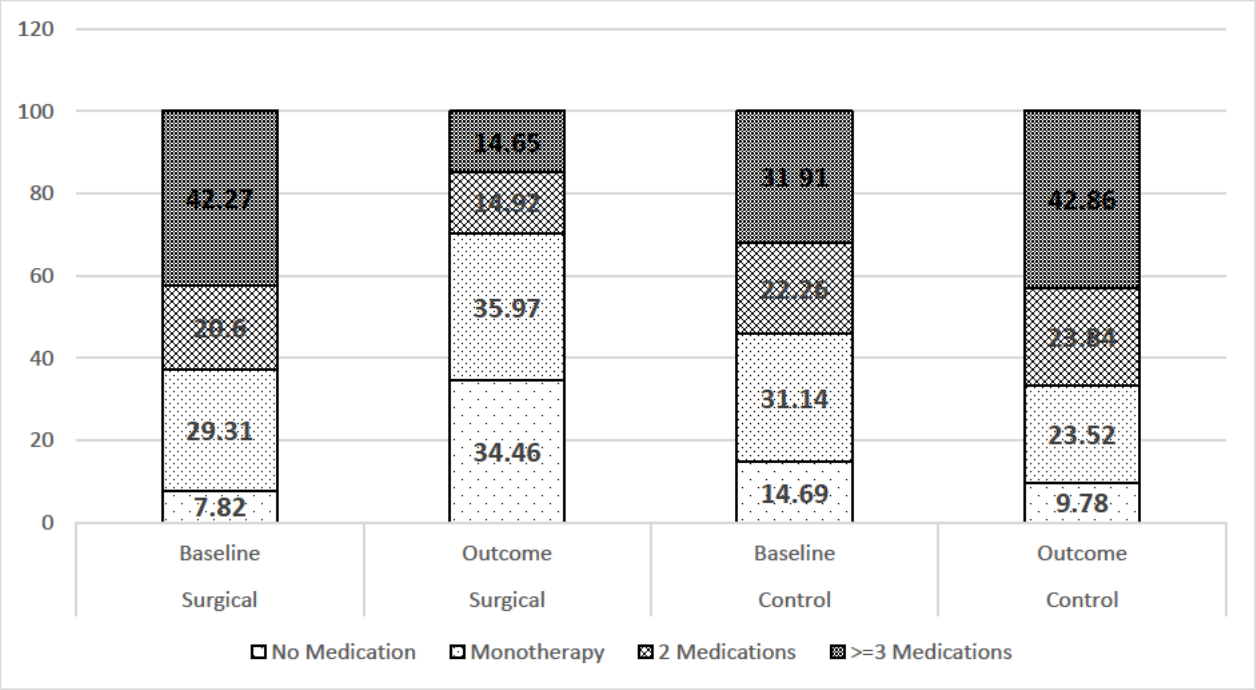


Figure 2: Percentage of patients on glucose lowering medications before and after index date (pre- and post-surgery) in surgical and control groups.

6.3.4.5 Change in weight

Data on weight before and after index date was available for 1067 (94.8%) surgical and 1943 (87.6%) control participants. Over the median (IQR) follow-up of 3.2 years (1.4-5.4), the

surgical group achieved a greater %WL (mean, 95% CI) of 21.6% (20.8% to 22.4%) compared to 4.6% (4.1% to 5.0%) in the control group.

A greater weight reduction was noted in the surgical group compared to their matched controls for all surgical procedures, %WL (mean (95% CI)): GB 14.6% (12.8% to 16.3%) vs 4.6% (3.6% to 5.5%); SG 20.6% (19.1% to 22.1%) vs 4.2% (3.2% to 5.2%); RYGB 25.0% (24.0% to 25.9%) vs 4.8% (4.2% to 5.3%); and DS 21.2% (14.5% to 28.1%) vs 1.7% (2.7% to 6.0%). Similarly, a greater weight reduction was noted in both insulin and non-insulin users in the surgical compared to the control group, %WL: 22.6% (95% CI 21.2 to 24.1%) vs 4.1% (95% CI 2.8% to 5.4%) in insulin users and 21.3% (95% CI 20.4% to 22.2%) vs 4.6% (95% CI 4.2% to 5.1%) in non-insulin users.

6.3.5 Discussion

Our study provides real-world evidence of superior effect of bariatric surgery in people with type 2 diabetes and obesity in achieving better glycaemic control and meeting glycaemic targets with less glucose lowering medications over median (IQR) follow-up of 3.6 (1.7- 5.9) years compared to routine care. These results occurred within the context of higher insulin prescriptions at baseline and less glucose lowering medications prescriptions in the surgical group compared to routine care. Bariatric surgery was associated with significant greater weight loss in people with type 2 diabetes compared to routine care.

The effect of bariatric surgery on glycaemic status is well evidenced in clinical studies. Guidance on choice and titration of glucose lowering medications post bariatric surgery is currently not well defined (22, 23). In our study, we found metformin, sulphonylurea, insulin and GLP-1 agonists were commonly used medications.

Diabetes cure or reversal has been identified as a top research priority by a project led by patients with type 2 diabetes and their carers (24). The DiRECT trial showed diabetes remission rate of 36% over two years based on a diabetes remission definition of HbA1c ≤ 6.5% (48 mmol/mol), using an integrated structured weight management programme. The LookAHead study defined diabetes remission as fasting plasma glucose <126 mg/dL and HbA1c ≤6.5% and off glucose- lowering medication showed diabetes remission rate of 7.3% (95% CI 6.2% to 8.4%) at four years' follow-up using an intensive lifestyle intervention (6). A meta-analysis of eight RCTs found bariatric surgery achieved higher a remission rate compared to a non-surgical intervention with a risk ratio 5.41 (95% CI 2.47 to 11.85) over 1-2 years' follow-up, and 8.36 (2.71 to 25.85) over 3-5 years' follow-up (25). In a systematic review of RCTs comparing bariatric surgery vs non-surgical treatments showed a 22% higher chance of diabetes remission in the surgical compared to control group, with a relative risk 22.1 (95% CI 3.2 to 154.3) in a complete case analysis (26).

Our results support these findings and show that achieving HbA1c in the normoglycemic range is possible (for more than half of patients) within a real-world setting with bariatric surgery, while this was not observed in the routine care group using pharmacotherapy. Insulin use has been shown to be predictor of poorer glycaemic outcomes and diabetes remission in post bariatric surgery patients (27). Despite higher insulin user in bariatric surgery at baseline, more patients managed to achieve targeted glycaemic control in surgical group compared to routine care.

In our study, we observed a HbA1c reduction of 1.3% (95% CI 1.1 to 1.5) and 70.3% and 79.9% of patients in the surgical group achieved HbA1c of ≤ 6.5% and ≤ 7.0%, respectively over a median follow up period of 3.4 years follow-up. Reduction in HbA1c was noted in all

surgical groups and was highest in the RYGB group followed by SG and GB. In our study, 70.3% and 79.9% of patients in the surgical group achieved HbA1c of ≤ 6.5% and ≤ 7.0%, respectively over a median follow up period of 3.4 years. The proportion of patients achieving the targeted HbA1c was higher than those noted in RCTs (9, 10). These differences could be because 29.1% and 42.9% of patients in our study had HbA1c ≤ 6.5% and ≤ 7.0%, respectively at baseline while all patients in both the RCTs (9, 10) had HbA1c > 7.0%. Good glycaemic status in surgical group was noted despite being on less glucose lowering medications. Percentage of patients on SGLT2I and GLP1A medication reduced in surgical group in post op stage. RCT GRAVITAS (GLP-1 Receptor Agonist Intervention for poor responders after bariatric surgery) by Miras et al showed adjuvant effect of Liraglutide on diabetes management of patients who underwent RYGB or SG (28). Patients on liraglutide managed to achieve reduction in HbA1c and weight over 26 weeks follow up (28). This study and review article by Pournaras.et.al (29) highlights that to achieve and maintain targeted HbA1c, multimodal treatment should be adapted for management of patients with type 2 diabetes. Continuation of GLP1A and SGLT2I class of medications in surgical group could have resulted in further reduction in HbA1c and better cardiovascular outcomes.

A retrospective observational study of patients with type 2 diabetes using the Clinical Practice Research Datalink, including 1320 patients in the surgical group and 1296 propensity score matched patients in the control group, found a positive impact of bariatric surgery on glycaemic status and diabetes remission defined by either a coded record of diabetes resolution or absence of prescription of diabetes medications for at least a six-month period (30). However, there was no further analysis based on type of surgery and the result was not adjusted for baseline HbA1c or diabetes duration.

The mechanism behind glycaemic improvement after bariatric surgery is complex and incompletely understood. The likely mechanism includes changes in beta cell reserve, insulin sensitivity, gluconeogenesis, glucose uptake and utilization in peripheral organs (31, 32). Weight loss has been associated with enhanced insulin sensitivity (33). In our study, patients who had bariatric surgery achieved a greater percentage weight loss compared to the control group (21.6% vs 4.6%). Weight loss due to bariatric surgery has been associated with changes in hormones(34), gut microbiome(35), taste and smell senses(36), intestinal enteroplasticty, and vagus nerve function (37). Bariatric surgery leads to an increase in satiety hormones GLP-1 and pancreatic peptide YY (PYY) and a decrease in the hunger hormone ghrelin (34). These hormonal changes differ from those seen following weight loss by dietary intervention which may explain the sustainability of bariatric surgery on metabolic effect (31, 34). Bariatric surgery alters bile acid and gut microbial environment creating a weight losing environment (35). Change in taste and smell after surgery impact the choice of food in post-bariatric surgery patients and leads to high calorie food being perceived as less rewarding (36, 38).

Weight loss may cause a reduction in ectopic fat in the pancreas, leading to a reduction in adipo-toxicity, a reduction in peripheral fat leading to down regulation of proinflammatory signals and improving pancreatic cell survival and insulin sensitivity (32). Reduction in triglyceride and ectopic fat in the liver and muscle may improve insulin sensitivity (32).

We have shown previously the relationship between bariatric surgery and reduction in micro- and macrovascular complications and mortality (14, 15). Taken together with the findings of this study, bariatric surgery can be seen to reduce the burden of type 2 diabetes on both patients and the health economy.

6.3.6 Limitations and strengths

Our findings should be interpreted within certain limitations. The IMRD-UK database is a validated primary care data source and had been used by our team and other researchers in numerous studies (14, 39-41). Because of the retrospective nature of the study and the limited data on some covariates, residual confounding cannot be excluded.
However, our study provides real-world data regarding the impact of bariatric surgery on glycaemic status and glucose lowering medications. The large sample size allowed us to explore the effect in different types of bariatric surgery. Our study included patients with type 2 diabetes on insulin as well as non-insulin users, and we were able to analyse the outcomes in these two groups separately.

6.3.7 Conclusion

Bariatric surgery was associated with a large reduction in HbA1c in patients with type 2 diabetes and obesity compared to routine care. It was also associated with a reduction in polypharmacy. Bariatric surgery is an effective treatment for patients with type 2 diabetes and obesity and can result in HbA1c in the normoglycemic range. Increased utilization of bariatric surgery may reduce the burden of diabetes-related complications for both patients and the health system.

Ethics

Use of IQVIA Medical Research Data (IMRD-UK) is approved by the UK Research Ethics Committee (reference number: 18/LO/0441); in accordance with this approval, the study

protocol was reviewed and approved by an independent Scientific Review Committee (SRC) (reference number: 18THIN097). IMRD-UK incorporates data from The Health Improvement Network (THIN), A Cegedim Database. Reference made to THIN is intended to be descriptive of the data asset licensed by IQVIA. This work used de-identified data provided by patients as a part of their routine primary care.

Copyright Statement

IMRD is a registered trademark of Cegedim SA in the United Kingdom and other countries. Reference made to the IMRD database is intended to be descriptive of the data asset licensed by IQVIA.

Author contributions:

AAT, PS and KN had the original idea for the study. PS, AAT, and KN designed the study. KG undertook data extraction. PS designed and performed the analysis, which was reviewed by KN, AS and NA. PS, AS, KN and AAT contributed to the data analysis and interpretation. PS wrote the first draft of the paper, which was revised and edited by NA, SB, KAT, RS, KG, AAT and KN. PS, AAT and KN affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. PS and KN had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest: There are no potential conflicts of interest relevant to this article.

Funding: None.

Competing Interest:

KN received funding from AstraZeneca (RSBD20464). KN reports fees from Sanofi and Boehringer Ingelheim outside the submitted work. AAT reports grants from Novo Nordisk,

personal fees from Novo Nordisk, non-financial support from Novo Nordisk, personal fees from Eli Lilly, non-financial support from Eli Lilly, personal fees from Janssen, personal fees from AZ, non-financial support from AZ, non-financial support from Impeto medical, non-financial support from Resmed, non-financial support from Aptiva, personal fees from BI, non-financial support from BI, personal fees from BMS, nonfinancial support from BMS, personal fees from NAPP, non-financial support from NAPP, personal fees from MSD, non-financial support from MSD, personal fees from Nestle, personal fees from Gilead, grants from Sanofi, and personal fees from Sanofi outside the submitted work. AAT is currently an employee of Novo Nordisk. This work was performed before AAT becoming a Novo Nordisk employee and Novo Nordisk had no role in this project. SB has received consultation and/or lecture fees from Sanofi Aventis,Astra Zeneca, Eli Lilly, Boehringer Ingelheim, NAPP, MSD, grants and personal fees from Novonordisk Ltd outside the submitted work. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

6.3.8 References:

1. Stratton IM, Adler AI, Neil HAW, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ (Clinical research ed). 2000;321(7258):405-12.
2. M B, M S, B R, S W, M G, FR K. Impact of Reducing Glycated Hemoglobin on Healthcare Costs Among a Population with Uncontrolled Diabetes. Applied health economics and health policy. 2018;16(5).
3. Edelman SV, Polonsky WH. Type 2 Diabetes in the Real World: The Elusive Nature of Glycemic Control. 2017.
4. National Diabetes Audit -. Report 1: Care Processes and Treatment Targets 2018 [Available from: https://www.hqip.org.uk/wp-content/uploads/2018/03/National-Diabetes-Audit-2016-17-Report-1-Care-Processes-and-Treatment-T....pdf.
5. Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet. 2018;391(10120):541-51.
6. GreggEW, ChenH, WagenknechtLE, ClarkJM, DelahantyLM, BantleJ, et al. Association of an Intensive Lifestyle Intervention With Remission of Type 2 Diabetes. JAMA. 2012;308(23).
7. O'BrienPE, A H, L B, S S, P B, A S, et al. Long-Term Outcomes After Bariatric Surgery: A Systematic Review and Meta-analysis of Weight Loss at 10 or More Years for All Bariatric Procedures and a Single-Centre Review of 20-Year Outcomes After Adjustable Gastric Banding. Obesity surgery. 2019;29(1).
8. Golzarand M, Toolabi K, Farid R. The bariatric surgery and weight losing: a meta-analysis in the long- and very long-term effects of laparoscopic adjustable gastric banding, laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy on weight loss in adults. Surgical endoscopy. 2017;31(11):4331-45.
9. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Aminian A, Brethauer SA, et al. Bariatric Surgery versus Intensive Medical Therapy for Diabetes - 5-Year Outcomes. N Engl J Med. 2017;376(7):641-51.
10. Mingrone G, Guidone C, Iaconelli A, Nanni G, Castagneto M, Panunzi S, et al. Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 Year follow-up of an open-label, single-centre, randomised controlled trial. The Lancet. 2015;386(9997):964-73.
11. Courcoulas Anita P, Belle Steven H, Neiberg Rebecca H, Pierson Sheila K, Eagleton Jessie K, Kalarchian Melissa A, et al. Three-Year Outcomes of Bariatric Surgery vs Lifestyle Intervention for Type 2 Diabetes Mellitus Treatment: A Randomized Clinical Trial. JAMA surgery. 2015;150(10):931-40.
12. Borisenko O, Colpan Z, Dillemans B, Funch-Jensen P, Hedenbro J, Ahmed AR. Clinical Indications, Utilization, and Funding of Bariatric Surgery in Europe. Obes Surg. 2015;25(8):1408-16.
13. DixonJB. Regional Differences in the Coverage and Uptake of Bariatric-Metabolic Surgery: A Focus on Type 2 Diabetes. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2016;12(6).

14. SinghP, SubramaniaA, AdderleyN, GokhaleK, SinghalR, BellaryS, et al. Impact of Bariatric Surgery on Cardiovascular Outcomes and Mortality: A Population-Based Cohort Study. The British journal of surgery. 2020;107(4):432- 42.
15. Singh P, Adderley N, Subramanian A, Gokhale K, Singhal R, Toulis KA, et al. The Impact of Bariatric Surgery on Incident Microvascular Complications in Patients With Type 2 Diabetes: A Matched Controlled Population-Based Retrospective Cohort Study. Diabetes Care 2021. 2021;44 (1):116-24.
16. THIN-HES Privacy Notice 2019 [Available from: https://www.iqvia.com/locations/united-kingdom/information-for-members-of-the-public/thin-hes-data.
17. Doran T, Fullwood C, Gravelle H, Reeves D, Kontopantelis E, Hiroeh U, et al. Pay-for-Performance Programs in Family Practices in the United Kingdom. http://dxdoiorg/101056/NEJMsa055505. 2009.
18. Maguire A, Blak BT, Thompson M. The importance of defining periods of complete mortality reporting for research using automated data from primary care. Pharmacoepidemiology and drug safety. 2009;18(1):76-83.
19. LévesqueLE, HanleyJA, KezouhA, SuissaS. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ (Clinical research ed). 2010;340.
20. ADA. STANDARDS OF MEDICAL CARE IN DIABETES—2020. The Journal of Clinical and Applied Research and Education. 2019;38(1).
21. NICE guideline N. Type 2 diabetes in adults: management | Guidance and guidelines | NICE. 2017.
22. ThorellA, Hagström-ToftE. Treatment of diabetes prior to and after bariatric surgery. Journal of diabetes science and technology. 2012;6(5).
23. MechanickJI, ApovianC, BrethauerS, GarveyWT, JoffeAM, KimJ, et al. Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures - 2019 update: cosponsored by American Association of Clinical Endocrinologists/American College of Endocrinology, The Obesity Society, American Society for Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2020;16(2).
24. FinerS, RobbP, CowanK, DalyA, RobertsonE, FarmerA. Top ten research priorities for type 2 diabetes: results from the Diabetes UK-James Lind Alliance Priority Setting Partnership. The lancet Diabetes & endocrinology. 2017;5(12).
25. WuGZ, CaiB, YuF, FangZ, FuXL, ZhouHS, et al. Meta-analysis of bariatric surgery versus non-surgical treatment for type 2 diabetes mellitus. Oncotarget. 2016;7(52).
26. Gloy VL, Briel M, Bhatt DL, Kashyap SR, Schauer PR, Mingrone G, et al. Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials. BMJ (Clinical research ed). 2013;347:f5934.
27. SinghP, AdderleyNJ, HazlehurstJ, PriceM, TahraniAA, NirantharakumarK, et al. Prognostic Models for Predicting Remission of Diabetes Following Bariatric Surgery: A Systematic Review and Meta-analysis. Diabetes care. 2021;44(11).
28. MirasAD, Pérez-PevidaB, AldhwayanM, KamockaA, McGloneER, Al-NajimW, et al. Adjunctive liraglutide treatment in patients with persistent or recurrent type 2 diabetes after

metabolic surgery (GRAVITAS): a randomised, double-blind, placebo-controlled trial. The lancet Diabetes & endocrinology. 2019;7(7).
29. DJ P, CW lR. Type 2 diabetes: multimodal treatment of a complex disease. Lancet (London, England). 2015;386(9997).
30. Douglas IJ, Bhaskaran K, Batterham RL, Smeeth L. Bariatric Surgery in the United Kingdom: A Cohort Study of Weight Loss and Clinical Outcomes in Routine Clinical Care. PLoS medicine. 2015;12(12):e1001925.
31. Batterham RL, Cummings DE. Mechanisms of Diabetes Improvement Following Bariatric/Metabolic Surgery. Diabetes Care. 2016;39(6):893-901.
32. WilsonR, AminianA, TahraniAA. Metabolic surgery: A clinical update. Diabetes, obesity & metabolism. 2021;23 Suppl 1.
33. Clamp LD, Hume DJ, Lambert EV, Kroff J. Enhanced insulin sensitivity in successful, long-term weight loss maintainers compared with matched controls with no weight loss history. Nutr Diabetes. 2017;7(6):e282-.
34. Pucci A, Batterham RL. Mechanisms underlying the weight loss effects of RYGB and SG: similar, yet different. J Endocrinol Invest. 2019;42(2):117-28.
35. LiuH, HuC, ZhangX, JiaW. Role of gut microbiota, bile acids and their cross-talk in the effects of bariatric surgery on obesity and type 2 diabetes. Journal of diabetes investigation. 2018;9(1).
36. ScholtzS, MirasAD, ChhinaN, PrechtlCG, SleethML, DaudNM, et al. Obese patients after gastric bypass surgery have lower brain-hedonic responses to food than after gastric banding. Gut. 2014;63(6).
37. An Z, Wang H, Mokadem M. Role of the Autonomic Nervous System in Mechanism of Energy and Glucose Regulation Post Bariatric Surgery. Front Neuroscience. 2021.
38. ZakeriR, BatterhamRL. Potential mechanisms underlying the effect of bariatric surgery on eating behaviour. Current opinion in endocrinology, diabetes, and obesity. 2018;25(1).
39. Adderley NJ, Nirantharakumar K, Marshall T. Risk of stroke and transient ischaemic attack in patients with a diagnosis of resolved atrial fibrillation: retrospective cohort studies. BMJ (Clinical research ed). 2018;361:k1717.
40. Subramanian A, Adderley NJ, Tracy A, Taverner T, Hanif W, Toulis KA, et al. Risk of Incident Obstructive Sleep Apnea Among Patients With Type 2 Diabetes. Diabetes Care. 2019.
41. Caleyachetty R, Thomas GN, Toulis KA, Mohammed N, Gokhale KM, Balachandran K, et al. Metabolically Healthy Obese and Incident Cardiovascular Disease Events Among 3.5 Million Men and Women. Journal of the American College of Cardiology. 2017;70(12):1429-37.

Chapter 7: Prognostic models for predicting remission of diabetes following bariatric surgery: A systematic review and meta-analysis

7.1 Contents of chapter

Literature review found bariatric surgery is successful in achieving diabetes remission in patients with preserved pancreatic beta cell function e.g. younger age, shorter duration of diabetes, and higher C-peptide level, and space to reduce insulin resistance e.g. extra body mass index, fat distribution pattern.(1) Prediction models encapsulating these factors could be good tool to help clinician and patient to make informed choice.

A systematic review published in 2016 identified 8 studies and revealed 2 prediction model DiaRem (2) and ABCD (3) with external validation and 4 other models in developmental stage.(4)

However, things have moved fast and many more prediction models including DiaBetter (5), DRS (6) and IMS (7) has emerged to envisage diabetes remission in patients undergoing bariatric surgery or metabolic surgery. The prediction model described in previous systematic review had been externally validated in more studies, in different population and in patients undergoing sleeve gastrectomy since this systematic review. There are studies presenting more than one prediction model and compared them (8, 9).

Considering the growing literature in this area and increasing use of bariatric surgery worldwide, there is a need to undertake systematic review to identify the available prediction model, critically summarise their findings in patients with type 2 diabetes undergoing bariatric surgery.

In this chapter, I have presented systematic review to identify available prediction models and assess how good they are in predicting diabetes remission in patients undergoing bariatric surgery. This chapter is presented in format of a published article

7.2 References

1. Park JY. Prediction of Diabetes Remission after Bariatric or Metabolic Surgery. 2018.
2. Still Christopher D, Wood GC, Benotti P, Petrick Anthony T, Gabrielsen J, Strodel William E, et al. Preoperative prediction of type 2 diabetes remission after Roux-en-Y gastric bypass surgery: a retrospective cohort study. The lancet Diabetes & endocrinology. 2014;2(1):38-45.
3. Lee W-J, Hur Kyung Y, Lakadawala M, Kasama K, Wong Simon KH, Chen S-C, et al. Predicting success of metabolic surgery: age, body mass index, C-peptide, and duration score. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery. 2013;9(3):379-84.
4. Zhang R, Borisenko O, Telegina I, Hargreaves J, Ahmed AR, Sanchez Santos R, et al. Systematic review of risk prediction models for diabetes after bariatric surgery. The British journal of surgery. 2016;103(11):1420-7.
5. Pucci A, Tymoszuk U, Cheung WH, Makaronidis JM, Scholes S, Tharakan G, et al. Type 2 diabetes remission 2 years post Roux-en-Y gastric bypass and sleeve gastrectomy: The role of the weight loss and comparison of DiaRem and DiaBetter scores. Diabetic Medicine. 2017.
6. Ugale S, Gupta N, Modi KD, Kota SK, Satwalekar V, Naik V, et al. Prediction of remission after metabolic surgery using a novel scoring system in type 2 diabetes – a retrospective cohort study. Journal of Diabetes & Metabolic Disorders. 2014;13(1):89.
7. Aminian A, Brethauer SA, Andalib A, Nowacki AS, Jimenez A, Corcelles R, et al. Individualized Metabolic Surgery Score: Procedure Selection Based on Diabetes Severity. Annals of surgery. 2017;266(4):650-7LID.
8. Lee W-J, Chong K, Chen S-C, Zachariah J, Ser K-H, Lee Y-C, et al. Preoperative Prediction of Type 2 Diabetes Remission After Gastric Bypass Surgery: a Comparison of DiaRem Scores and ABCD Scores. Obesity surgery. 2016;26(10):2418-24.
9. Kam H, Tu Y, Pan J, Han J, Zhang P, Bao Y, et al. Comparison of Four Risk Prediction Models for Diabetes Remission after Roux-en-Y Gastric Bypass Surgery in Obese Chinese Patients with Type 2 Diabetes Mellitus. Obesity surgery. 2020;30(6):2147-57.

7.3 Manuscript 4: Prognostic models for predicting remission of diabetes following bariatric surgery: A systematic review and meta-analysis

Singh P., Adderley N.J., Hazlehurst J., Price M., Tahrani A.A., Nirantharakumar K., Bellary S. Prognostic Models for Predicting Remission of Diabetes Following Bariatric Surgery: A Systematic Review and Meta-analysis. Diabetes Care 2021 Nov; 44(11): 2626-2641. (First published 20 October 2021) https://doi.org/10.2337/dc21-0166

Prognostic Models for Predicting Remission of Diabetes Following Bariatric Surgery: A Systematic Review and Meta-analysis

Pushpa Singh,[1,2] Nicola J. Adderley,[3] Jonathan Hazlehurst,[1,2] Malcolm Price,[3] Abd A. Tahrani,[1,2,4] Krishnarajah Nirantharakumar,[2,3,4,5] and Srikanth Bellary[2,6]

Diabetes Care 2021;44:2626–2641 | https://doi.org/10.2337/dc21-0166

META-ANALYSIS

BACKGROUND

Remission of type 2 diabetes following bariatric surgery is well established, but identifying patients who will go into remission is challenging.

PURPOSE

To perform a systematic review of currently available diabetes remission prediction models, compare their performance, and evaluate their applicability in clinical settings.

DATA SOURCES

A comprehensive systematic literature search of MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) was undertaken. The search was restricted to studies published in the last 15 years and in the English language.

STUDY SELECTION

All studies developing or validating a prediction model for diabetes remission in adults after bariatric surgery were included.

DATA EXTRACTION

The search identified 4,165 references, of which 38 were included for data extraction. We identified 16 model development and 22 validation studies.

DATA SYNTHESIS

Of the 16 model development studies, 11 developed scoring systems and 5 proposed logistic regression models. In model development studies, 10 models showed excellent discrimination with area under the receiver operating characteristic curve ≥0.800. Two of these prediction models, ABCD and DiaRem, were widely externally validated in different populations, in a variety of bariatric procedures, and for both short- and long-term diabetes remission. Newer prediction models showed excellent discrimination in test studies, but external validation was limited.

LIMITATIONS

While the key messages were consistent, a large proportion of the studies were conducted in small cohorts of patients with short duration of follow-up.

CONCLUSIONS

Among the prediction models identified, the ABCD and DiaRem models were the most widely validated and showed acceptable to excellent discrimination. More studies validating newer models and focusing on long-term diabetes remission are needed.

[1]Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, U.K.
[2]Department of Diabetes and Endocrinology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, U.K.
[3]Institute of Applied Health Research, University of Birmingham, Birmingham, U.K.
[4]Centre for Endocrinology, Diabetes and Metabolism, Birmingham Health Partners, Birmingham, U.K.
[5]Midlands Health Data Research, Birmingham, U.K.
[6]School of Life and Health Sciences, Aston University, Birmingham, U.K.

Corresponding author: Krishnarajah Niranthara Kumar

Received 21 January 2021 and accepted 15 August 2021

This article contains supplementary material online at https://doi.org/10.2337/figshare.15173232.

K.N. and S.B. are joint senior authors and contributed equally to this manuscript.

© 2021 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at https://www.diabetesjournals.org/content/license.

Bariatric surgery is an established cost-effective treatment option in patients with type 2 diabetes. In addition to sustained weight loss, it is associated with significant improvements in glycemic control, including achieving type 2 diabetes remission (1–3), and reduction in the risk of micro- and macrovascular complications and mortality (4–6). The proportion of patients achieving diabetes remission following bariatric surgery varies between studies and is estimated to be between 30 and 70%. This proportion lessens with longer follow-up and with longer diabetes duration at the time of surgery (7–9). This observed variation in the remission prevalence may be attributed to differences in definitions of diabetes remission, the population studied, the type of bariatric surgery, and the duration of follow-up.

Type 2 diabetes is one of the main indications for bariatric surgery in people with obesity (10). Given the variation in the rates of diabetes remission following bariatric surgery, a number of studies aiming to identify predictors of diabetes remission following bariatric surgery have been published (11–14). Variables associated with better β-cell function such as younger age, shorter diabetes duration, high C-peptide, lack of insulin treatment, and lower preoperative HbA_{1c} (15) and lower preoperative BMI have been identified as predictors of type 2 diabetes remission postsurgery.

In consideration of the importance of predicting diabetes remission for individualizing care and helping patients and health care professionals to make informed decisions, several scoring systems incorporating the above-mentioned variables to predict diabetes remission have been developed (16–18). With acknowledgment of the mounting literature in this area and the increasing use of bariatric surgery worldwide, there is a need to describe the available prediction models and assess their ability to predict diabetes remission in patients with type 2 diabetes undergoing bariatric surgery and their utility in clinical practice.

METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (19). The protocol was registered on International prospective register of systematic reviews (PROSPERO), reg. no. CRD42019124644.

Data Sources and Searches

We searched MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations, Embase (Ovid), and Cochrane Central Register of Controlled Trials (CENTRAL). An example of the search strategy used in Embase can be found in Supplementary Table 1. Key search terms were type 2 diabetes, remission, and bariatric surgery. The search terms for prognostic/predictive models included prediction, prognosis, sensitivity, specificity, ROC (receiver operating characteristics) curve, and AUC (area under the ROC curve) with wild cards as well as other search terms as per published guidance (20).

The search was limited to articles published in the English language and in the last 15 years, as the concept of diabetes remission was established and coined by the American Diabetes Association in 2009. The final search was performed on 26 January 2019 and updated on 8 August 2020 (Fig. 1). EPPI-Reviewer 4 software was used for compiling the references, first screening by title and abstract, second screening of full text, and collaborating among reviewers (21).

Study Selection

First screening by title and abstract was performed by two reviewers (P.S. and S.B.) independently. Discrepancies were discussed to reach a consensus. We included clinical studies (observational or interventional studies) (Setting, S) involving adults with type 2 diabetes (Participants, P) who subsequently had bariatric/metabolic surgery (Interventions, I) and those who developed or validated a prediction model to predict diabetes remission (Outcome, O). Multiple definitions of diabetes remission were used, but we included only studies with definitions of HbA_{1c} of $\leq$6.5% (48 mmol/mol) and participants being off glucose-lowering medication, with follow-up of at least a year.

We excluded review articles, studies with participants including children/adolescents or those with gastric cancer or gastric ulcer, studies where the intervention was other than bariatric/metabolic surgery, studies with an outcome of diabetes remission defined as HbA_{1c} >6.5% (48 mmol/mol), studies with a follow-up period <12 months, and studies where the analysis was limited to identifying predictors.

Data Extraction and Quality Assessment

The data extraction template was drafted on DistillerSR software (22). Data were collected by P.S. and independently collected by second reviewers (N.J.A., J.H., and S.B.). We adapted the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS) toolkit (23) to design the data collection domains; we gathered data on the country, data source, type of study, demographics of participants, type of bariatric procedure, length of follow-up, definition of diabetes remission, statistical method used for model development, and performance measures (Supplementary Table 3). We calculated the discrimination scores for models when this was not reported by the authors and where data to calculate them were available in the publication.

Risk of Bias Assessment

We used a customized version of the Prediction model Risk Of Bias ASsessment Tool (PROBAST) to assess risk of bias and applicability (24). The assessment was done under four domains for risk of bias—participants, predictors, outcomes, and analysis—and three domains for applicability and generalizability: participants, predictors, and outcomes. The participants domain covers bias in patient selection and study design, the predictors domain is related to definition of predictors included in the prediction model, the outcome domain covers definition and measurement of the outcome, and the analysis domain relates to statistical analysis, handling missing data and overfitting (24) (Supplementary Table 4).

Statistical Analysis

A prediction model has three main phases: model development (preferably with internal validation), external validation, and investigation of clinical impact (25). Model development and validation involve identifying predictors, selecting the important predictors by regression analysis/modeling, proposing a model by assigning relative weights to the individual predictors included, conducting internal validation, and validating in

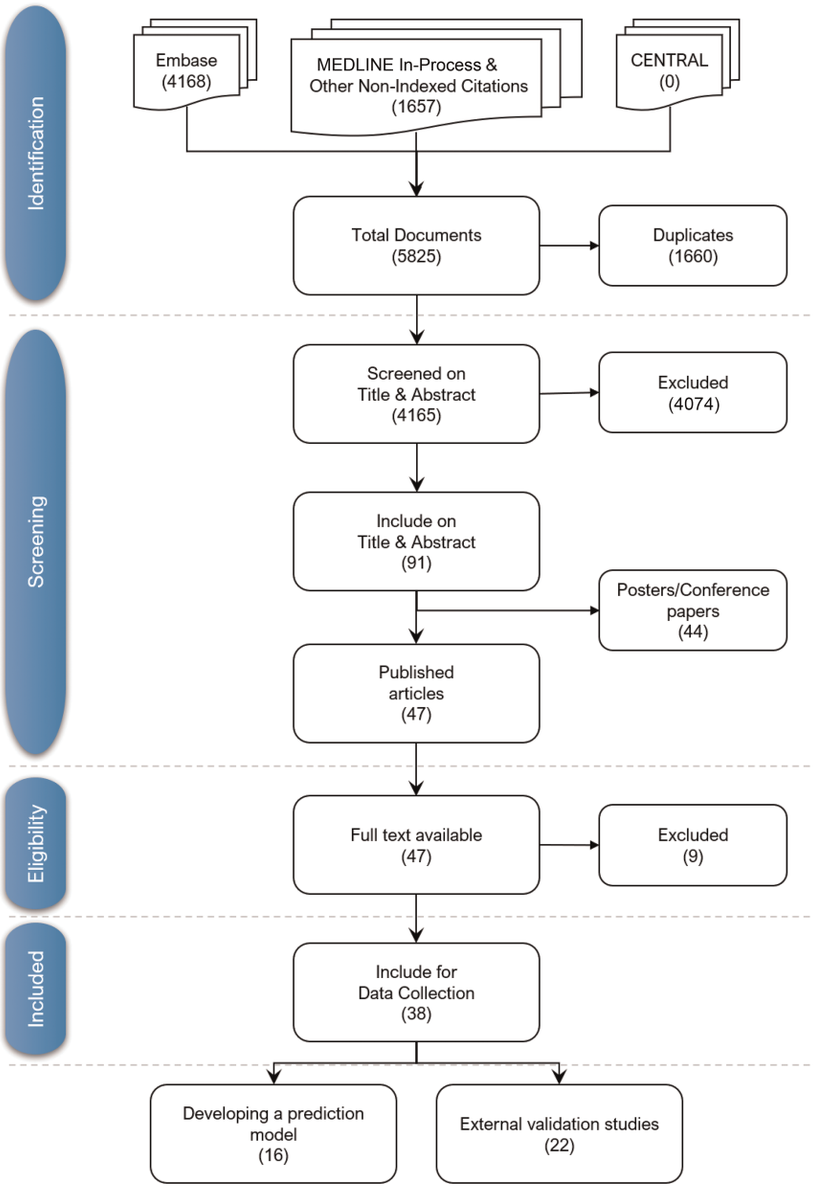


Figure 1 PRISMA flowchart.

an external cohort to avoid overfitting (26). In this review, we classed the studies with development and internal validation of a prediction model as model development studies and studies with external validation of prediction models in a new cohort as validation studies.

We explored these phases for the identified prediction models and assessed the performance (26,27). We assessed the performance of the models based on discrimination, defined as the ability to distinguish between those who will and who will not achieve the outcome of interest, and calibration, defined as the ratio of those expected to have a desired outcome to those observed to achieve the outcome.

Data Synthesis and Analysis

For prediction models presented as a scoring system, the sensitivity and specificity will vary depending on different cut points. Therefore, we chose to assess discrimination using area under the ROC curve (AUC), which covers all the sensitivity and specificity values at different cut points (28) and allows comparison of the prediction models. AUC of 0.5 signifies no ability to discriminate. For our study, we followed the categorizations used by Zhang et al. (29), defining 0.501–0.699 as poor discrimination, 0.700–0.799 as acceptable discrimination, 0.800–0.899 as excellent discrimination, and 0.900–1.000 as outstanding. For studies where AUC was not reported, where possible we calculated discrimination using published tables providing information on the participants, their score, and their outcome in terms of remission and nonremission. We used Stata for the analysis, generating AUC graphs and values (with 95% CI). Calibration was estimated by calculating the expected number (E) who should experience diabetes remission as reported in the model/score development paper and obtaining the observed number (O) from the tables providing information on score and outcome. This information was then used to calculate E-to-O ratio (30). E-to-O ratio of 1 represents perfect calibration, <1 represents underestimation of the events, and >1 represents overestimation (30).

As our search yielded studies with significant heterogeneity, we undertook three separate random-effects meta-analyses of studies based on *1*) their duration of follow-up, *2*) the HbA_{1c} cutoffs used to define remission, and *3*) the type of bariatric surgery (Fig. 2*A*–*F*). We excluded studies from analysis where AUC was not known or could not be estimated with 95% CI.

Our first meta-analysis was based on follow-up duration; studies were grouped into those with follow-up of 1 year and those with follow-up of >1 year. In studies where diabetes remission was defined using two HbA_{1c} cutoff values (e.g., 6.0% [42 mmol/mol] and 6.5% [48 mmol/mol]), we included the AUC for the higher cutoff only to avoid duplication of data sources.

The second meta-analysis was based on HbA_{1c} cutoffs, and studies were grouped into those with HbA_{1c} cutoffs of 6.5% (48 mmol/mol) and 6% (42 mmol/mol). In studies where diabetes remission was assessed at two follow-up points, we included the data with longer follow-up duration.

The third meta-analysis was based on type of surgery; studies were grouped into Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) groups. We excluded studies in which the discrimination score was not available for specific interventions separately. Similar to the previous two meta-analyses, we included the AUC for the higher HbA_{1c} cutoff and

Table 1—Model development studies with their predictors

Prediction model	Predictors included	Discrimination (AUC) in model development studies	Discrimination (AUC) in external validation studies
ABCD; Lee et al. (16), 2013	Age, BMI, C-peptide, and diabetes duration	0.792 (0.728–0.856)*	Fig. 2*A*, *C*, and *E*
DiaRem; Stuart et al. (17), 2014	Age, HbA_{1c}, diabetes medication other than metformin, and insulin use	0.840 (0.795–0.886)*	Fig. 2*B*, *D*, and *F*
Robertson et al. (31), 2013	BMI, diabetes duration, HbA_{1c}, fasting glucose, and diabetes medication	0.950 (0.838–0.992)	Shen et al.: 0.681 ± 0.056
DRS; Ugale et al. (33), 2014	Age, baseline BMI, diabetes duration, microvascular complications, macrovascular complication, insulin use, and stimulated C-peptides	NA	Ahuja et al.: 0.732 (0.633–0.83)*
Ad-DiaRem; Aron-Wisnewsky et al. (34), 2017	Age, HbA_{1c}, insulin use, diabetes medication other than metformin, number of glucose-lowering agents, and diabetes duration	0.911	Shen et al. 0.849 ± 0.039, Dicker et al. 0.85 (0.76–0.93), Kamocka et al. at 1 year 0.752 (0.688–0.808), Kamocka et al. at 3 years 0.794 (0.715–0.860), 5y-DR 84%
DiaBetter; Pucci et al. (35), 2017	HbA_{1c}, diabetes duration, and kind of diabetes medication	0.867 (0.817–0.916)	Shen et al. 0.826 ± 0.041, Kamocka et al. at 1 year 0.760 (0.697–0.815), Kamocka et al. at 3 years 0.804 (0.726–0.868),
MS; Aminian et al. (18), 2017	Number of diabetes medication, insulin use, diabetes duration, and HbA_{1c}	NA	Shen et al. 0.849 ± 0.040, Park et al. 0.76 (0.685–0.836),* Chen et al. 0.766 (0.716–0.817)* in GB, Chen et al. 0.599 (0.501–0.697)* in SG, Umemura et al. 0.516 (0.330–0.702)*
DiaRem2; Stuart et al. (36), 2018	Age, HbA_{1c}, diabetes medication other than metformin and insulin use, diabetes duration	0.876	NA
5y-DR (37), 2018	Preoperative factors: diabetes duration, no. of medications, HbA_{1c} Postoperative factors: no. of medications, fasting CBG, weight loss, 1-year remission	90%	NA
MDR (38), 2020	Age, HOMA2-B, diabetes duration, and HbA_{1c}	0.79 (0.71–0.88)	NA
Umemura et al. (39), 2020	insulin, diabetes duration	0.865 (0.775–0.954)*	NA
Hayes et al. (40), 2011	insulin use and HbA_{1c}	NA	0.632 ± 0.059
Dixon et al. (13), 2013	BMI, diabetes duration, C-peptide	0.90 (0.84–0.95)	0.800 ± 0.047
Ramos-Levi et al. (41), 2014	Model 1, age, sex, FG, diabetes duration, insulin	0.838 (0.725–0.951)	
	Model 2: age, sex, FG, diabetes duration, insulin, C-peptide	0.923 (0.852–0.996)	0.811 ± 0.047
	Model 3: age, sex, FG, diabetes duration, insulin, % wt loss	0.923 (0.851–0.996)	
	Model 4: age, sex, FG, diabetes duration, insulin, % wt loss, C-peptide	0.981 (0.951–1.000)	
Cotterard et al. (42), 2015	Age, sex, BMI, fasting glycemia, HbA_{1c}, hypertension, diabetes duration, insulin therapy, number of antidiabetes drugs, C-peptide	NA	NA
Stanford et al. (43), 2016	Diabetes duration, FPG, use of noninsulin antidiabetes medications, and use of insulin	0.860 (0.763–0.957)	NA

CBG, capillary blood glucose; FG, fasting glucose; FPG, fasting plasma glucose; GB, gastric bypass; HOMA2-B, HOMA2 of β-cell function; NA, not available; SG, sleeve gastrectomy; wt, weight
*Calculated by authors of this systematic review

Table 2—Study characteristics of model development studies

Publication reference	Source of data	Participant characteristics					Outcomes	Types of surgery	Presentation	Validation	
		Groups and numbers	Age (years)	BMI (kg/m^2)	Diabetes duration (years)	HbA_{1c} (%)				Val Dev	Ext Val
ABCD; Lee et al (16), 2013	Retrospective, Taiwan, multicenter, 2005–2010	*N* = 63; 17 M, 56 F					*n* = 48 (76%), FU = 1 year	RYGB	Scoring system	Y	Y
		R	36 5 ± 10 7	40 9 ± 8 9	2 1 ± 3 7	8 2 ± 1 8					
		NR	44 5 ± 7 7	33 3 ± 7 4	4 1 ± 4 5	8 5 ± 1 8					
DiaRem; Stein et al (17), 2014	Retrospective, US, multicenter, 1 January 2004–February 2011	*N* = 690; 184 M, 506 F					*n* = 463 (67%), FU = 14 months	RYGB	Scoring system	Y	Y
		N (*n* = 438)	48 8 ± 10 3	49 5 ± 8 0	6 8 ± 1 2	NA					
		(*n* = 252)	53 6 ± 8 9	49 2 ± 8 8	8 2 ± 1 7	NA					
Robert et al (31), 2013	Retrospective, observation, France, 2007–2010	*N* = 46; M:F = 1:3	45 3 ± 1 6	49 5 ± 1 22	3 (QR 2 0–6 42)	7 44 ± 0 24	DR = 62 8% at 1 year of FU	RYGB (26), GB (11), SG (9)	Scoring system	N	Y
DRS; Ugale et al (33), 2014	Retrospective, India, single, 1 February 2008–March 2010	*N* = 75; 49 M, 26 F					*n* = 42 (56%), FU = 1–2 5 years	SG	Scoring system	N	Y
		SG	51 7 ± 13 3	23 4 ± 4 5	9 9 ± 4 8	8 1 ± 0 59					
		DSG	57 6 ± 11 5	25 6 ± 4 5	10 1 ± 5	9 ± 0 78					
Ad-DiaRem; Aron-Wisnewsky et al (34), 2017	Retrospective, France, 1999–2014	*N* = 213; M 30%					*n* = 97 (45 5%), FU = 1 year	RYGB	Scoring system	Y	Y
		R	46 ± 10	48 1 ± 7 4	3 5 ± 3 8	7 0 ± 1 1					
		NR	53 ± 9	45 4 ± 7	11 1 ± 7 6	8 4 ± 1 6					
DiaBetter; Pucci et al (35), 2017	Retrospective, UK, single, 1 January 2008–December 2015	*N* = 210					*n* = 144 (68 6%), FU = 2 years	RYGB, SG	Scoring system	Y	Y
		RYGB (107)	51 6 ± 8	43 1 ± 6 3	5 6 ± 5 1	4 7 ± 5 4					
		SG (103)	49 7 ± 8 8	48 2 ± 7 8	7 8 ± 1 5	7 3 ± 1 4					
MS; Aminian et al (18), 2017	Retrospective, US, single, 2004–2011	*N* = 659; F = 451 (68%)	51 ± 10	46 4 ± 9 0	6 (3–11)	7 4 (6 4–8 6)	*n* = 291 (44 2%), FU = 5 years	RYGB, SG	Scoring system	N	Y
DiaRem2; Stein et al (36), 2018	Retrospective, US, single, 2009–2015	*N* = 307; F = 69%	51 2 ± 10 1	49 2 ± 10 3	6	NA	*n* = 135 (44 0%), FU = 1 year	RYGB	Scoring system	N	N

Continued on p. 2631

Table 2—Continued

Publication reference	Source of data	Participant characteristics					Outcomes	Types of surgery	Presentation	Validation	
		Groups and numbers	Age (years)	BMI (kg/m^2)	Diabetes duration (years)	HbA_{1c} (%)				V Dev	Ext V
5y-DR (37), 2018	Retrospective, France	*N* = 175; F = 136 (77.71%)	48.3 ± 10.3	47.37 ± 7.43	6.75 ± 6.53	7.5 ± 1.6	66 (37.7) at 1 year, 94 (53.7) at 5 years, FU = 5.1 ± 0.7 years	RYGB	Scoring system	Y	N
MDR; Mohan et al. (38), 2020	Retrospective, Singapore, 2007–2018	*N* = 114	46 ± 9	40.1 ± 6.6	6 (2–10)	8.8 ± 1.9	54 (47.4%), FU = 1 year	RYGB, SG	Scoring system	N	N
Umemura et al. (39), 2020	Retrospective, Japan, single, 2008–2018	*N* = 49; F = 22 (44.9%)	46.2 ± 12.6	42.5 ± 6.4	5.6 ± 5.7	8.0 ± 1.9	*n* = 38 (77.6%), FU = 1 year	SG	Scoring system	N	N
Hayes et al. (40), 2011	New Zealand, single, 1 November 1997–May 2007	*N* = 127; 45 M, 82 F	48.5 ± 10.1	46.8 ± 9.4	4.5 ± 5	7.7 ± 1.7	*n* = 107 (84.3%), FU = 1 year	RYGB	Logistic regression	Y	Y
Dixon et al. (13), 2013	Retrospective, Taiwan, single	*N* = 154; 49 M	39.5 ± 10.7	37.2 ± 8.8	2 (0.5–5.0)	9.1 ± 1.7	*n* = 107 (69.5%), FU = 1 year	RYGB	Logistic regression	N	Y
Ramos-Levi et al. (41), 2014	Retrospective, Spain, single, 2006–2011	*N* = 141; 30 M, 81 F	53	43.7 ± 5.6	5 (2.0–10.0)	7.3 (6.5–8.4)	*n* = 74 (52.5%), FU = 1 year	RYGB, SG, DS	Logistic regression	N	Y
Cottam et al. (42), 2015	France, single	*N* = 84; 15 M, 45 F					*n* = 50 (59.5%), FU = 1 year	RYGB	Logistic regression	N	N
		DR (*n* = 50)	46.96 ± 9.14	46.93 ± 5.82	3.86 ± 4.64	7.01 ± 1.03					
		DNR (*n* = 34)	54.47 ± 11.02	46.1 ± 6.62	14.21 ± 7.63	8.21 ± 1.32					
Stanford et al. (43), 2016	Retrospective, Canada, single, 1 January 2011–June 2014	*N* = 98; 22 M, 76 F	49.7 ± 8.5	49.7 (48.1–51.1)	6.7 ± 6.6	7.6 (7.3–7.9)	*n* = 52 of 77 (67.5%), FU = 1 year	RYGB, SG	Logistic regression	N	N

Data are mean ± SD or median (interquartile range) unless otherwise indicated. *N* = total number of participants, *n* = number of participants achieving diabetes remission. DS, duodenal switch; Ext V, external validation; F, female; FU, follow-up; GB, gastric band; , insulin; DSG, leaving interposition with divided sleeve gastrectomy; M, male; N , non insulin; NR, nonremitters; R, remitters; single, single center; V Dev, validated internal/external cohort in model development stage; Y, yes

Table 3—Study characteristics of validation studies

Publication reference	Source of data	Participant characteristics					Outcomes/events	Types of surgery	Study validated
		Groups and numbers	Age (years)	BMI (kg/m^2)	Diabetes duration (years)	HbA_{1c} (%)			
Lee et al. (44), 2015, modified	Retrospective, single, Taiwan, 2006–2013	*N* = 85; 44 M, 41 F	41.9 ± 10.9	39.0 ± 7.4	2.7 ± 3.1	8.1 ± 1.7	*n* (CR+PR) = 63 of 85 (74.1%), FU = 1 year	SG	ABCD
Lee et al. (45), 2015	Retrospective, single, Taiwan, 2006–2009	*N* = 157; 52 M, 105 F	35.7	39.8 ± 8.0	NA	8.3 ± 1.9	*n* = 111 (77.1%) at 1 year, *n* = 97 (71.3%) at 5 years, FU = 6 years (5–8)	RYGB, SG	ABCD
Lee et al. (46), 2015	Single, Taiwan, 2007–2013	*N* = 80 of 512 had BMI <30 kg/m^2; F = 50 (62.5%)	47.7 ± 9.1	26.9 ± 2.2	6.5 ± 5.1	9.1 ± 1.8	*n* (CR) = 20 (25%), FU = 1 year	RYGB, SG	ABCD
Sampaio-Neto et al. (47), 2015	Retrospective, single, Brazil, 2012–2013	*N* = 70; 6 M, 64 F	47.9 ± 9.9	NA	NA	7.6 ± 1.8	*n* (CR+PR) = 42 (35 + 7) (60%), FU = 1 year	RYGB	DiaRem
Lee et al. (48), 2016	Retrospective, single, Taiwan, 2007–2013	*N* = 245; 95 M, 150 F	44.2 ± 10.4	35.7 ± 7.8	5.8 ± 5.0	8.8 ± 1.6	*n* = 130 (53.1%), FU = 1 year	RYGB	DiaRem, ABCD
Lee et al. (49), 2017	Prospective, single, Taiwan, 2007–2014	*N* = 579; 230 M, 349 F; SG 48 M, 61 F; RYGB 182 M, 288 F					*n* = 361 (62.3%)/579 at 1 year, *n* = 71 (49.7%)/143 at 5 years	RYGB, SG	ABCD
		SG (*N* = 109)	43.2 ± 11.0	35.7 ± 7.2	3.3 ± 3.5	8.8 ± 1.5			
		RYGB (*N* = 470)	41.8 ± 10.9	36.9 ± 7.2	4.5 ± 4.8	8.6 ± 1.7			
Mehaffey et al. (50), 2017	Prospective, U.S., 2004–2013	*N* = 57, 75% F, 2 years FU; *N* = 31, 55% F, 10 years FU					*n* at 2 years = 37 (65%), *n* at 10 years = 18 (58%)	RYGB	DiaRem
		2-year FU	49.2	52.1 ± 1.5	NA	8.3			
		10-year FU	45.8	48.0 ± 6.6	NA	7.7			
Honarmand et al. (51), 2017	Retrospective, MC, U.S., 2010–2015	*N* = 900; 667 F	51.0 ± 9.1	49 ± 8.07	NA	7.6 ± 1.5	*n* = 333 (37%), FU = 1 year	RYGB	DiaRem

Continued on p. 2633

Table 3—Continued

Publication reference	Source of data	Participant characteristics: Groups and numbers	Age (years)	BMI (kg/m^2)	Diabetes duration (years)	HbA_{1c} (%)	Outcomes/events	Types of surgery	Study validated
Tharakan et al. (52), 2017	Retrospective, single, UK, 2007–2014	*N* = 262; 105 M, 157 F	51 ± 9.5	45.3 ± 7.1	NA	8.2 ± 1.8	*n* = 85 (32.5%), FU = 1 year	RYGB	DiaRem
Raj et al. (53), 2017	Prospective, single, India, 2014–2015	*N* = 53; 26 M, 27 F	45.86 ± 11.69	43.25 ± 7.4	3 (range 0–40)	8.07 ± 1.98	*n* = 43 (81.1%), FU = 1 year	RYGB, SG	ABCD
Sek et al. (54), 2018	Retrospective, single, Japan, 2007–2015	*N* = 72; 37 M, 35 F	46.8 ± 9.0	31.7 ± 2.0	9.6 ± 6.9	8.9 ± 1.5	*n* (CR) = 22 (31%), *n* (PR) = 32 (49%), FU = 1 year	SG	ABCD
Shen et al. (55), 2018	Retrospective, Taiwan, 2011–2016	*N* = 128; 58 M, 70 F	42.4 ± 10.6	39.2 ± 5.8	3.2 ± 3.8	8.0 ± 1.7	*n* (CR) = 92 (71.9%), *n* (PR) = 103 (80.5%), FU = 1 year	SG	ABCD, MS, DiaRem, Ad-DiaRem, DiaBetter
Natoh et al. (56), 2018	Retrospective, MC, Japan, 2005–2015	*N* = 298; 140 M, 158 F					*n* (CR+PR) = 247 (82.9%), FU = 1 year	LSG, LSG/DJB	ABCD
		LSG (*N* = 177)	45.2	45.2	5.9 ± 6.1	7.3 ± 6.0			
		LSG/DJB (*N* = 131)	45.2	43.5	7.7 ± 1.7	8.3 ± 1.7			
Ahuja et al. (57), 2018	Retrospective, single, India, 2010–2015	*N* = 102	45.63 ± 11.12	44.85 ± 9.24	5.3 ± 5.08	8.26 ± 1.8	*n* = 72 (70.6%), FU = 1 year	RYGB	DiaRem, DRS, ABCD
Amak et al. (58), 2018	Retrospective, single, Taiwan, 2007–2015	*N* = 406; F = 64%	42.6	36.4	3.1	8.6	*n* = 291 (71.7%), FU = 5 years	RYGB	ABCD
Chen et al. (59), 2018	Single, Taiwan, 2004–2012	*N* = 310; 114 M, 196 F	40.1 ± 11.1	37.8 ± 7.6	3.6 ± 4.4	8.6 ± 1.8	*n* = 224 (72.3%), FU = 5 years	RYGB, SG	MS, ABCD
Wood et al. (60), 2018	Retrospective, single, US, 2002–2014	*N* = 520; 124 M, 396 F	46.7–53.0	NA	NA	7.2 to 7.5	*n* = 249; RYGB *n* = 173, SG *n* = 63, GB *n* = 13	RYGB, SG, GB	DiaRem

Continued on p. 2634

Table 3—Continued

Pub cat on reference	Source of data	Part c pant character st cs					Outcomes/events	Types of surgery	Study va dated
		Groups and numbers	Age (years)	BM (kg/m^2)	D abetes durat on (years)	HbA$_{1c}$ (%)			
D cker et a (61), 2019	Retrospect ve, srae , 1999–2011	*N* = 2,190; 64 8% F	47 1 ± 10 9	43 5 ± 6 3	NA	7 7 ± 1 6	*n* = 897 (59 7%)/1,502 at 2 years, *n* = 782 (53 6%)/1,459 at 5 years	RYGB, SG, GB	Ad-D aRem, D aRem
Kam et a (62), 2020	Retrospect ve, Ch na	*N* = 214 at 1 year, 117 (54 7%) F; 131 at 3 years	48 (37–57)	30 6 (28 7–32 9)	6 0 (3–10)	8 0 (7 1–9 8)	113 of 214 (52 8%) at 1 year, 59 of 131 (45 0%) at 3 years	RYGB	ABCD, D aRem, Ad-D aRem, D aBetter
Park et a (63), 2020	Retrospect ve, Korea	*N* = 135, 103 (76%) F	40 ± 11	39 0 ± 6 3	1 (0–5)	7 5 (6 8–8 9)	*n* = 88 (65 2%), FU = 1 year	RYGB, SG	MS
Lee et a (64), 2020	Retrospect ve, 2006–2014	*N* = 59, 38 F	47 7 ± 12 4	37 6 ± 5 1	2 7 ± 3 1	8 3 ± 2 2	37 (62 7%) at 1 year, 24 (42 4%) at 5 years	SG	ABCD
Guerron et a (65), 2020	Retrospect ve, North Caro na, 2000–2007	*N* = 602, 441 (73 3%) F	50 6 ± 10 2	47 1 ± 7 8	NA	7 5 ± 1 4	*n* (CR) = 215 (35 7%), *n* (on y PR) = 134 (22 3%)	RYGB, SG, BPD/DS, LAGB	D aRem

Data are mean ± SD or med an (nterquart e range) un ess otherw se nd cated *N* = tota number of part c pants *n* = number of part c pants ach ev ng d abetes rem ss on BPD, b opancreat c d vers on; CR, comp ete rem ss on; DS, duodena sw tch; F, fema e; FU, fo ow-up; GB, gastr c band; LAGB, aparoscop c adjustab e gastr c band; LSG, aparoscop c s eeve gastrectomy; LSG/DJB, aparoscop c s eeve gastrectomy w th duodena -jejuna bypass; M, ma e; MC, mu t center; NA, not ava ab e; PR, part a rem ss on; s ng e, s ng e center

longer follow-up duration where AUC was available for more than one HbA$_{1c}$ cutoff or length of follow-up.

RESULTS

Following the initial search, we retrieved 5,825 articles. After removal of 1,660 duplicates, 4,165 publications were identified for title and abstract screening: 91 publications were identified as eligible for full text screening, and 44 were excluded, as these were conference papers or posters with limited information, especially on methods and risk of bias. The remaining 47 published articles were screened by full text; 9 were excluded after screening of the full text (reasons outlined in Supplementary Table 2). The remaining 38 published articles were retained for data extraction.

Study Characteristics

Of the 38 studies included in this review, 16 focused on model development (Tables 1 and 2) and 22 focused on external validation (Table 3). External validation studies were defined as studies validating a predefined prediction model in a different population or time period from the population/time period used to develop the model.

Model Development Studies

Of the 16 model development studies, 11 produced scoring systems, while the other 5 were logistic regression prediction models. The scoring systems were as follows: ABCD, for age, BMI, C-peptide, and duration (Lee et al. [16]), from Taiwan in 2013; Robert et al. (31) from France in 2013; Diabetes Remission score (DiaRem) (Still et al. [17,32]) from the U.S. in 2014; diabetes remission score (DRS) (Ugale et al. [33]) from India in 2014; Individualized Metabolic Surgery (IMS) score (Aminian et al. [18]) from the U.S. in 2017; Advanced-DiaRem (Ad-DiaRem) (Aron-Wisnewsky et al. [34]) from France in 2017; DiaBetter (Pucci et al. [35]) from the U.K. in 2017; DiaRem2 (Still et al. [36]) in 2018, an updated version of the preexisting DiaRem model developed by the same group; 5-year diabetes remission (5y-DR) (Debédat et al. [37]) from France in 2018; Metabolic Surgery Diabetes Remission (MDR) score (Moh et al. [38]) from Japan in 2020; and Umemura et al. (39) from Singapore in 2020. The five logistic

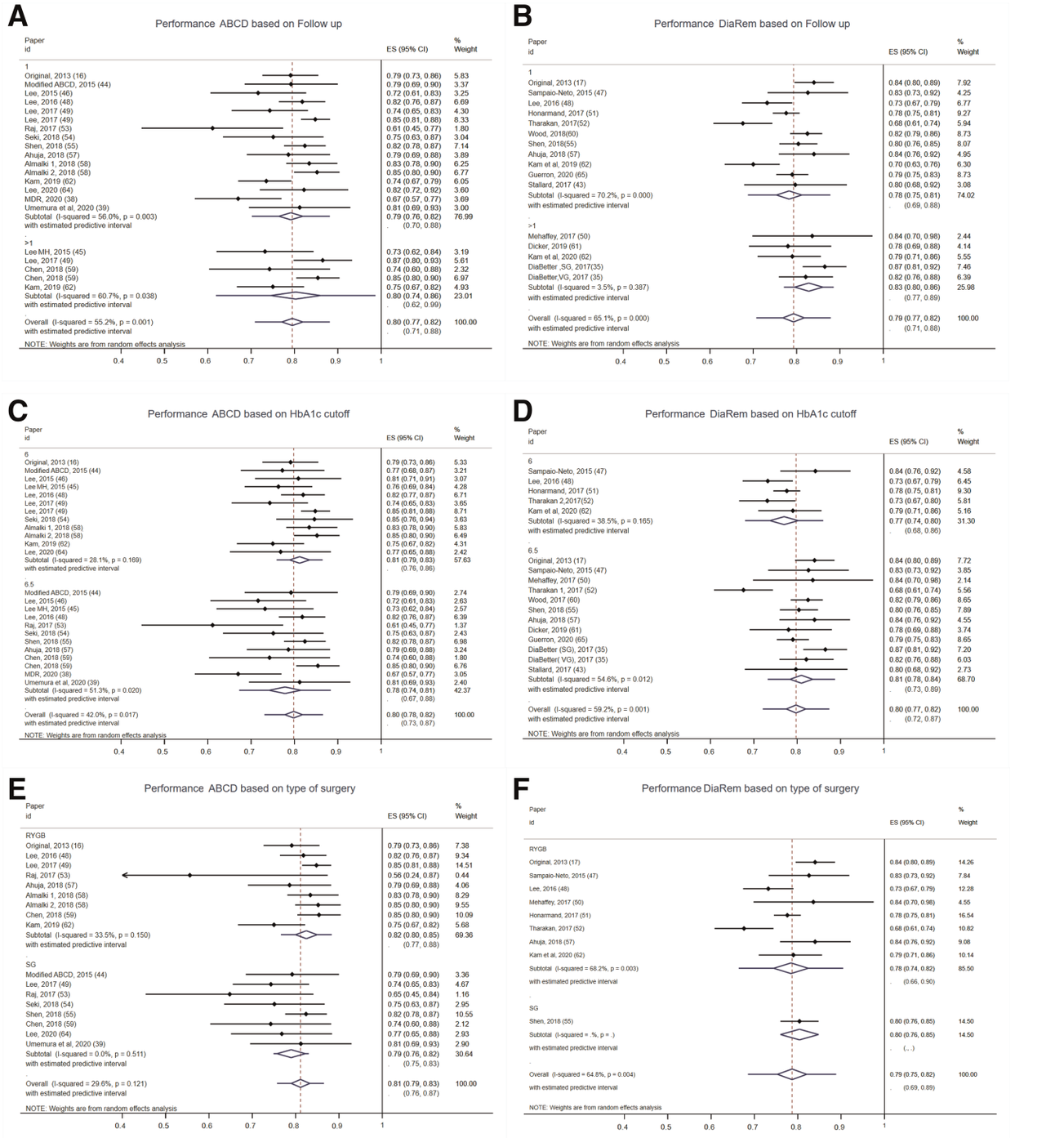


Figure 2 Meta analysis. *A*: Performance of ABCD based on follow up. *B*: Performance of DiaRem based on follow up. *C*: Performance of ABCD based on HbA_{1c} cutoff defining diabetes duration. *D*: Performance of DiaRem based on HbA_{1c} cutoff defining diabetes duration. *E*: Performance of ABCD based on type of bariatric surgery. *F*: Performance of DiaRem based on type of bariatric surgery. ES, effect size.

regression models were those of Hayes et al. (40) from New Zealand in 2011, Dixon et al. (13) from Taiwan in 2013, Ramos-Levi et al. (41) from Spain in 2014, Cotillard et al. (42) from France in 2015, and Stallard et al. (43) from Canada in 2016 (Table 2).

Participants

Of 16 studies, 14 used retrospective data and 2 used prospective data (13,40). Eight studies included participants who had undergone RYGB (13,16,17,34,36,37, 40,42), two studies included participants who had SG (33,39), and the remaining studies included more than one type of bariatric surgical procedure (18,31,35,38, 41,43). Study sample size ranged from 46 to 690 participants, with a female preponderance except in two studies, DRS (Ugale et al. [33]) and the study of Umemura et al. (39), which had higher male

representation. The mean age of participants ranged between 36.5 and 57.6 years and mean BMI from 23.4 (33) to 49.7 kg/m^2. Diabetes duration was available for all studies except that of Umemura et al. (39). Mean diabetes duration ranged from 2.1 years in the study by Lee et al. (16) (ABCD model) to 9.9 years in that of Ugale et al. (33) (DRS model). Preoperative HbA_{1c} ranged from 6.8% (51 mmol/mol) in the study by Still et al. (17) (DiaRem score) to 9.1% (76 mmol/mol) in the study of Dixon et al. (13).

Follow-up Duration

The median follow-up range was 1–5 years. The majority of the studies reported remission rates at 1 year. Three studies reported longer follow-up: 2 years in DiaBetter (Pucci et al. [35]) and 5 years in IMS (Aminian et al. [18]) and 5y-DR (Debédat et al. [37]).

Outcome Definition

Different definitions for diabetes remission were noted with some focusing on complete diabetes remission (defined as HbA_{1c} <6.0% [42 mmol/mol] and no antidiabetes medication for at least 12 months) (13,16,31,37) and others combining complete and partial diabetes remission (defined as <6.5% [48 mmol/mol] and off medications for 12 months) (17,18,34,38,39). DiaRem2 (36) and Stallard et al. (43) defined diabetes remission as an HbA_{1c} of <5.7% (39 mmol/mol) and ≤5.9% (41 mmol/mol), respectively, after patients were off antidiabetes medications at 12 months.

Method/Analysis and Presentation

Predictors in the models varied and included age, baseline BMI, C-peptide, diabetes duration, HbA_{1c}, insulin use, glucose-lowering medications, sex, and micro- and macrovascular complications. 5y-DR (37) included postoperative variables as predictors in the prediction model. The number of predictors ranged from 2 (40) to 10 (42). For five prediction models a logistic regression model was proposed; for the models of Dixon et al. (13) and Hayes et al. (40) a logarithmic equation was given, while Ramos-Levi et al. (41), Cotillard et al. (42), and Stallard et al. (43) defined the predictors to be included in the prediction model but gave no equation in their publication.

The method for deriving the scoring system varied among the 11 models. For DiaRem (17) and DiaRem2 (36) investigators reported hazard ratios using Cox regression and odds ratios of the final logistic models, respectively, to create a scoring system. Umemura et al. (39) used a weighing algorithm and gave an odds ratio. In IMS (18) a nomogram and benchmarks selected by an expert panel were used. Ad-DiaRem (34) and 5y-DR (37) used machine learning; Ad-DiaRem used a sparse support vector machine and formulated a linear integer programming task, and 5y-DR used a fully corrective binning approach to assign intervals and weight for each variable. MDR (38) used quartile and tertile cutoffs to obtain the weighting of each of the predictors in the scoring system. ABCD (16), Robert et al. (31), DRS (33), and DiaBetter (35) offered no information on how the weighting for individual predictors was decided.

Performance

For representing the model performance, AUC was presented in the publications of Ad-DiaRem (34), Dixon et al. (13), Robert et al. (31), Ramos-Levi et al. (41), Stallard et al. (43), DiaBetter (35), DiaRem2 (36), 5y-DR (37), and MDR (38). We calculated the AUC for ABCD (16), DiaRem (17) and the study by Umemura et al. (39) (Supplementary Material). No AUC or performance was reported for DRS (33), IMS (18) or by Hayes et al. (40) or Cotillard et al. (42), and data in the publications were insufficient to calculate these.

Of 12 prediction models for which AUC was available, 10 (Dixon et al. [13], Ramos-Levi et al. [41], Stallard et al. [43], DiaRem [17], Robert et al. [31], Ad-DiaRem [34], DiaBetter [35], DiaRem2 [36], 5y-DR [37], and Umemura et al. [39]) had excellent discrimination (0.80–0.89) and two (ABCD [16] and MDR [38]) had acceptable discrimination (0.70–0.79), irrespective of diabetes remission definition (Table 1).

Risk of Bias Assessment

The studies developing DiaRem (17) and Ad-DiaRem (34) were found to have low risk of bias, and that of Dixon et al. (13) was of unclear risk. The remaining model development studies had high risk of bias, mainly due to deficiencies in the analysis domain. However, the applicability in practice was of low risk in all model development studies (Supplementary Table 5).

Validation Studies

We identified 22 studies externally validating the prediction models (44–65). Study characteristics are summarized in Table 3. Of the 22 external validation studies, 9 validated the ABCD score, 6 validated DiaRem, 1 validated IMS, and the remaining 6 compared two or more models.

Participants

In 19 studies retrospective data were used (44–48,51,52,54–65), and in 3 data were collected prospectively (49,50,53). The sample size ranged from 53 (53) to 2,190 (61), and mean age ranged from 35.7 years (45) to 51.0 years (51,52,65). All studies had a female predominance except one (54). Mean BMI ranged from 26.9 kg/m^2 (46) to 52.1 kg/m^2 (50). Median diabetes duration ranged from 1 year (63) to 9.6 years (54), and mean presurgery HbA_{1c} ranged from 7.2% (55 mmol/mol) (60) to 9.1% (76 mmol/mol) (46).

Eight studies included participants who underwent RYGB (47,48,50–52,57,58,62), five included participants who underwent SG (44,54–56,64), and the remaining nine included a range of surgery types (45,46, 49,53,59–61,63,65) (Table 3).

Follow-up Duration

One study had a follow-up period of 10 years (50), six studies had a follow-up period of 5 years (45,49,58,59,61,64), one had 3 years' follow-up (62), and the remaining studies had follow-up of 1 year.

Outcome Definition

For defining diabetes remission, the HbA_{1c} cutoff was taken as 5.7% (39 mmol/mol) in two studies (51,65) and 6.0% (42 mmol/mol) in 13 studies (44–49,52,54, 55,58,62,64), and in the remaining studies diabetes remission was def-ined as HbA_{1c} ≤6.5% (48 mmol/mol).

Performance

Although 16 models were identified in model development studies, few of these were externally validated in more than one external cohort; models that were externally validated in more than one

cohort were predominantly scoring systems. Direct comparison of the models was seen in only six studies (48,55, 57,59,61,62).

Here we present the assessment of validation studies based on the prediction models validated. As ABCD and DiaRem scores were validated most frequently, we present these studies first followed by the remainder of the prediction models externally validated.

ABCD Score

In the original model development paper, the authors also reported an external validation in a new cohort (16). We calculated the AUC to be 0.79 (95% CI 0.73–0.86) (acceptable discrimination) (Table 1 and Fig. 2) and calibration (E-to-O ratio) as 1.01 in the external cohort. In a subsequent study, ABCD score cutoff values for each variable were modified (44). In this cohort, we calculated AUC as 0.77 (0.68–0.87) and 0.79 (0.69–0.90) for complete and partial diabetes remission, respectively (44). Calibration was not available.

The ABCD score with the new cutoffs (44) has been externally validated in 13 studies (45,46,48,49,53–59,62,64). Of these 13 validation studies, 5 looked at long-term diabetes remission at 3–5 years (45,49,59,62,64) and the remaining 8 at 1 year. In one study poor discrimination was found (53), while in others the discrimination was found to be acceptable to excellent depending on the type of surgery and follow-up duration. Model development studies for MDR (38) and Umemura et al. (39) also validated ABCD in their cohort and found the performance to be poor and excellent, respectively.

It was difficult to ascertain calibration score, as it was not widely available, and when available the results were inconsistent. Calibration was only mentioned in two studies (55,62) and found to be overestimating by 13% (55) and 12% (62) for diabetes remission at 1 year and underestimating by 15% (62) at 3 years.

ABCD Meta-analysis. For ABCD, meta-analysis of the results from multiple studies showed acceptable discrimination with AUC of 0.79 (95% CI 0.76–0.82) for 1-year follow-up and 0.80 (0.74–0.86) for longer-term follow-up (Fig. 2*A*). At the different HbA_{1c} cutoffs, discrimination was excellent with an AUC of 0.81 (95% CI 0.79–0.83) for HbA_{1c} cutoff of 6.0% (42 mmol/mol) and acceptable at 0.78 (0.74–0.81) for HbA_{1c} cutoff of 6.5% (48 mmol/mol) (Fig. 2*B*). For RYGB, meta-analysis showed excellent discrimination for ABCD with an AUC of 0.82 (95% CI 0.80–0.85), while for SG, discrimination was acceptable with AUC of 0.79 (0.76–0.82) (Fig. 2*C*).

DiaRem Score

The DiaRem score has been externally validated in 11 studies (47,48,50–52,55, 57,60–62,65) (Table 1 and Fig. 2). Three studies looked at long-term (>1 year) (50,61,62) diabetes remission, and the remaining focused on remission at 1 year.

Excellent discrimination was found for five external validation studies (47,50,55, 57,60), acceptable for five (48,51,61,62, 65), and poor for one (52).

Calibration was presented in two studies (55,62). We were able to calculate the E-to-O ratio for a further six studies: DiaRem underestimated the probability of diabetes remission in the studies by Ahuja et al. (57) (E-to-O ratio 0.67) and Mehaffey et al. (50) (E-to-O ratio 0.63 at 2 years and 0.71 at 10 years). It overestimated the probability of diabetes remission in the other four studies (47,48,51,52), with E-to-O ratios of 1.31, 1.71, 1.14, and 1.25 in the studies by Honarmand et al. (51), Lee et al. (48), Sampaio-Neto et al. (47), and Tharakan et al. (52), respectively. Calibration was inconsistent across the studies.

In the model development studies of Ad-DiaRem (34), DiaBetter (35), DiaRem2 (36), and 5y-DR (37), DiaRem was validated in their cohorts and excellent discrimination was found, while Stallard et al. (43) found good discrimination.

DiaRem Meta-analysis. In meta-analysis, discrimination for DiaRem was as follows: AUC 0.78 (95% CI 0.75–0.81) for short-term and 0.83 (95% CI 0.80–0.86) for longer-term follow-up (Fig. 2*B*). At HbA_{1c} cutoffs of 6.0% (42 mmol/mol) and 6.5% (48 mmol/mol), the AUCs were 0.77 (95% CI 0.74–0.80) and 0.81 (95% CI 0.78–0.84), respectively (Fig. 2*D*).

For RYGB, meta-analysis showed acceptable discrimination for DiaRem with AUC of 0.78 (95% CI 0.74–0.82). No meta-analysis was performed for SG, as there was only one study identified with validation of DiaRem in an SG cohort (Fig. 2*F*).

Performance of Other Prediction Models

The discrimination scores for other prediction model are summarized in Table 1. The IMS score was externally validated by three validation studies (55,59,63) and one model development study (Umemura et al. [39]). Discrimination was found to be excellent in the study by Shen et al. (55) and acceptable in the RYGB cohort of Chen et al. (59) and in the study by Park et al. (63) but poor in the SG cohort of Chen et al. (59) and Umemura et al. (39).

Ad-DiaRem (34) was externally validated in three validation studies (55,61, 62) and 5y-DR model development study (37). Kam et al. (62) in their study found acceptable performance, while the other three found excellent performance.

DiaBetter (35), Dixon et al. (13), and Ramos-Levi et al. (41) were noted to have excellent discrimination (55), and DRS (33) had good performance in one external validation study (57). The Robert et al. (31) and Hayes et al. (40) prediction models performed poorly in one external validation with an AUC <0.70 (55). No external validation studies are available for DiaRem2 (36), Stallard et al. (43), Cotillard et al. (42), 5y-DR (37), MDR (38), or Umemura et al. (39).

Calibration in an external validation study for Ad-DiaRem, DiaBetter, Dixon et al., and Ramos-Levi et al. found the models to be overestimating with predicted (or expected)-to-observed ratios of 1.06, 1.05, 1.13, and 1.12, respectively (55). Hayes et al. and Robert et al. were noted to be overestimating by 23–30% with predicted-to-observed ratios of 1.23 and 1.30, respectively (55).

Risk of Bias Assessment

Guerron et al. (65) had low risk of bias, three studies (45,50,53) were classified as high risk of bias as a result of the analysis domain, and the remaining external validation studies had unclear risk of bias (Supplementary Table 6). We rated risk of bias in the analysis domain as unclear either if information on missing data was not reported or was not included in the analysis or if model performance was not reported; if neither was reported, we rated the domain as high risk of bias. However, no concerns were raised in terms of applicability, with all studies rated as low risk.

Ideally, a sensitivity analysis restricted to low risk of bias studies should be performed. In our review, only one external

validation study—validating the DiaRem model—was rated as low risk of bias (65); results of the meta-analyzed studies for DiaRem were consistent with the findings of this study.

CONCLUSIONS

In this systematic review, we have identified currently available models for predicting diabetes remission following bariatric surgery. We assessed and compared the performance of these models and evaluated their applicability in clinical settings. The most externally validated models in our review were ABCD and DiaRem. Although the ABCD and DiaRem models were primarily developed for predicting diabetes remission at 1-year follow-up, they have been validated in studies predicting long-term diabetes remission. The AUC estimate for DiaRem for long-term diabetes remission and diabetes remission defined with an HbA_{1c} cutoff of 6.5% (48 mmol/mol) was higher than for ABCD. The AUC for ABCD for predicting short-term remission and diabetes remission defined by an HbA_{1c} cutoff of 6.0% (42 mmol/mol), was higher than that for DiaRem. Specifically for patients who underwent RYGB, AUC was higher in ABCD than for DiaRem. However, in all instances, CIs overlapped.

Due to the lack of discrimination (AUC) score with 95% CI, we were not able to include in our meta-analysis three studies (34,37,43) conducted on patients who underwent RYGB and validating DiaRem that otherwise showed excellent performance. Furthermore, many studies validating ABCD were conducted by the same authors who developed the ABCD model and included patient cohorts similar to the derivation population, raising the possibility of bias based on population selection. It was therefore not possible to determine whether one model was better than the other.

Remission of diabetes is an important outcome for patients considering bariatric surgery. A project by Diabetes UK, led by patients with type 2 diabetes and their carers, identified diabetes cure or reversal as a top research priority (66). With the increasing number of patients with obesity and type 2 diabetes now being offered bariatric surgery, it is important to identify those who are more likely to achieve remission. This will enable patients and health care professionals to make informed choices when considering different treatment options. However, given the wide choice of prediction models currently available, it is difficult to identify the ones that best predict remission and are easy to use in routine clinical practice.

The models identified in our review had certain common characteristics in relation to the predictors included and the duration of follow-up, which for most studies was 12 months. On the other hand, there was considerable heterogeneity in the definition of diabetes remission, cohort size, and populations studied, including types of bariatric surgery, thereby adding to the difficulty in comparing these models. We found significant variation in the threshold for HbA_{1c} used to define diabetes remission, with cutoffs ranging from 5.7 to 6.5% (39 to 48 mmol/mol), and with some studies using a combination of partial and complete remission. However, in this review, we found that the definition did not affect the performance of the prediction models significantly.

Duration of diabetes remission is an important consideration in assessment of the benefits of bariatric surgery in patients with type 2 diabetes. In our review, we observed that 13 of 16 model development studies were designed with the aim of predicting diabetes remission at 1 year, thus underscoring the need for longer follow-up of cohorts (18). The rate of diabetes remission has been inversely associated with diabetes duration and has been noted to be greatest in patients with shorter diabetes duration (12,67). Moreover, diabetes remission is highest during the first year following the intervention and declines over subsequent years and with longer follow-up (7–9). In the prospective Swedish Obese Subjects (SOS) study, with follow-up of $>$18 years, the incidence of diabetes remission was 72.3% at 2 years, 38.1% at 10 years, and 30.4% at 15 years (68). In a randomized controlled trial with 5 years' follow-up, findings indicated diabetes relapse in 53% of patients in the RYGB group and 37% in the biliopancreatic diversion group among patients who achieved diabetes remission at 2 years' follow-up (9). Similar results were reported in a retrospective multisite study from the U.S. with 5 years' follow-up (69). These findings suggest that diabetes may relapse over time and that in a high proportion of patients, remission of diabetes may only be achieved for a short term. Despite this, short-term diabetes remission may offer huge clinical and financial benefits to patients and health care systems. Besides the benefit of reduction in the incidence of micro- and macrovascular diabetes–related complications, short-term diabetes remission, through freedom from diabetes medications and reduced need for monitoring, may motivate patients to maintain weight loss and enhance their quality of life.

Future studies should therefore include a uniform and agreed definition of diabetes remission and a longer follow-up period to determine the effects of bariatric surgery on long-term diabetes remission. This is particularly important when considering the cost-effectiveness of bariatric surgery.

The outcomes of bariatric surgery such as weight loss and long-term metabolic benefit vary with the type of bariatric procedure (5,70,71). A network meta-analysis showed that the probability of achieving diabetes remission was greatest in mini–gastric bypass (91.2%), followed by biliopancreatic diversion without duodenal switch (87.3%), laparoscopic SG (61.4%), RYGB (59.3%), gastric banding (29.6%), and then great curvature plication (18.6%) (71). Despite this, none of the prediction models included the type of surgery as a predictor. However, when we analyzed the performance of prediction models in RYGB and SG separately, we found no major differences between the two procedures. With many new bariatric procedures becoming available, there is a need to develop and validate the models across the various bariatric procedures.

The indication for bariatric surgery in patients with BMI $<$35 kg/m^2 is contentious, and currently none of the guidelines recommend bariatric surgery in nonobese individuals. In a recent systematic review and meta-analysis Ji et al. (72) evaluated 12 studies examining the impact of bariatric surgery in patients with type 2 diabetes and BMI $<$30 kg/m^2 over a follow-up period ranging from 6 months to 3 years. They found a 1.58% ($\sim$16 mmol/mol) reduction in HbA_{1c} at 2 years using a random-effects model (72). However, investigators of other studies comparing the impact of bariatric surgery in populations with and without obesity observed that surgery in a population

without obesity is a less effective tool for diabetes management (73). We found two studies—a model development study by Ugale et al. (33) and the validation study of Lee et al. (46)—with a focus on cohorts with mean BMI ≤30 kg/m^2; Ugale et al. did not provide model discrimination, and Lee et al. found acceptable discrimination in this normal weight population. Based on available data, it is difficult to assess the performance of prediction models in those with low BMI. The impact of BMI on the performance of the prediction models is important and requires further study.

Susceptibility to type 2 diabetes is known to vary among people of different ethnicities, and it is likely that these differences may extend to remission of diabetes following bariatric surgery. In the studies included in our review, the test cohort for DiaRem was 98% Caucasian, while for ABCD, the participants were from five Asian clinics. We identified one validation study where Wood et al. (60), validating the DiaRem score in a White and Hispanic population, noted an AUC of 0.84 (0.80–0.88) and 0.79 (0.71–0.86) in White and Hispanic patients, respectively. A meta-analysis including 14 studies showed greater weight loss in Caucasians compared with African Americans, but no difference was noted in the outcome of diabetes remission between these two ethnic groups (74,75). None of the prediction models identified ethnicity as a predictor, and data on direct comparisons between ethnic groups were limited to the above-mentioned studies. We were therefore unable to explore any possible differences between ethnicity and incidence of diabetes remission post–bariatric surgery.

Five of the models, including two scoring systems, ABCD (16) and DRS (33), and three logistic regression models, of Dixon et al. (13), Ramos-Levi et al. (41), and Cotillard et al. (42), included C-peptide levels (13,16,33,41,42) as one of the predictors. C-peptide can be measured as urinary C-peptide, urinary C-peptide–to–creatinine ratio, or venous blood C-peptide levels measured as random, fasting, or in a stimulated state (glucagon stimulation test, mixed-meal tolerance test) (76). These factors may pose difficulties in standardization and can present as a limitation in using certain scoring systems that have C-peptide as one of the predictors. Moreover, C-peptide is not measured routinely in the diagnosis or management of type 2 diabetes in most clinical settings. Prediction models using C-peptide, therefore, cannot be widely used by primary care physicians or in the early stages of weight management consultation. Models such as DiaRem and Ad-DiaRem that focus predominantly on routinely measured clinical parameters may therefore have greater applicability across a wider range of clinical settings. If C-peptide is available, however, ABCD (16) is a reliable prediction model with a similar predictive performance and has the advantage of being validated in different bariatric procedures and for long-term diabetes remission (49,59,62). 5y-DR (37) included postoperative number of glucose-lowering medications, fasting capillary blood glucose, weight loss, and 1-year remission to predict long-term diabetes remission. Postoperative parameters will not be available in the clinical consultation setting for bariatric surgery, and, hence, use of this prediction model is limited.

Treatment with insulin has been used in many models as a predictor. Patient preference for noninsulin treatments and therapeutic inertia are recognized causes for delay in treatment with insulin (77). In instances where insulin treatment is delayed, treatment with insulin as a predictor can overestimate the chances of remission. Conversely, if insulin is initiated early, the possibility of diabetes remission may be underestimated.

The inconsistency in calibration scores with existing models either overestimating or underestimating the observed remission rates suggests that there are other variables that could influence remission. The utility of the prediction models largely depends on the clinical setting and resources available. The choice of a model used to predict remission must therefore be tailored to these factors.

Strengths and Limitations

We believe our study is the first systematic review summarizing prediction model performance for diabetes remission in patients undergoing bariatric surgery. We calculated the discrimination score (AUC) for the studies where data were available and where AUC was not reported by the authors themselves.

While the robust search strategy used in this review is a strength of our study, there are certain limitations: we restricted our search to articles published in English and published in the last 15 years. We were also unable to contact the authors for further information regarding the performance of prediction models, where pertinent information was not available. It is possible that some relevant articles were not included in the review and meta-analysis. However, not many prediction models were available before our search date and the likely impact of this on our findings would be minimal.

While the key messages were consistent, a large proportion of the studies were conducted in small cohorts of patients with short duration of follow-up. In the majority of external validation studies routinely collected data were used; consequently, follow-up data were not available for all patients who underwent bariatric surgery. While the studies had predefined inclusion and exclusion criteria for participants, with complete data at 1 year of follow-up for those included, there remains a possibility of selection bias due to lack on information on patients lost to follow-up in the routinely collected source data. Validation studies in large cohorts with longer follow-up are therefore needed to overcome these limitations.

Conclusion

This systematic review identified 16 prediction models, with DiaRem (17) and ABCD (16) as the two most widely validated models to predict diabetes remission following bariatric surgery. Newer models published in the last 3–4 years showed promising results in test cohorts, but there is a limited number of external validation studies. More external validation studies are needed for assessing the performance and clinical applicability of the new prediction models. Future studies should also examine these models in real-world clinical settings to assess the impact on patient outcomes.

Acknowledgments. Sue Bayliss (Institute of Applied Health Research, University of Birmingham, Birmingham, U.K.) reviewed the search strategy.

Funding. A.A.T. is a clinician scientist supported by the National Institute for Health Research (NIHR) in the U.K. (CS 2013 13 029). M.P. was supported by the NIHR Birmingham

Biomedical Research Centre at the University Hospitals Birmingham NHS Foundation Trust and the University of Birmingham.

The views expressed are those of the author(s) and not necessarily those of the National Health Service, the NIHR, or the Depart ment of Health and Social Care.

Duality of Interest. K N. reports funding from AstraZeneca (RSBD20464) and fees from Sanofi and Boehringer Ingelheim outside the submitted work. SB has received consultation and/or lec ture fees from Sanofi Aventis, Astra Zeneca, Eli Lilly, Boehringer Ingelheim, NAPP, MSD, grants and personal fees from Novonordisk Ltd. outside the submitted work. A.A.T. reports personal fees and nonfinancial support from Novo Nordisk, Eli Lilly, AstraZeneca, and Boehringer Ingelheim; per sonal fees from Janssen; and nonfinancial sup port from Impeto Medical, ResMed, and Aptiva outside the submitted work. No other potential conflicts of interest relevant to this article were reported.

The funders had no role in the study design, data collection, or analysis; decision to publish; or preparation of the manuscript.

Author Contributions. P.S., K.N., and S.B. developed the original study question. P.S. and S.B. conducted the screening. Data collection and risk of bias assessment were performed by P.S., N.J.A. J H., and S.B. P.S. and M P. performed the analysis, and this was interpreted by P.S., A.A.T., K.N., and S.B. P.S. wrote the first draft of the manuscript, which was revised and edited by N.J.A., A.A.T., K.N., and S.B. All authors reviewed and approved the final draft of the manuscript.

References

1. Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. N Engl J Med 2012;366:1577 1585
2. Schauer PR, Bhatt DL, Kirwan JP, et al.; STAMPEDE Investigators. Bariatric surgery versus intensive medical therapy for diabetes 5 year outcomes. N Engl J Med 2017;376:641 651
3. Mistry P, Currie V, Super P, le Roux CW, Tahrani AA, Singhal R. Changes in glycaemic control, blood pressure and lipids 5 years following laparoscopic adjustable gastric banding combined with medical care in patients with type 2 diabetes: a longitudinal analysis. Clin Obes 2018;8:151 158
4. Avenell A, Robertson C, Skea Z, et al. Bariatric surgery, lifestyle interventions and orlistat for severe obesity: the REBALANCE mixed methods systematic review and economic evaluation. Health Technol Assess 2018;22:1 246
5. Singh P, Subramanian A, Adderley N, et al. Impact of bariatric surgery on cardiovascular outcomes and mortality: a population based cohort study. Br J Surg 2020;107:432 442
6. Singh P, Adderley N, Subramanian A, Gokhale K, Singhal R, Toulis KA, et al. The impact of bariatric surgery on incident microvascular complications in patients with type 2 diabetes: a matched controlled population based retrospective cohort study. Diabetes Care 2021;44:116 124
7. Brethauer SA, Aminian A, Romero Talamás H, et al. Can diabetes be surgically cured? Long term metabolic effects of bariatric surgery in obese patients with type 2 diabetes mellitus. Ann Surg 2013;258:628 636
8. Schauer PR, Mingrone G, Ikramuddin S, Wolfe B. Clinical outcomes of metabolic surgery: efficacy of glycemic control, weight loss, and remission of diabetes. Diabetes Care 2016;39 902 911
9. Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow up of an open label, single centre, randomised controlled trial. Lancet 2015;386:964 973
10. Rubino F, Nathan DM, Eckel RH, et al.; Delegates of the 2nd Diabetes Surgery Summit. Metabolic surgery in the treatment algorithm for type 2 diabetes: a joint statement by international diabetes organizations. Diabetes Care 2016;39: 861 877
11. Mahmood F, Munasinghe A, MacAno C, et al. Factors predicting remission or improvement of type 2 diabetes after gastric bypass. Surg Obes Relat Dis 2016;12(7 Suppl.):S165 S166
12. Panunzi S, Carlsson L, De Gaetano A, et al. Determinants of diabetes remission and glycemic control after bariatric surgery. Diabetes Care 2016;39:166 174
13. Dixon JB, Chuang L M, Chong K, et al. Predicting the glycemic response to gastric bypass surgery in patients with type 2 diabetes. Diabetes Care 2013;36:20 26
14. Blackstone R, Bunt JC, Cortes MC, Sugerman HJ. Type 2 diabetes after gastric bypass: remission in five models using HbA1c, fasting blood glucose, and medication status. Surg Obes Relat Dis 2012;548 555
15. Park JY. Prediction of diabetes remission after bariatric or metabolic surgery. J Obes Metab Syndr 2018;27:213 222
16. Lee W J, Hur KY, Lakadawala M, et al. Predicting success of metabolic surgery: age, body mass index, C peptide, and duration score. Surg Obes Relat Dis 2013;9:379 384
17. Still CD, Wood GC, Benotti P, et al. Preoperative prediction of type 2 diabetes remission after Roux en Y gastric bypass surgery: a retrospective cohort study. Lancet Diabetes Endocrinol 2014;2:38 45
18. Aminian A, Brethauer SA, Andalib A, et al. Individualized Metabolic Surgery score: proce dure selection based on diabetes severity. Ann Surg 2017;266:650 657
19. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta analyses: the PRISMA statement. PLoS Med 2009;6:e1000097
20. Geersing GJ, Bouwmeester W, Zuithoff P, Spijker R, Leeflang M, Moons KG. Search filters for finding prognostic and diagnostic prediction studies in Medline to enhance systematic reviews. PLoS One 2012;7:e32844
21. EPPI Reviewer. Accessed 8 November 2017. Available from https://eppi ioe ac.uk/cms/Default. aspx?alias=eppi ioe.ac.uk/cms/er4
22. Distiller SR, 2020. Accessed 13 April 2020. Available from https://www.evidencepartners. com/products/distillersr systematic review software/
23. Moons KGM, de Groot JAH, Bouwmeester W, et al. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. PLoS Med 2014;11: e1001744
24. Wolff RF, Moons KGM, Riley RD, et al.; PROBAST Group. PROBAST: a tool to assess the risk of bias and applicability of prediction model studies. Ann Intern Med 2019;170:51 58
25. Moons KG, Altman DG, Vergouwe Y, Royston P. Prognosis and prognostic research: application and impact of prognostic models in clinical practice. BMJ 2009;338:b606
26. Moons KG, Kengne AP, Woodward M, et al. Risk prediction models: I. Development, internal validation, and assessing the incremental value of a new (bio)marker. Heart 2012;98:683 690
27. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. Epidemiology 2010;21:128 138
28. Mandrekar JN. Receiver operating charac teristic curve in diagnostic test assessment. J Thorac Oncol 2010;5:1315 1316
29. Zhang R, Borisenko O, Telegina I, et al. Systematic review of risk prediction models for diabetes after bariatric surgery. Br J Surg 2016;103:1420 1427
30. Hanson RK. Assessing the calibration of actuarial risk scales: a primer on the E/O index, 2016. Accessed on 5 November 2020. Available from https://journals.sagepub.com/doi/10.1177/ 0093854816683956
31. Robert M, Ferrand Gaillard C, Disse E, et al. Predictive factors of type 2 diabetes remission 1 year after bariatric surgery: impact of surgical techniques. Obes Surg 2013;23:770 775
32. Still CD, Wood GC, Benotti P, et al. A probability score for preoperative prediction of type 2 diabetes remission following RYGB surgery. Lancet Diabetes Endocrinol. 1 January 2015 [Epub ahead of print]. Accessed 28 October 2019. Available from https://www.ncbi nlm.nih.gov/ pmc/articles/PMC3932625/
33. Ugale S, Gupta N, Modi KD, et al. Prediction of remission after metabolic surgery using a novel scoring system in type 2 diabetes a retrospective cohort study. J Diabetes Metab Disord 2014;13:89
34. Aron Wisnewsky J, Sokolovska N, Liu Y, et al. The advanced DiaRem score improves prediction of diabetes remission 1 year post Roux en Y gastric bypass. Diabetologia 2017;60:1892 1902
35. Pucci A, Tymoszuk U, Cheung WH, et al. Type 2 diabetes remission 2 years post Roux en Y gastric bypass and sleeve gastrectomy: the role of the weight loss and comparison of DiaRem and DiaBetter scores. Diabet Med 2018;35:360 367
36. Still CD, Benotti P, Mirshahi T, Cook A, Wood GC. DiaRem2: incorporating duration of diabetes to improve prediction of diabetes remission after metabolic surgery. Surg Obes Relat Dis 2019;15: 717 724
37. Debédat J, Sokolovska N, Coupaye M, et al. Long term relapse of type 2 diabetes after Roux en Y gastric bypass: prediction and clinical relevance. Diabetes Care 2018;41:2086 2095
38. Moh MC, Cheng A, Tan CH, et al. Metabolic Surgery Diabetes Remission (MDR) score: a new preoperative scoring system for predicting type 2 diabetes remission at 1 year after metabolic surgery in the Singapore multi ethnic Asian Setting. Obes Surg 2020;30:3387 3393
39. Umemura A, Sasaki A, Nitta H, et al. Prognostic factors and a new preliminary scoring system for remission of type 2 diabetes mellitus

after laparoscopic sleeve gastrectomy. Surg Today 2020;50:1056 1064
40. Hayes MT, Hunt LA, Foo J, Tychinskaya Y, Stubbs RS. A model for predicting the resolution of type 2 diabetes in severely obese subjects following Roux en Y gastric bypass surgery. Obes Surg 2011;21:910 916
41. Ramos Levi AM, Matia P, Cabrerizo L, et al. Statistical models to predict type 2 diabetes remission after bariatric surgery. J Diabetes 2014;6:472 477
42. Cotillard A, Poitou C, Duchâteau Nguyen G, et al. Type 2 diabetes remission after gastric bypass: what is the best prediction tool for clinicians? Obes Surg 2015;25:1128 1132
43. Stallard R, Sahai V, Drover JW, Chun S, Keresztes C. Defining and using preoperative predictors of diabetic remission following bariatric surgery. JPEN J Parenter Enteral Nutr 2018;42: 573 580
44. Lee W J, Almulaifi A, Tsou JJ, Ser K H, Lee Y C, Chen S C. Laparoscopic sleeve gastrectomy for type 2 diabetes mellitus: predicting the success by ABCD score. Surg Obes Relat Dis 2015;11:991 996
45. Lee MH, Lee W J, Chong K, et al. Predictors of long term diabetes remission after metabolic surgery. J Gastrointest Surg 2015;19:1015 1021
46. Lee W J, Almulaifi A, Chong K, et al. The effect and predictive score of gastric bypass and sleeve gastrectomy on type 2 diabetes mellitus patients with BMI < 30 kg/m(2). Obes Surg 2015;25:1772 1778
47. Sampaio Neto J, Nassif LS, Branco Filho AJ, et al. Eternal validation of the DiaRem score as remission predictor of diabetes mellitus type 2 in obese patients undergoing Roux en Y gastric bypass. Arq Bras Cir Dig 2015;28(Suppl. 1):19 22
48. Lee W J, Chong K, Chen S C, et al. Preoperative prediction of type 2 diabetes remission after gastric bypass surgery: a comparison of DiaRem scores and ABCD scores. Obes Surg 2016;26:2418 2424
49. Lee W J, Chong K, Aung L, Chen S C, Ser K H, Lee Y C. Metabolic surgery for diabetes treatment: sleeve gastrectomy or gastric bypass? World J Surg 2017;41:216 223
50. Mehaffey JH, Mullen MG, Mehaffey RL, et al. Type 2 diabetes remission following gastric bypass: does diarem stand the test of time? Surg Endosc 2017;31 538 542
51. Honarmand K, Chetty K, Vanniyasingam T, Anvari M, Chetty VT. Type 2 diabetes remission rates 1 year post Roux en Y gastric bypass and validation of the DiaRem score: the Ontario Bariatric Network experience. Clin Obes 2017;7: 176 182
52. Tharakan G, Scott R, Szepietowski O, et al. Limitations of the DiaRem score in predicting remission of diabetes following Roux En Y gastric bypass (RYGB) in an ethnically diverse population from a single institution in the UK. Obes Surg 2017;27:782 786
53. Raj PP, Bhattacharya S, Saravana Kumar S, et al. Do bariatric surgery related type 2 diabetes remission predictors add clinical value? A study on Asian Indian obese diabetics. Obes Surg 2017;2113 2119
54. Seki Y, Kasama K, Yasuda K, Yokoyama R, Porciuncula JP, Kurokawa Y. The effects of laparoscopic sleeve gastrectomy with duoden ojejunal bypass on Japanese patients with BMI < 35 kg/m^2 on type 2 diabetes mellitus and the prediction of successful glycemic control. Obes Surg 2018;28:2429 2438
55. Shen SC, Wang W, Tam KW, et al. Validating risk prediction models of diabetes remission after sleeve gastrectomy. Obes Surg 2019;29:221 229
56. Naitoh T, Kasama K, Seki Y, et al. Efficacy of sleeve gastrectomy with duodenal jejunal bypass for the treatment of obese severe diabetes patients in Japan: a retrospective multicenter study. Obes Surg 2018;28:497 505
57. Ahuja A, Tantia O, Chaudhuri T, et al. Predicting remission of diabetes post metabolic surgery: a comparison of ABCD, diarem, and DRS scores. Obes Surg 2018;28:2025 2031
58. Almalki OM, Lee W J, Chong K, Ser K H, Lee Y C, Chen S C. Laparoscopic gastric bypass for the treatment of type 2 diabetes: a comparison of Roux en Y versus single anastomosis gastric bypass. Surg Obes Relat Dis 2018;14:509 515
59. Chen J C, Hsu N Y, Lee W J, Chen S C, Ser K H, Lee Y C. Prediction of type 2 diabetes remission after metabolic surgery: a comparison of the individualized metabolic surgery score and the ABCD score. Surg Obes Relat Dis 2018;14:640 645
60. Wood GC, Horwitz D, Still CD, et al. Performance of the DiaRem score for predicting diabetes remission in two health systems following bariatric surgery procedures in Hispanic and non Hispanic white patients. Obes Surg 2018;28:61 68
61. Dicker D, Golan R, Aron Wisnewsky J, et al. Prediction of long term diabetes remission after RYGB, sleeve gastrectomy, and adjustable gastric banding using DiaRem and advanced DiaRem Scores. Obes Surg 2019;29:796 804
62. Kam H, Tu Y, Pan J, et al. Comparison of four risk prediction models for diabetes remission after Roux en Y gastric bypass surgery in obese Chinese patients with type 2 diabetes mellitus. Obes Surg 2020;30:2147 2157
63. Park DG, Chung Y, Kim SH, Kim YJ. Diabetes remission rate after sleeve gastrectomy or Roux en Y gastric bypass; utilizing Individualized metabolic surgery score for Korean patients. J Metab Bariatr Surg 2020;9:13 18
64. Lee MH, Almalki OM, Lee WJ, Chen SC, Chen JC, Wu CC. Laparoscopic sleeve gastrectomy for type 2 diabetes mellitus: long term result and recurrence of diabetes. Obes Surg 2020; 30:3669 3674
65. Guerron AD, Perez JE, Risoli T Jr, Lee HJ, Portenier D, Corsino L. Performance and impro vement of the DiaRem score in diabetes remission prediction: a study with diverse procedure types. Surg Obes Relat Dis 2020;16:1531 1542
66. Finer S, Robb P, Cowan K, Daly A, Robertson E, Farmer A. Top ten research priorities for type 2 diabetes: results from the Diabetes UK James Lind Alliance Priority Setting Partnership. Lancet Diabetes Endocrinol 2017;5:935 936
67. Jans A, Naslund I, Ottosson J, Szabo E, Naslund E, Stenberg E. Duration of type 2 diabetes and remission rates after bariatric surgery in Sweden 2007 2015: a registry based cohort study. PLoS Med 2019;16:e1002985
68. Sjostrom L, Peltonen M, Jacobson P, et al. Association of bariatric surgery with long term remission of type 2 diabetes and with microvascular and macrovascular complications. JAMA 2014;311:2297 2304
69. Arterburn DE, Bogart A, Sherwood NE, et al. A multisite study of long term remission and relapse of type 2 diabetes mellitus following gastric bypass. Obes Surg 2013;23:93 102
70. Dogan K, Gadiot RP, Aarts EO, et al. Effectiveness and safety of sleeve gastrectomy, gastric bypass, and adjustable gastric banding in morbidly obese patients: a multicenter, retrospec tive, matched cohort study. Obes Surg 2015;25: 1110 1118
71. Ding L, Fan Y, Li H, et al. Comparative effectiveness of bariatric surgeries in patients with obesity and type 2 diabetes mellitus: a network meta analysis of randomized controlled trials. Obes Rev 2020;21:e13030
72. Ji G, Li P, Li W, et al. The effect of bariatric surgery on Asian patients with type 2 diabetes mellitus and body mass index < 30 kg/m^2: a systematic review and meta analysis. Obes Surg 2019;29:2492 2502
73. Segal Lieberman G, Segal P, Dicker D. Revisiting the role of BMI in the guidelines for bariatric surgery. Diabetes Care 2016;39(Suppl. 2):S268 S273
74. Admiraal WM, Celik F, Gerdes VE, Dallal RM, Hoekstra JB, Holleman F. Ethnic differences in weight loss and diabetes remission after bariatric surgery: a meta analysis. Diabetes Care 2012;35; 1951 1958
75. Ng J, Seip R, Stone A, Ruano G, Tishler D, Papasavas P. Ethnic variation in weight loss, but not co morbidity remission, after laparoscopic gastric banding and Roux en Y gastric bypass. Surg Obes Relat Dis 2015;94 100
76. Leighton E, Sainsbury CA, Jones GC. A practical review of C peptide testing in diabetes. Diabetes Ther 2017;8:475 487
77. Peyrot M, Rubin RR, Lauritzen T, et al.; International DAWN Advisory Panel. Resistance to insulin therapy among patients and providers: results of the cross national Diabetes Attitudes, Wishes, and Needs (DAWN) study. Diabetes Care 2005;28:2673 2679

Chapter 8: Summary and future direction

8.1 Summary of findings

Type 2 diabetes and obesity are global health challenges. Both diseases are associated with increased risk of morbidity and mortality and have a negative impact on patients' quality of life. In addition, type 2 diabetes and obesity are associated with significant costs to health care systems and the wider economy globally. Hence, there is a major interest in treating and preventing obesity, type 2 diabetes, and their complications. Weight loss has been shown to have many beneficial benefits on the health of patients with obesity or type 2 diabetes.

Although bariatric surgery is currently the most effective method to achieve long term sustained weight loss in patients with obesity, there is limited data on the impact of bariatric surgery on hard clinical outcomes in the UK population. In addition, there is lack of data about the best pre-operative predictors of outcome following bariatric surgery particularly weight loss and type 2 diabetes remission. Hence, in my research I conducted a series of population- based studies examining the outcomes of bariatric surgery in the UK population and a systematic review to assess prediction model of diabetes remission following bariatric surgery

Using real- world primary care data, I have shown in chapter 3 that bariatric surgery was associated with a 65% reduction in hypertension, 20% reduction in composite cardiovascular disease (CVD) and 30% reduction in mortality in patients with obesity who underwent surgery compared to patients with obesity who did not have bariatric surgery. Our subgroup analysis based on the type of surgery showed that reduction in incident hypertension was

seen irrespective of the type of bariatric procedure. On the other hand, the observed reduction in incident composite CVD was primarily evident in gastric bypass (RYGB) cohort and this was mainly driven by a significant reduction in incident heart failure. The reduction in mortality was mainly evident the gastric band (GB) and gastric bypass groups compared to their matched control.

Bariatric surgery offered significant weight loss even in an elderly population compared to routine care (Chapter 4), but cardiovascular and mortality benefit was not noted.

In chapter 5, I have shown that bariatric surgery was associated with 47% reduction in incident composite microvascular complications irrespective of type of surgery in patients with type 2 diabetes and obesity compared to those receiving routine care.

Examining the individual microvascular outcomes (diabetes related foot disease, DFD; sight threatening retinopathy, STDR; and chronic kidney disease, CKD) in different surgical group showed wide variation. GB had a favourable impact on DFD and STDR; SG had a favourable impact on CKD only; and RYGB had a favourable impact on CKD and DFD. These observations could be because of variation in hormonal changes and different intensity of change in body composition and metabolic profile in the various types of bariatric surgery.

I have also demonstrated in chapter 6 the superior effect of bariatric surgery in people with type 2 diabetes and obesity in achieving better glycaemic control and meeting glycaemic targets with less glucose lowering medications compared to routine care.

In UK, NHS spends £9 billion/ year on management of patients with cardiovascular disease and £8 billion in treating diabetes related complications. My work indicates that offering

bariatric surgery to patients with obesity and type 2 diabetes could contribute to clinical and financial benefit to patients and health care system and decrease the burden of disease. Given these benefits, access to bariatric surgery should be expanded and provided to wider population.

In the current situation, limited resources would necessitate identifying patients who are most likely to benefit from bariatric surgery (1). In chapter 7, I undertook a systematic review of currently available prediction models for type 2 diabetes remission following bariatric surgery. The review identified 16 prediction models using various predictors such as age, baseline HbA1c, baseline BMI, insulin use, C-peptide, and diabetes duration, to predict diabetes remission in patients who had undergone bariatric surgery. Two prediction models - ABCD and DiaRem - were the most widely validated and showed acceptable to excellent performance. Newer prediction models such as DiaBetter and DiaRem2 also showed excellent performance in model development study and the limited available studies. Using prediction model will help clinician and patients to make informed choice while opting for bariatric surgery. This will encourage clinicians in primary care to consult patients with obesity for bariatric surgery and refer appropriately.

8.2 Future studies

8.2.1 Prognosis of cardiovascular disease

Although the work described in my thesis has addressed key aspects concerning the long-term benefit of bariatric surgery it opens up new areas for research. In my study, I have

shown statistically non- significant reduction in incidence composite cardiovascular disease in surgical group compared to control group. Outcomes like cardiovascular disease have long latency period and will need longer follow up study and it is likely that the limited duration of follow up in my studies could have contributed to uncertainties in this area. SOS study reported number needed to treat was 16 to prevent one incidence of myocardial infarction over 15 years follow up (2). We therefore need further studies with longer follow up.

I demonstrated the positive impact of bariatric surgery on incidence composite cardiovascular disease in patients with obesity and no history of cardiovascular disease at baseline (before index date). In my dataset, 759 patients (out of 15165) had at least one of cardiovascular disease (ischaemic heart disease, heart failure, cerebrovascular accident) and hence not included in analysis. Impact of bariatric surgery on prognosis of cardiovascular disease is lacking. We need study to examine if bariatric surgery offers benefit in patients with obesity and previous cardiovascular events and whether it can prevent further events or stabilise the severity of condition in those with established disease. However, conducting such study could be ethically challenging as patients undergoing bariatric surgery need to be fit for surgery.

8.2.2 Study comparing bariatric surgery vs newer pharmacotherapy or dietary intervention

In recent years, literature evidenced positive impact of low- calorie diet on weight loss and cardiovascular risk factor. DiRECT study and DIADEM-I study showed that dietary intervention can offer significant weight loss and diabetes remission (3, 4). There have been

new developments in pharmacotherapy field like Glucagon like peptide-1 Agonist (GLP1A) and Sodium glucose cotransporter 2 inhibitor (SGLT2I) which have shown promising results on weight loss and cardiovascular risk factor in patients with obesity (5-7). We need study comparing head-to-head effect of bariatric surgery, newer pharmacotherapies, and very low-calorie diet (VLCD) on short- and long-term weight management and cardiovascular risk factors, including type 2 diabetes.

Conducting such study could be expensive. We need study using network meta-analysis to compare the various intervention – different type of bariatric surgery, pharmacotherapy and dietary intervention combining direct and indirect comparison (8).

The definition for life-style intervention used in literature has substantial heterogeneity (9). Going forward, we will need a standardised definition for life-style intervention, taking in consideration patients demographics, ethnicity, and cultures.

8.2.3 Weight loss in elderly population

In chapter 4, I showed though bariatric surgery offered significant weight loss in an elderly population, cardiovascular and mortality benefit was not noted. This could be due to small sample size and small follow up in our study. There is high prevalence of sarcopenic obesity in elderly population and associated with morbidity and mortality (10, 11). Hence with recent advancements in new imaging technologies for characterizing body composition like nuclear magnetic resonance imaging (NMRI) and computed tomography (CT) (12), future studies are needed to examine the impact of bariatric surgery on lean muscle mass and fat distribution especially in patients suspected of sarcopenic obesity. However, new

technologies for measuring body composition are expensive and currently not widely available.

Besides cardiovascular disease and chronic health conditions, obesity has been identified as independent risk factor for poor functional capacity and disability defined as ability to do activities daily living in elderly populations (11). Elderly population with obesity have been reported to have poor recovery from other medical condition and more prone to institutionalization.(11). Studies are needed to examine the impact of bariatric surgery on quality of life and above-mentioned parameters in elderly population.

8.2.4 Prognosis of diabetes related microvascular complications

In chapter 5, I presented the association between bariatric surgery and a reduction in incidence of macro and microvascular complications. In my dataset, 13689 patients had one of composite microvascular complication as baseline. Rapid improvement in glycaemic control, drastic change in muscle mass and vitamin deficiencies following bariatric surgery may result in worsening of vascular outcomes, at least in the short term. Intensive treatment as offered in pregnancy or achieved by insulin pump therapy or pancreatic transplant has been noted to cause rapid deterioration in diabetes retinopathy (13). The systematic review which included four large studies has shown that diabetic retinopathy improved in 20% but progressed further in 25% after bariatric surgery in patients with established diabetic retinopathy (14). We need studies to examine the impact of bariatric surgery on prognosis of existing microvascular complications in patients with obesity, type 2 diabetes and

established microvascular complication. Results from these studies will guide the weight management service how to monitor these patients in peri-operative stage to achieve better outcome.

8.2.5 Adjuvant effect of glucose lowering medication in post- operative stage

In chapter 6, I showed superior impact of bariatric surgery on glycaemic status despite being on lower number of glucose- lowering medication compared to control group. Percentage of patients on SGLT2I and GLP1A medication reduced in surgical group in post op stage. RCT by Miras et al showed adjuvant effect on diabetes management of patients who underwent RYGB or SG over a 26 weeks follow up (15). Continuation of GLP1A and SGLT2I class of medications in surgical group could have resulted in further reduction and better outcomes. Cardiovascular outcome trial for Liraglutide (LEADER) and semaglutide (SUSTAIN-6) have shown reduction in composite cardiovascular events in patients with type 2 diabetes (16). Recent studies conducted on patients without type 2 diabetes has shown beneficial impact of GLP1A and SGLT2I on cardio-renal condition (17). In light of emerging evidence, current clinical practice of stopping these medications in patients post bariatric surgery should be re-addressed.

8.2.6 Using term “diabetes remission”

In chapter 7, I presented a systematic review and identified 16 prediction models for diabetes remission in patients undergoing bariatric surgery. Term diabetes remission has been emerging area of interest in context of with or without bariatric surgery.

Despite wide heterogenicity in definitions for diabetes remission, there was a common theme. In all studies, diabetes remission was based on achieving a targeted glycaemic status defined by HbA1c cut-offs and/ or fasting blood glucose without glucose lowering medications

Although HbA1c is an important easily accessible and measurable parameter used in clinical practice to access the severity of diabetes condition, pathology of diabetes is not limited to hyperglycaemia and HbA1c.Patients with lower HbA1c are at lower risk of developing vascular complications but their risk is not nil. Equally, there are patients with poorly controlled diabetes and still no complication (18). We need more studies to understand this transient honeymoon stage of diabetes remission. There is currently no clear data about achieving diabetes remission and its impact on hard end point in term of diabetes care, diabetes related vascular complications.

Outside research area, term “diabetes remission” could be misleading and false reassurance to patients and healthcare professionals and could lead to disadvantage to these patients. Patients achieving targeted HbA1c and diagnosed as diabetes remission may not get annual diabetes care and medication like GLP1A and SGLT2I with cardio-renal protective effect might be stopped to fit the remission definition. Patients with diabetes relapse may present in future with poorly controlled diabetes and higher risk of vascular complications. Probably

patients achieving targeted glycaemic status off medication should be diagnosed as diabetes remission under surveillance.

We could argue improved glycaemic control without medication could reduce the burden of polypharmacy on patient and health care system. Diabetes cure or reversal has been identified as a top research priority by a project led by patients with type 2 diabetes and their carers (19). Patient with newly diagnosed diabetes will be motivated and engaged in weight management and diabetes management. Predicting diabetes remission could help healthcare professionals and patients to make informed choices about treatment options if remission is an outcome of interest to the patients. At a population level it is important for policy makers and payers to prioritise resources. However, concept of predicting diabetes remission should be used cautiously because of the above-mentioned limitations and bariatric surgery should not be limited to people who are likely to get remission.

8.2.7 Need for future prediction model

Bariatric surgery has been associated with significant sustained weight loss, remission and improvement of many other health conditions including hypertension, dyslipidaemia, and obstructive sleep apnoea (20, 21)

We need prediction model to predict long term weight loss and remission and improvement of obesity related health conditions like hypertension, dyslipidaemia, and sleep apnoea and quality of life.

8.3 Future Plans

Despite the increasing prevalence of obesity, the provision for weight management is constrained. The number of prescription item and cost for anti-obesity medications has gone down. There was an 8% reduction in the number of items prescribed in 2018 compared to 2017. Net ingredients cost of item was £8.1 million in 2018 compared to £44.8 million in 2008 (22).

Even though evidence of the beneficial effect of weight loss and bariatric surgery on metabolic outcomes are available, provision of Tier 3 (Specialist weight management services for people with severe and complex obesity) and 4 (Bariatric/ weight loss surgery) weight management services is inconsistent. A survey participated by 91% Clinical Commissioning Groups (CCG) found that only 57% of CCG commission Tier 3 service and 73% commission Tier 4 service (1). More evidence is needed to identify barriers in accessing weight management service from patients' aspect and expand weight management service to wider population to build healthier community.

The West Midland Clinical Research Network has recently funded a project called STOP Diabesity. As a part of this research team, I will be working in collaboration with clinicians, researchers, and statisticians in the West Midlands. One of the themes is the outcomes of post bariatric surgery including cardiovascular risk factor and mortality. I am currently involved in a project examining the effect of social deprivation and ethnicity on access to bariatric surgery and weight loss pharmacotherapy using the Clinical Practice Research Datalink (CPRD) database. UK National Statistical data has shown a higher prevalence of obesity in more deprived communities and certain ethnicities.(23) The CPRD study will help

to understand any inequalities in accessing health services. This information can be used to redesign the referral criteria to secondary and tertiary care for weight management and bariatric surgery, taking ethnicity and social deprivation status in account or to suggest a different threshold based on these factors for these cohort.

Following the work presented in this thesis, I will apply for a grant to undertake external validation and clinical impact studies for newer prediction models like DiaRem, DiaRem2, and DiaBetter for predicting diabetes remission in patients post bariatric surgery, in the CPRD data set.

I am also intending to develop a prediction model for health outcomes and quality of life which can be used in primary care. General practitioners are usually the first port of call for patients. I will design a prediction model including predictors which are easily available in primary care, does not require uncommon tests (like c-peptide) and could be adapted for patients coming from different ethnicity and social deprivation category

The West Midlands population is rich in diversity and culture and will be an ideal context for me to pursue my objectives.

8.4 References

1. Obesity AA-PPGO. The current landscape of obesity services: a report from the All-Party Parliamentary Group on Obesity 2019 [Available from: https://www.obesityappg.com/about.
2. RomeoS, MaglioC, BurzaMA, PirazziC, SjöholmK, JacobsonP, et al. Cardiovascular events after bariatric surgery in obese subjects with type 2 diabetes. Diabetes care. 2012;35(12).
3. Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. Lancet Diabetes Endocrinol. 2019;7(5):344-55.
4. TaheriS, ZaghloulH, ChagouryO, ElhadadS, AhmedSH, KhatibN E, et al. Effect of intensive lifestyle intervention on bodyweight and glycaemia in early type 2 diabetes (DIADEM-I): an open-label, parallel-group, randomised controlled trial. The lancet Diabetes & endocrinology. 2020;8(6).
5. Davies MJ, Diabetes Research Centre UoL, Leicester, United Kingdom, Bergenstal R, International Diabetes Center PNHS, Minneapolis, Minnesota, Bode B, Atlanta Diabetes Associates A, Georgia, et al. Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes: The SCALE Diabetes Randomized Clinical Trial. JAMA. 2017;314(7):687-99.
6. WildingJPH, BatterhamRL, CalannaS, DaviesM, LF VG, I L, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. The New England journal of medicine. 2021;384(11).
7. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015;November 26:2117- 28.
8. Anna Chaimani DMC, Tianjing Li, Julian PT Higgins, Georgia Salanti. Chapter 11: Undertaking network meta-analyses. Cochrane Handbook for Systematic Reviews of Interventions version 62 (updated February 2021) Cochrane, 2021. 2021.
9. Avenell A, Robertson C, Skea Z, Jacobsen E, Boyers D, Cooper D, et al. Bariatric surgery, lifestyle interventions and orlistat for severe obesity: the REBALANCE mixed-methods systematic review and economic evaluation. 2018.
10. KM C. Sarcopenia and sarcopenic obesity. The Korean journal of internal medicine. 2016;31(6).
11. Samper-Ternent R, Al Snih S. Obesity in Older Adults: Epidemiology and Implications for Disability and Disease. Rev Clin Gerontol. 2012;22(1):10-34.
12. R K. Body composition techniques. The Indian journal of medical research. 2018;148(5).
13. Dahl-Jørgensen K, Brinchmann-Hansen O, Hanssen KF, Sandvik L, Aagenaes O. Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin dependent diabetes mellitus: the Oslo study. 1985.

14. Douglas Cheung Noah JS, David Ehmann, Christopher Rudnisky, Xinzhe Shi, Shahzeer Karmali. The Impact of Bariatric Surgery on Diabetic Retinopathy: A Systematic Review and Meta-Analysis. Obesity Surgery. 2014;25(9):1604-9.
15. MirasAD, Pérez-PevidaB, AldhwayanM, KamockaA, McGloneER, Al-NajimW, et al. Adjunctive liraglutide treatment in patients with persistent or recurrent type 2 diabetes after metabolic surgery (GRAVITAS): a randomised, double-blind, placebo-controlled trial. The lancet Diabetes & endocrinology. 2019;7(7).
16. Alfayez OM, Almutairi AR, Aldosari A, Al Yami MS. Update on Cardiovascular Safety of Incretin-Based Therapy in Adults With Type 2 Diabetes Mellitus: A Meta-Analysis of Cardiovascular Outcome Trials. Can J Diabetes. 2019.
17. BrownE, HeerspinkHJL, CuthbertsonDJ, WildingJPH. SGLT2 inhibitors and GLP-1 receptor agonists: established and emerging indications. Lancet (London, England). 2021;398(10296).
18. NakamuraT, TsujimotoT, YasudaK, ChujoD, OhsugiM, TanabeA, et al. Poorly controlled type 2 diabetes with no progression of diabetes-related complications and low levels of advanced glycation end products: A Case report. Medicine. 2019;98(30).
19. FinerS, RobbP, CowanK, DalyA, RobertsonE, FarmerA. Top ten research priorities for type 2 diabetes: results from the Diabetes UK-James Lind Alliance Priority Setting Partnership. The lancet Diabetes & endocrinology. 2017;5(12).
20. HanY, JiaY, WangH, CaoL, ZhaoY. Comparative analysis of weight loss and resolution of comorbidities between laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass: A systematic review and meta-analysis based on 18 studies. International journal of surgery (London, England). 2020;76.
21. CastanhaCR, Tcbc-PeÁABF, CastanhaAR, BeloGQMB, LacerdaRMR, VilarL. Evaluation of quality of life, weight loss and comorbidities of patients undergoing bariatric surgery. Revista do Colegio Brasileiro de Cirurgioes. 2018;45(3).
22. digital NSN. Statistics on Obesity, Physical Activity and Diet, England, 2019 - NHS Digital: @NHSDigital; 2019 [Available from: https://digital.nhs.uk/data-and-information/publications/statistical/statistics-on-obesity-physical-activity-and-diet/statistics-on-obesity-physical-activity-and-diet-england-2019.
23. Baker C. Obesity Statistics 2021 [Available from: https://commonslibrary.parliament.uk/research-briefings/sn03336/.

Appendices

Table of Contents

Appendices 1
Read Codes 4
Diabetes 4
Bariatric Read Codes 9
Hypertension 10
Ischaemic Heart Disease 11
Heart Failure 15
Stroke & TIA 16
Retinopathy Codes 20
Amputations 27
Charcot 29
Foot 30
Gangrene 32
Peripheral neuropathy 33
Peripheral vascular disease 35
Acarbose 36
DDP4i 36
Glinides 37
Glitazones 38
GLP1 39
Insulin 40
Metformin 49
SGLT2i 52
Sulphonylurea 53
Appendices for Chapter 3 56
Appendices for manuscript 1 56
Supplementary Figure S1: Unadjusted Nelson–Aalen cumulative hazard estimates for cardiovascular disease and mortality 56

Supplementary Table S1: Impact of bariatric surgery on cardiovascular outcomes in participants with and without type 2 diabetes mellitus 57
Supplementary Table S2: Impact of bariatric surgery on mortality in participants with and without type 2 diabetes mellitus 58
Appendices for Chapter 5 59
Appendices for manuscript 2 59
Supplementary Figure 1: Flowchart showing participant selection 59
Supplement Figure 2: Unadjusted Nelson-Aalen cumulative hazard estimates for composite microvascular complications, DFD1, STDR and CKD 60
Appendices for Chapter 7 61
Appendices for manuscript 4 61
Supplementary Table 1: Search strategy used in Embase 61
Supplementary Table 2: Papers excluded on full-text 62
Supplementary Table 3: Data collection questionnaire 63
Supplementary Table 4: PROBAST data collection questionnaire 65
Supplementary Table 5: Risk of bias assessment and applicability for model development studies 67
Supplementary Table 6: Risk of bias assessment and applicability for external validation studies 68
Supplementary Material 7: Example of AUC analysis 69
Model development studies Predicting success of metabolic surgery: age, body mass index, C-peptide, and duration score. 69
Lee et al 2013 (16) 69
A probability score for preoperative prediction of type 2 diabetes remission following RYGB surgery. Still CD, Wood GC, Benotti P, Petrick AT, Gabrielsen J, Strodel WE, et al. Lancet Diabetes Endocrinol. 2014 score (17) 69
Prognostic factors and a new preliminary scoring system for remission of type 2 diabetes mellitus after laparoscopic sleeve gastrectomy; Akira Umemura (39) 70
Validation studies Preoperative Prediction of Type 2 Diabetes Remission After Gastric Bypass Surgery: 71
A Comparison of DiaRem Scores and ABCD Scores. Lee et al (48) 71
Predictors of long-term diabetes remission after metabolic surgery; Lee MH et al (45) 72
The Effect and Predictive Score of Gastric Bypass and Sleeve Gastrectomy on Type 2 Diabetes Mellitus Patients with BMI <30 kg/m^2 (46) 73
Metabolic Surgery for Diabetes Treatment: Sleeve Gastrectomy or Gastric Bypass World journal of surgery. 2017;41(1):216-23. Lee W-J, Chong K, Aung L, Chen S-C, Ser K-H, Lee Y-C (49) 74
Do Bariatric Surgery-Related Type 2 Diabetes Remission Predictors Add Clinical Value? A Study on Asian Indian Obese Diabetics; Raj et al (53) 75

The Effects of Laparoscopic Sleeve Gastrectomy with Duodenojejunal Bypass on Japanese Patients with BMI < 35 kg/m2 on Type 2 Diabetes Mellitus and the Prediction of Successful Glycemic Contro; Seki et al (54) 76

Predicting remission of diabetes post metabolic surgery: a comparison of ABCD, diarem, and DRS scores; Ahuja et al (57)..... 77

Laparoscopic gastric bypass for the treatment of type 2 diabetes: a comparison of Roux-en-Y versus single anastomosis gastric bypass. 2018;14(4); Almalki et al (58) 78

References 79

Read Codes

Diabetes

Code	Description
C10..00	Diabetes mellitus
C100.00	Diabetes mellitus with no mention of complication
C100100	Diabetes mellitus, adult onset, no mention of complication
C100111	Maturity onset diabetes
C100112	Non-insulin dependent diabetes mellitus
C100z00	Diabetes mellitus NOS with no mention of complication
C101.00	Diabetes mellitus with ketoacidosis
C101100	Diabetes mellitus, adult onset, with ketoacidosis
C101y00	Other specified diabetes mellitus with ketoacidosis
C101z00	Diabetes mellitus NOS with ketoacidosis
C102.00	Diabetes mellitus with hyperosmolar coma
C102100	Diabetes mellitus, adult onset, with hyperosmolar coma
C102z00	Diabetes mellitus NOS with hyperosmolar coma
C103.00	Diabetes mellitus with ketoacidotic coma
C103100	Diabetes mellitus, adult onset, with ketoacidotic coma
C103y00	Other specified diabetes mellitus with coma
C103z00	Diabetes mellitus NOS with ketoacidotic coma
C104.00	Diabetes mellitus with renal manifestation
C104.11	Diabetic nephropathy
C104100	Diabetes mellitus, adult onset, with renal manifestation
C104y00	Other specified diabetes mellitus with renal complications
C104z00	Diabetes mellitus with nephropathy NOS
C105.00	Diabetes mellitus with ophthalmic manifestation
C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation
C105y00	Other specified diabetes mellitus with ophthalmic complicatn
C105z00	Diabetes mellitus NOS with ophthalmic manifestation
C106.00	Diabetes mellitus with neurological manifestation
C106.11	Diabetic amyotrophy
C106.12	Diabetes mellitus with neuropathy
C106.13	Diabetes mellitus with polyneuropathy
C106100	Diabetes mellitus, adult onset, + neurological manifestation
C106y00	Other specified diabetes mellitus with neurological comps
C106z00	Diabetes mellitus NOS with neurological manifestation
C107.00	Diabetes mellitus with peripheral circulatory disorder

C107.11	Diabetes mellitus with gangrene
C107.12	Diabetes with gangrene
C107100	Diabetes mellitus, adult, + peripheral circulatory disorder
C107200	Diabetes mellitus, adult with gangrene
C107400	NIDDM with peripheral circulatory disorder
C107y00	Other specified diabetes mellitus with periph circ comps
C107z00	Diabetes mellitus NOS with peripheral circulatory disorder
C108y00	Other specified diabetes mellitus with multiple comps
C108z00	Unspecified diabetes mellitus with multiple complications
C109.00	Non-insulin dependent diabetes mellitus
C109.11	NIDDM - Non-insulin dependent diabetes mellitus
C109.12	Type 2 diabetes mellitus
C109.13	Type II diabetes mellitus
C109000	Non-insulin-dependent diabetes mellitus with renal comps
C109011	Type II diabetes mellitus with renal complications
C109012	Type 2 diabetes mellitus with renal complications
C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps
C109111	Type II diabetes mellitus with ophthalmic complications
C109112	Type 2 diabetes mellitus with ophthalmic complications
C109200	Non-insulin-dependent diabetes mellitus with neuro comps
C109211	Type II diabetes mellitus with neurological complications
C109212	Type 2 diabetes mellitus with neurological complications
C109300	Non-insulin-dependent diabetes mellitus with multiple comps
C109311	Type II diabetes mellitus with multiple complications
C109312	Type 2 diabetes mellitus with multiple complications
C109400	Non-insulin dependent diabetes mellitus with ulcer
C109411	Type II diabetes mellitus with ulcer
C109412	Type 2 diabetes mellitus with ulcer
C109500	Non-insulin dependent diabetes mellitus with gangrene
C109511	Type II diabetes mellitus with gangrene
C109512	Type 2 diabetes mellitus with gangrene
C109600	Non-insulin-dependent diabetes mellitus with retinopathy
C109611	Type II diabetes mellitus with retinopathy
C109612	Type 2 diabetes mellitus with retinopathy
C109700	Non-insulin dependent diabetes mellitus - poor control
C109711	Type II diabetes mellitus - poor control
C109712	Type 2 diabetes mellitus - poor control
C109800	Reaven's syndrome
C109900	Non-insulin-dependent diabetes mellitus without complication
C109911	Type II diabetes mellitus without complication
C109912	Type 2 diabetes mellitus without complication
C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
C109A11	Type II diabetes mellitus with mononeuropathy
C109A12	Type 2 diabetes mellitus with mononeuropathy

C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
C109B11	Type II diabetes mellitus with polyneuropathy
C109B12	Type 2 diabetes mellitus with polyneuropathy
C109C00	Non-insulin dependent diabetes mellitus with nephropathy
C109C11	Type II diabetes mellitus with nephropathy
C109C12	Type 2 diabetes mellitus with nephropathy
C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma
C109D11	Type II diabetes mellitus with hypoglycaemic coma
C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
C109E00	Non-insulin depend diabetes mellitus with diabetic cataract
C109E11	Type II diabetes mellitus with diabetic cataract
C109E12	Type 2 diabetes mellitus with diabetic cataract
C109F00	Non-insulin-dependent d m with peripheral angiopath
C109F11	Type II diabetes mellitus with peripheral angiopathy
C109F12	Type 2 diabetes mellitus with peripheral angiopathy
C109G00	Non-insulin dependent diabetes mellitus with arthropathy
C109G11	Type II diabetes mellitus with arthropathy
C109G12	Type 2 diabetes mellitus with arthropathy
C109H00	Non-insulin dependent d m with neuropathic arthropathy
C109H11	Type II diabetes mellitus with neuropathic arthropathy
C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
C109J00	Insulin treated Type 2 diabetes mellitus
C109J11	Insulin treated non-insulin dependent diabetes mellitus
C109J12	Insulin treated Type II diabetes mellitus
C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10A.00	Malnutrition-related diabetes mellitus
C10A.11	Jamaica type diabetes
C10A000	Malnutrition-related diabetes mellitus with coma
C10A100	Malnutrition-related diabetes mellitus with ketoacidosis
C10A200	Malnutrition-related diabetes mellitus with renal complicatn
C10A300	Malnutrit-related diabetes mellitus wth ophthalmic complicat
C10A400	Malnutrition-related diabetes mellitus wth neuro complicatns
C10A500	Malnutritn-relat diabetes melitus wth periph circul complctn
C10A600	Malnutrition-related diabetes mellitus with multiple comps
C10A700	Malnutrition-related diabetes mellitus without complications
C10AW00	Malnutrit-related diabetes mellitus with unspec complics
C10AX00	Malnutrit-relat diabetes mellitus with other spec comps
C10B.00	Diabetes mellitus induced by steroids
C10B000	Steroid induced diabetes mellitus without complication
C10C.00	Diabetes mellitus autosomal dominant
C10C.11	Maturity onset diabetes in youth
C10D.00	Diabetes mellitus autosomal dominant type 2
C10D.11	Maturity onset diabetes in youth type 2
C10ER00	Latent autoimmune diabetes mellitus in adult

C10F.00	Type 2 diabetes mellitus
C10F.11	Type II diabetes mellitus
C10F000	Type 2 diabetes mellitus with renal complications
C10F011	Type II diabetes mellitus with renal complications
C10F100	Type 2 diabetes mellitus with ophthalmic complications
C10F111	Type II diabetes mellitus with ophthalmic complications
C10F200	Type 2 diabetes mellitus with neurological complications
C10F211	Type II diabetes mellitus with neurological complications
C10F300	Type 2 diabetes mellitus with multiple complications
C10F311	Type II diabetes mellitus with multiple complications
C10F400	Type 2 diabetes mellitus with ulcer
C10F411	Type II diabetes mellitus with ulcer
C10F500	Type 2 diabetes mellitus with gangrene
C10F511	Type II diabetes mellitus with gangrene
C10F600	Type 2 diabetes mellitus with retinopathy
C10F611	Type II diabetes mellitus with retinopathy
C10F700	Type 2 diabetes mellitus - poor control
C10F711	Type II diabetes mellitus - poor control
C10F800	Reaven's syndrome
C10F811	Metabolic syndrome X
C10F900	Type 2 diabetes mellitus without complication
C10F911	Type II diabetes mellitus without complication
C10FA00	Type 2 diabetes mellitus with mononeuropathy
C10FA11	Type II diabetes mellitus with mononeuropathy
C10FB00	Type 2 diabetes mellitus with polyneuropathy
C10FB11	Type II diabetes mellitus with polyneuropathy
C10FC00	Type 2 diabetes mellitus with nephropathy
C10FC11	Type II diabetes mellitus with nephropathy
C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
C10FD11	Type II diabetes mellitus with hypoglycaemic coma
C10FE00	Type 2 diabetes mellitus with diabetic cataract
C10FE11	Type II diabetes mellitus with diabetic cataract
C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
C10FF11	Type II diabetes mellitus with peripheral angiopathy
C10FG00	Type 2 diabetes mellitus with arthropathy
C10FG11	Type II diabetes mellitus with arthropathy
C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
C10FH11	Type II diabetes mellitus with neuropathic arthropathy
C10FJ00	Insulin treated Type 2 diabetes mellitus
C10FJ11	Insulin treated Type II diabetes mellitus
C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10FK11	Hyperosmolar non-ketotic state in type II diabetes mellitus
C10FL00	Type 2 diabetes mellitus with persistent proteinuria
C10FL11	Type II diabetes mellitus with persistent proteinuria

C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
C10FM11	Type II diabetes mellitus with persistent microalbuminuria
C10FN00	Type 2 diabetes mellitus with ketoacidosis
C10FN11	Type II diabetes mellitus with ketoacidosis
C10FP00	Type 2 diabetes mellitus with ketoacidotic coma
C10FP11	Type II diabetes mellitus with ketoacidotic coma
C10FQ00	Type 2 diabetes mellitus with exudative maculopathy
C10FQ11	Type II diabetes mellitus with exudative maculopathy
C10FR00	Type 2 diabetes mellitus with gastroparesis
C10FR11	Type II diabetes mellitus with gastroparesis
C10FS00	Maternally inherited diabetes mellitus
C10G.00	Secondary pancreatic diabetes mellitus
C10G000	Secondary pancreatic diabetes mellitus without complication
C10H.00	Diabetes mellitus induced by non-steroid drugs
C10H000	DM induced by non-steroid drugs without complication
C10J.00	Insulin autoimmune syndrome
C10J000	Insulin autoimmune syndrome without complication
C10K.00	Type A insulin resistance
C10K000	Type A insulin resistance without complication
C10L.00	Fibrocalculous pancreatopathy
C10L000	Fibrocalculous pancreatopathy without complication
C10M.00	Lipoatrophic diabetes mellitus
C10M000	Lipoatrophic diabetes mellitus without complication
C10N.00	Secondary diabetes mellitus
C10N000	Secondary diabetes mellitus without complication
C10N100	Cystic fibrosis related diabetes mellitus
C10P.00	Diabetes mellitus in remission
C10P100	Type II diabetes mellitus in remission
C10P111	Type 2 diabetes mellitus in remission
C10y.00	Diabetes mellitus with other specified manifestation
C10y100	Diabetes mellitus, adult, + other specified manifestation
C10yy00	Other specified diabetes mellitus with other spec comps
C10yz00	Diabetes mellitus NOS with other specified manifestation
C10z.00	Diabetes mellitus with unspecified complication
C10z100	Diabetes mellitus, adult onset, + unspecified complication
C10zy00	Other specified diabetes mellitus with unspecified comps
C10zz00	Diabetes mellitus NOS with unspecified complication

Bariatric Read Codes

Code	Description
7616	Other connection of stomach to jejunum
7616000	Bypass of stomach by anastomosis of stomach to jejunum NEC
7622000	Bypass of duodenum by anastomosis of stomach to jejunum
761H011	Insertion of gastric balloon
761H411	
7622z00	Bypass of duodenum NOS
761H600	Attention to gastric balloon
ZV45P00	[V]Presence of gastric bypass
7613111	Mason vertical banded gastroplasty
7616600	Laparoscopic gastric bypass
7622	Bypass of duodenum
7616y00	Other specified other connection of stomach to jejunum
7616z00	Other connection of stomach to jejunum NOS
7616013	Mason high gastric bypass
7642500	Duodenal switch
7613000	Gastroplasty NEC
7611	Partial excision of stomach
7615000	Bypass stomach by anastomosis stomach to transposed jejunum
761H000	Insertion of gastric bubble
761H100	Attention to gastric bubble
7615	Connection of stomach to transposed jejunum
761H400	Removal of gastric balloon
761H500	Insertion of gastric balloon
7611400	Sleeve gastrectomy and duodenal switch
7611600	Laparoscopic sleeve gastrectomy
7613500	Partitioning of stomach NEC
7611500	Sleeve gastrectomy NEC
7613600	Maintenance of gastric band
7613300	Partitioning of stomach using band
7613400	Partitioning of stomach using staples
7611200	Partial gastrectomy and anastomosis stomach to jejunum NEC
7613100	Partitioning of stomach
7611100	Partial gastrectomy & anastomosis stomach to transp jejunum
7613200	Laparoscopic adjustable gastric banding
7611y00	Other specified partial excision of stomach
7611z00	Partial excision of stomach NOS
7615y00	Other specified connection of stomach to transposed jejunum
7615z00	Connection of stomach to transposed jejunum NOS

Hypertension

Code	Description
G2...00	Hypertensive disease
G2...11	BP - hypertensive disease
G20..00	Essential hypertension
G20..11	High blood pressure
G20..12	Primary hypertension
G200.00	Malignant essential hypertension
G201.00	Benign essential hypertension
G202.00	Systolic hypertension
G203.00	Diastolic hypertension
G20z.00	Essential hypertension NOS
G20z.11	Hypertension NOS
G21..00	Hypertensive heart disease
G210.00	Malignant hypertensive heart disease
G210000	Malignant hypertensive heart disease without CCF
G210100	Malignant hypertensive heart disease with CCF
G210z00	Malignant hypertensive heart disease NOS
G211.00	Benign hypertensive heart disease
G211000	Benign hypertensive heart disease without CCF
G211100	Benign hypertensive heart disease with CCF
G211z00	Benign hypertensive heart disease NOS
G21z.00	Hypertensive heart disease NOS
G21z000	Hypertensive heart disease NOS without CCF
G21z011	Cardiomegaly - hypertensive
G21z100	Hypertensive heart disease NOS with CCF
G21zz00	Hypertensive heart disease NOS
G22..00	Hypertensive renal disease
G22..11	Nephrosclerosis
G220.00	Malignant hypertensive renal disease
G221.00	Benign hypertensive renal disease
G222.00	Hypertensive renal disease with renal failure
G22z.00	Hypertensive renal disease NOS
G22z.11	Renal hypertension
G23..00	Hypertensive heart and renal disease
G230.00	Malignant hypertensive heart and renal disease
G231.00	Benign hypertensive heart and renal disease
G232.00	Hypertensive heart&renal dis wth (congestive) heart failure
G233.00	Hypertensive heart and renal disease with renal failure
G234.00	Hyperten heart&renal dis+both(congestv)heart and renal fail
G23z.00	Hypertensive heart and renal disease NOS

G24..00	Secondary hypertension
G240.00	Secondary malignant hypertension
G240000	Secondary malignant renovascular hypertension
G240z00	Secondary malignant hypertension NOS
G241.00	Secondary benign hypertension
G241000	Secondary benign renovascular hypertension
G241z00	Secondary benign hypertension NOS
G244.00	Hypertension secondary to endocrine disorders
G24z.00	Secondary hypertension NOS
G24z000	Secondary renovascular hypertension NOS
G24z100	Hypertension secondary to drug
G24zz00	Secondary hypertension NOS
G25..00	Stage 1 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
G25..11	Stage 1 hypertension
G250.00	Stage 1 hyperten (NICE 2011) without evidnce end organ damge
G251.00	Stage 1 hyperten (NICE 2011) with evidnce end organ damge
G26..00	Severe hypertension (Nat Inst for Health Clinical Ex 2011)
G26..11	Severe hypertension
G27..00	Hypertension resistant to drug therapy
G28..00	Stage 2 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
G2y..00	Other specified hypertensive disease
G2z..00	Hypertensive disease NOS
Gyu2.00	[X]Hypertensive diseases
Gyu2000	[X]Other secondary hypertension
Gyu2100	[X]Hypertension secondary to other renal disorders

Ischaemic Heart Disease

Code	**Description**
G3...00	Ischaemic heart disease
G3...11	Arteriosclerotic heart disease
G3...12	Atherosclerotic heart disease
G3...13	IHD - Ischaemic heart disease
G30..00	Acute myocardial infarction
G30..11	Attack - heart
G30..12	Coronary thrombosis
G30..13	Cardiac rupture following myocardial infarction (MI)
G30..14	Heart attack
G30..15	MI - acute myocardial infarction
G30..16	Thrombosis - coronary

G30..17	Silent myocardial infarction
G300.00	Acute anterolateral infarction
G301.00	Other specified anterior myocardial infarction
G301000	Acute anteroapical infarction
G301100	Acute anteroseptal infarction
G301z00	Anterior myocardial infarction NOS
G302.00	Acute inferolateral infarction
G303.00	Acute inferoposterior infarction
G304.00	Posterior myocardial infarction NOS
G305.00	Lateral myocardial infarction NOS
G306.00	True posterior myocardial infarction
G307.00	Acute subendocardial infarction
G307000	Acute non-Q wave infarction
G307100	Acute non-ST segment elevation myocardial infarction
G308.00	Inferior myocardial infarction NOS
G309.00	Acute Q-wave infarct
G30A.00	Mural thrombosis
G30B.00	Acute posterolateral myocardial infarction
G30X.00	Acute transmural myocardial infarction of unspecif site
G30X000	Acute ST segment elevation myocardial infarction
G30y.00	Other acute myocardial infarction
G30y000	Acute atrial infarction
G30y100	Acute papillary muscle infarction
G30y200	Acute septal infarction
G30yz00	Other acute myocardial infarction NOS
G30z.00	Acute myocardial infarction NOS
G31..00	Other acute and subacute ischaemic heart disease
G310.00	Postmyocardial infarction syndrome
G310.11	Dressler's syndrome
G311.00	Preinfarction syndrome
G311.11	Crescendo angina
G311.12	Impending infarction
G311.13	Unstable angina
G311.14	Angina at rest
G311000	Myocardial infarction aborted
G311011	MI - myocardial infarction aborted
G311100	Unstable angina
G311200	Angina at rest
G311300	Refractory angina
G311400	Worsening angina
G311500	Acute coronary syndrome
G311z00	Preinfarction syndrome NOS
G312.00	Coronary thrombosis not resulting in myocardial infarction
G31y.00	Other acute and subacute ischaemic heart disease

G31y000	Acute coronary insufficiency
G31y100	Microinfarction of heart
G31y200	Subendocardial ischaemia
G31y300	Transient myocardial ischaemia
G31yz00	Other acute and subacute ischaemic heart disease NOS
G32..00	Old myocardial infarction
G32..11	Healed myocardial infarction
G32..12	Personal history of myocardial infarction
G33..00	Angina pectoris
G330.00	Angina decubitus
G330000	Nocturnal angina
G330z00	Angina decubitus NOS
G331.00	Prinzmetal's angina
G331.11	Variant angina pectoris
G332.00	Coronary artery spasm
G33z.00	Angina pectoris NOS
G33z000	Status anginosus
G33z100	Stenocardia
G33z200	Syncope anginosa
G33z300	Angina on effort
G33z400	Ischaemic chest pain
G33z500	Post infarct angina
G33z600	New onset angina
G33z700	Stable angina
G33zz00	Angina pectoris NOS
G34..00	Other chronic ischaemic heart disease
G340.00	Coronary atherosclerosis
G340.11	Triple vessel disease of the heart
G340.12	Coronary artery disease
G340000	Single coronary vessel disease
G340100	Double coronary vessel disease
G341.00	Aneurysm of heart
G341.11	Cardiac aneurysm
G341000	Ventricular cardiac aneurysm
G341100	Other cardiac wall aneurysm
G341111	Mural cardiac aneurysm
G341200	Aneurysm of coronary vessels
G341300	Acquired atrioventricular fistula of heart
G341z00	Aneurysm of heart NOS
G342.00	Atherosclerotic cardiovascular disease
G343.00	Ischaemic cardiomyopathy
G344.00	Silent myocardial ischaemia
G34y.00	Other specified chronic ischaemic heart disease
G34y000	Chronic coronary insufficiency

G34y100	Chronic myocardial ischaemia
G34yz00	Other specified chronic ischaemic heart disease NOS
G34z.00	Other chronic ischaemic heart disease NOS
G34z000	Asymptomatic coronary heart disease
G35..00	Subsequent myocardial infarction
G350.00	Subsequent myocardial infarction of anterior wall
G351.00	Subsequent myocardial infarction of inferior wall
G353.00	Subsequent myocardial infarction of other sites
G35X.00	Subsequent myocardial infarction of unspecified site
G36..00	Certain current complication follow acute myocardial infarct
G360.00	Haemopericardium/current comp folow acut myocard infarct
G361.00	Atrial septal defect/curr comp folow acut myocardal infarct
G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn
G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI
G37..00	Cardiac syndrome X
G38..00	Postoperative myocardial infarction
G380.00	Postoperative transmural myocardial infarction anterior wall
G381.00	Postoperative transmural myocardial infarction inferior wall
G382.00	Postoperative transmural myocardial infarction other sites
G383.00	Postoperative transmural myocardial infarction unspec site
G384.00	Postoperative subendocardial myocardial infarction
G38z.00	Postoperative myocardial infarction, unspecified
G39..00	Coronary microvascular disease
G3y..00	Other specified ischaemic heart disease
G3z..00	Ischaemic heart disease NOS
Gyu3.00	[X]Ischaemic heart diseases
Gyu3000	[X]Other forms of angina pectoris
Gyu3100	[X]Other current complicatns following acute myocard infarct
Gyu3200	[X]Other forms of acute ischaemic heart disease
Gyu3300	[X]Other forms of chronic ischaemic heart disease
Gyu3400	[X]Acute transmural myocardial infarction of unspecif site
Gyu3500	[X]Subsequent myocardial infarction of other sites
Gyu3600	[X]Subsequent myocardial infarction of unspecified site

Heart Failure

Code	Description
1O1..00	Heart failure confirmed
2JZ..00	On optimal heart failure therapy
661M500	Heart failure self-management plan agreed
661N500	Heart failure self-management plan review
662f.00	New York Heart Association classification - class I
662g.00	New York Heart Association classification - class II
662h.00	New York Heart Association classification - class III
662i.00	New York Heart Association classification - class IV
662p.00	Heart failure 6 month review
662T.00	Congestive heart failure monitoring
662W.00	Heart failure annual review
679W100	Education about deteriorating heart failure
8B29.00	Cardiac failure therapy
8H2S.00	Admit heart failure emergency
8HBE.00	Heart failure follow-up
8HTL000	Referral to rapid access heart failure clinic
G232.00	Hypertensive heart&renal dis wth (congestive) heart failure
G234.00	Hyperten heart&renal dis+both(congestv)heart and renal fail
G554000	Congestive cardiomyopathy
G58..00	Heart failure
G58..11	Cardiac failure
G580.00	Congestive heart failure
G580.11	Congestive cardiac failure
G580.14	Biventricular failure
G580000	Acute congestive heart failure
G580100	Chronic congestive heart failure
G580200	Decompensated cardiac failure
G580300	Compensated cardiac failure
G580400	Congestive heart failure due to valvular disease
G581.00	Left ventricular failure
G581.11	Asthma - cardiac
G581.12	Pulmonary oedema - acute
G581.13	Impaired left ventricular function
G581000	Acute left ventricular failure
G582.00	Acute heart failure
G583.00	Heart failure with normal ejection fraction
G583.11	HFNEF - heart failure with normal ejection fraction
G583.12	Heart failure with preserved ejection fraction
G58z.00	Heart failure NOS

G58z.11	Weak heart
G58z.12	Cardiac failure NOS
G5y4z00	Post cardiac operation heart failure NOS
SP11111	Heart failure as a complication of care
SP11200	Cardiorespiratory failure as a complication of care

Stroke & TIA

Code	DESCRIPTION
G6...00	Cerebrovascular disease
G60..00	Subarachnoid haemorrhage
G600.00	Ruptured berry aneurysm
G601.00	Subarachnoid haemorrhage from carotid siphon and bifurcation
G602.00	Subarachnoid haemorrhage from middle cerebral artery
G603.00	Subarachnoid haemorrhage from anterior communicating artery
G604.00	Subarachnoid haemorrhage from posterior communicating artery
G605.00	Subarachnoid haemorrhage from basilar artery
G606.00	Subarachnoid haemorrhage from vertebral artery
G60X.00	Subarachnoid haemorrh from intracranial artery, unspecif
G60z.00	Subarachnoid haemorrhage NOS
G61..00	Intracerebral haemorrhage
G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage
G61..12	Stroke due to intracerebral haemorrhage
G610.00	Cortical haemorrhage
G611.00	Internal capsule haemorrhage
G612.00	Basal nucleus haemorrhage
G613.00	Cerebellar haemorrhage
G614.00	Pontine haemorrhage
G615.00	Bulbar haemorrhage
G616.00	External capsule haemorrhage
G617.00	Intracerebral haemorrhage, intraventricular
G618.00	Intracerebral haemorrhage, multiple localized
G619.00	Lobar cerebral haemorrhage
G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
G61X000	Left sided intracerebral haemorrhage, unspecified
G61X100	Right sided intracerebral haemorrhage, unspecified
G61z.00	Intracerebral haemorrhage NOS
G62..00	Other and unspecified intracranial haemorrhage
G620.00	Extradural haemorrhage - nontraumatic

G621.00	Subdural haemorrhage - nontraumatic
G622.00	Subdural haematoma - nontraumatic
G623.00	Subdural haemorrhage NOS
G62z.00	Intracranial haemorrhage NOS
G63..00	Precerebral arterial occlusion
G63..11	Infarction - precerebral
G63..12	Stenosis of precerebral arteries
G630.00	Basilar artery occlusion
G631.00	Carotid artery occlusion
G631.11	Stenosis, carotid artery
G631.12	Thrombosis, carotid artery
G632.00	Vertebral artery occlusion
G633.00	Multiple and bilateral precerebral arterial occlusion
G634.00	Carotid artery stenosis
G63y.00	Other precerebral artery occlusion
G63y000	Cerebral infarct due to thrombosis of precerebral arteries
G63y100	Cerebral infarction due to embolism of precerebral arteries
G63z.00	Precerebral artery occlusion NOS
G64..00	Cerebral arterial occlusion
G64..11	CVA - cerebral artery occlusion
G64..12	Infarction - cerebral
G64..13	Stroke due to cerebral arterial occlusion
G640.00	Cerebral thrombosis
G640000	Cerebral infarction due to thrombosis of cerebral arteries
G641.00	Cerebral embolism
G641.11	Cerebral embolus
G641000	Cerebral infarction due to embolism of cerebral arteries
G64z.00	Cerebral infarction NOS
G64z.11	Brainstem infarction NOS
G64z.12	Cerebellar infarction
G64z000	Brainstem infarction
G64z100	Wallenberg syndrome
G64z111	Lateral medullary syndrome
G64z200	Left sided cerebral infarction
G64z300	Right sided cerebral infarction
G64z400	Infarction of basal ganglia
G65..00	Transient cerebral ischaemia
G65..11	Drop attack
G65..12	Transient ischaemic attack
G65..13	Vertebro-basilar insufficiency
G650.00	Basilar artery syndrome
G650.11	Insufficiency - basilar artery
G651.00	Vertebral artery syndrome
G651000	Vertebro-basilar artery syndrome

G652.00	Subclavian steal syndrome
G653.00	Carotid artery syndrome hemispheric
G654.00	Multiple and bilateral precerebral artery syndromes
G655.00	Transient global amnesia
G656.00	Vertebrobasilar insufficiency
G657.00	Carotid territory transient ischaemic attack
G65y.00	Other transient cerebral ischaemia
G65z.00	Transient cerebral ischaemia NOS
G65z000	Impending cerebral ischaemia
G65z100	Intermittent cerebral ischaemia
G65zz00	Transient cerebral ischaemia NOS
G66..00	Stroke and cerebrovascular accident unspecified
G66..11	CVA unspecified
G66..12	Stroke unspecified
G66..13	CVA - Cerebrovascular accident unspecified
G660.00	Middle cerebral artery syndrome
G661.00	Anterior cerebral artery syndrome
G662.00	Posterior cerebral artery syndrome
G663.00	Brain stem stroke syndrome
G664.00	Cerebellar stroke syndrome
G665.00	Pure motor lacunar syndrome
G666.00	Pure sensory lacunar syndrome
G667.00	Left sided CVA
G668.00	Right sided CVA
G669.00	Cerebral palsy, not congenital or infantile, acute
G67..00	Other cerebrovascular disease
G670.00	Cerebral atherosclerosis
G670.11	Precerebral atherosclerosis
G671.00	Generalised ischaemic cerebrovascular disease NOS
G671000	Acute cerebrovascular insufficiency NOS
G671100	Chronic cerebral ischaemia
G671z00	Generalised ischaemic cerebrovascular disease NOS
G672.00	Hypertensive encephalopathy
G672.11	Hypertensive crisis
G673.00	Cerebral aneurysm, nonruptured
G673000	Dissection of cerebral arteries, nonruptured
G673100	Carotico-cavernous sinus fistula
G673200	Carotid artery dissection
G673300	Vertebral artery dissection
G674.00	Cerebral arteritis
G674000	Cerebral amyloid angiopathy
G675.00	Moyamoya disease
G676.00	Nonpyogenic venous sinus thrombosis
G676000	Cereb infarct due cerebral venous thrombosis, nonpyogenic

G677.00	Occlusion/stenosis cerebral arts not result cerebral infarct
G677000	Occlusion and stenosis of middle cerebral artery
G677100	Occlusion and stenosis of anterior cerebral artery
G677200	Occlusion and stenosis of posterior cerebral artery
G677300	Occlusion and stenosis of cerebellar arteries
G677400	Occlusion+stenosis of multiple and bilat cerebral arteries
G678.00	Cereb autosom dominant arteriop subcort infarcts leukoenceph
G679.00	Small vessel cerebrovascular disease
G67A.00	Cerebral vein thrombosis
G67B.00	Reversible cerebral vasoconstriction syndrome
G67B.11	Call-Fleming syndrome
G67y.00	Other cerebrovascular disease OS
G67z.00	Other cerebrovascular disease NOS
G68..00	Late effects of cerebrovascular disease
G680.00	Sequelae of subarachnoid haemorrhage
G681.00	Sequelae of intracerebral haemorrhage
G682.00	Sequelae of other nontraumatic intracranial haemorrhage
G683.00	Sequelae of cerebral infarction
G68W.00	Sequelae/other + unspecified cerebrovascular diseases
G68X.00	Sequelae of stroke,not specfd as h'morrhage or infarction
G6W..00	Cereb infarct due unsp occlus/stenos precerebr arteries
G6X..00	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
G6y..00	Other specified cerebrovascular disease
G6z..00	Cerebrovascular disease NOS
Gyu6.00	[X]Cerebrovascular diseases
Gyu6000	[X]Subarachnoid haemorrhage from other intracranial arteries
Gyu6100	[X]Other subarachnoid haemorrhage
Gyu6200	[X]Other intracerebral haemorrhage
Gyu6300	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
Gyu6400	[X]Other cerebral infarction
Gyu6500	[X]Occlusion and stenosis of other precerebral arteries
Gyu6600	[X]Occlusion and stenosis of other cerebral arteries
Gyu6700	[X]Other specified cerebrovascular diseases
Gyu6C00	[X]Sequelae of stroke,not specfd as h'morrhage or infarction
Gyu6D00	[X]Sequelae/other + unspecified cerebrovascular diseases
Gyu6E00	[X]Subarachnoid haemorrh from intracranial artery, unspecif
Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified
Gyu6G00	[X]Cereb infarct due unsp occlus/stenos precerebr arteries

Retinopathy Codes

Code	Description
6688	Registered partially sighted
6688	Registered partially sighted
6688.11	Registered partially blind
6689	Registered blind
6689	Registered blind
6689.11	Registered severely sight impaired
668B.00	Poor visual acuity
7270	Operations on vitreous body
7276	Pan retinal photocoagulation for diabetes
7276	Pan retinal photocoagulation for diabetes
3128000	Fundoscopy normal
3128200	Dilated fundoscopy normal
7270100	Extirpation of vitreous body NEC
7270200	Injection of vitreous substitute into vitreous body
7270300	Injection into vitreous body NEC
7270400	Pars plana vitrectomy
7270411	Vitrectomy using pars plana approach
7270500	Air/gas exchange of vitreous
7270600	Internal tamponade of retina using gas
7270800	Internal tamponade of retina using liquid
7270900	Internal tamponade of retina using oil
7272012	Photocoagulation of the retina NEC
7272013	Laser therapy lesion of retina
7272300	Laser destruction of lesion of retina
7272500	Panretinal laser photocoagulation to lesion of retina NEC
7272600	Laser photocoagulation to lesion of retina NEC
7272800	Panretinal laser photocoagulation to lesion of retina
7272900	Focal laser photocoagulation of retina
7273000	Epiretinal dissection
7274800	Injection of therapeutic substance around the eye
7277600	Injection of therapeutic substance into macula
1a00000	Uses guide dog for the blind
1B75.00	Loss of vision, Severe visual loss
1B77.00	Deteriorating vision, Severe visual loss
22E6.00	O/E - glass (prosthetic) eye
22E6.11	O/E - false eye
22E6.12	O/E - glass eye
22E6.13	O/E - prosthetic eye
22EF.00	O/E - has one eye

2B68.00	O/E - visual acuity R-eye=6/60
2B69.00	O/E -R-eye counts fingers only
2B6A.00	O/E-R-eye perceives light only
2B6A.11	O/E - blind R-eye
2B6B.00	O/E - R-eye completely blind
2B6C.00	O/E - R-eye sees hand movements
2B6E.00	O/E - visual acuity R-eye=3/60
2B6L.00	O/E - pinhole visual acuity R-eye=6/60
2B6P.00	O/E - pinhole R-eye sees hand movements
2B6Q.00	O/E - pinhole R-eye counts fingers only
2B6R.00	O/E - pinhole R-eye perceives light only
2B6S.00	O/E - pinhole R-eye completely blind
2B6T.00	O/E - R-eye visual acuity (corrected) 1/60
2B6V.00	O/E - R-eye visual acuity (corrected) 2/60
2B6W.00	O/E - R-eye visual acuity (corrected) 4/60
2B6X.00	O/E - R-eye visual acuity (corrected) 5/60
2B78.00	O/E - visual acuity L-eye=6/60
2B79.00	O/E -L-eye counts fingers only
2B7A.00	O/E-L-eye perceives light only
2B7A.11	O/E - blind L-eye
2B7B.00	O/E - L-eye completely blind
2B7C.00	O/E - L-eye sees hand movements
2B7E.00	O/E - visual acuity L-eye=3/60
2B7L.00	O/E - pinhole visual acuity L-eye=6/60
2B7P.00	O/E - pinhole L-eye sees hand movements
2B7Q.00	O/E - pinhole L-eye counts fingers only
2B7R.00	O/E - pinhole L-eye perceives light only
2B7S.00	O/E - pinhole L-eye completely blind
2B7T.00	O/E - L-eye visual acuity (corrected) 1/60
2B7V.00	O/E - L-eye visual acuity (corrected) 2/60
2B7W.00	O/E - L-eye visual acuity (corrected) 4/60
2B7X.00	O/E - L-eye visual acuity (corrected) 5/60
2BB1.00	O/E - retina normal
2BB4.00	O/E - retinal microaneurysms
2BB5.00	O/E - retinal haemorrhages
2BB6.00	O/E - retinal exudates
2BB7.00	O/E - retinal vascular prolif.
2BB8.00	O/E - vitreous haemorrhages
2BBa.00	O/E- non-referable retinopathy
2BBD.00	O/E - Right retina normal
2BBE.00	O/E - Left retina normal
2BBF.00	Retinal abnormality-diabetes related
2BBI.00	O/E - no retinopathy
2BBJ.00	O/E - no right diabetic retinopathy

2BBK.00	O/E - no left diabetic retinopathy
2BBk.00	O/E - right eye stable treated prolif diabetic retinopathy
2BBL.00	O/E - Diabetic maculopathy present both eyes
2BBl.00	O/E - left eye stable treated prolif diabetic retinopathy
2BBM.00	O/E - diabetic maculopathy absent both eyes
2BBm.00	O/E - right eye clinically significant macular oedema
2BBn.00	O/E - left eye clinically significant macular oedema
2BBo.00	O/E - sight threatening diabetic retinopathy
2BBO.00	O/E - Laser photocoagulation scars
2BBP.00	O/E - right eye background diabetic retinopathy
2BBQ.00	O/E - left eye background diabetic retinopathy
2BBr.00	Impair vision due diab retinop
2BBR.00	O/E - right eye preproliferative diabetic retinopathy
2BBS.00	O/E - left eye preproliferative diabetic retinopathy
2BBT.00	O/E - right eye proliferative diabetic retinopathy
2BBV.00	O/E - left eye proliferative diabetic retinopathy
2BBW.00	O/E - right eye diabetic maculopathy
2BBX.00	O/E - left eye diabetic maculopathy
2BBY.00	O/E - referable retinopathy
5B4..11	Retinal laser therapy
5B42.00	Laser therapy - retinal lesion
668C.00	Certificate of vision impairment
668D.00	Registered sight impaired
7270A00	Removal of internal tamponade agent from vitreous body
7270C00	Injection of vitreous substitute into vitreous body NEC
7270D00	Injection of Ranibizumab into vitreous body
7270y00	Other specified operation on vitreous body
7270z00	Operation on vitreous body NOS
727C000	Insertion sustained release device posterior segment of eye
727C100	Injection of steroid into posterior segment of eye
727C200	Injection therapeutic substance posterior segment of eye NEC
727Cy00	Other specified operations on posterior segment of eye
727Cz00	Operations on posterior segment of eye NOS
7L19E00	Injection of triamcinolone
8D36.00	Removable artificial eye
8F6..11	Blind rehabilitation
8F61.00	Blind rehabilitation
8F62.00	Blind lead dog rehabilitation
8HlE.00	Referral to visual impairment multidisciplinary team
9m08.00	Exclu diab ret screen as blind
9Nfa.00	Requires deafblind manual alphabet interpreter
9Nfb.00	Requires deafblind block alphabet interpreter
9NfB.00	Requires deafblind communicator guide
9Nfc.00	Requires deafblind haptic communication interpreter

9NlD.00	Seen by visual impairment teacher
C105.00	Diabetes mellitus with ophthalmic manifestation
C105000	Diabetes mellitus, juvenile type, + ophthalmic manifestation
C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation
C105y00	Other specified diabetes mellitus with ophthalmic complicatn
C105z00	Diabetes mellitus NOS with ophthalmic manifestation
C108100	Insulin-dependent diabetes mellitus with ophthalmic comps
C108111	Type I diabetes mellitus with ophthalmic complications
C108112	Type 1 diabetes mellitus with ophthalmic complications
C108700	Insulin dependent diabetes mellitus with retinopathy
C108711	Type I diabetes mellitus with retinopathy
C108712	Type 1 diabetes mellitus with retinopathy
C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps
C109111	Type II diabetes mellitus with ophthalmic complications
C109112	Type 2 diabetes mellitus with ophthalmic complications
C109600	Non-insulin-dependent diabetes mellitus with retinopathy
C109611	Type II diabetes mellitus with retinopathy
C109612	Type 2 diabetes mellitus with retinopathy
C10A300	Malnutrit-related diabetes mellitus wth ophthalmic complicat
C10E100	Type 1 diabetes mellitus with ophthalmic complications
C10E111	Type I diabetes mellitus with ophthalmic complications
C10E112	Insulin-dependent diabetes mellitus with ophthalmic comps
C10E700	Type 1 diabetes mellitus with retinopathy
C10E711	Type I diabetes mellitus with retinopathy
C10E712	Insulin dependent diabetes mellitus with retinopathy
C10EP00	Type 1 diabetes mellitus with exudative maculopathy
C10EP11	Type I diabetes mellitus with exudative maculopathy
C10F600	Type 2 diabetes mellitus with retinopathy
C10F611	Type II diabetes mellitus with retinopathy
C10FQ00	Type 2 diabetes mellitus with exudative maculopathy
C10FQ11	Type II diabetes mellitus with exudative maculopathy
F404100	Blind hypotensive eye
F404200	Blind hypertensive eye
F420.00	Diabetic retinopathy
F420000	Background diabetic retinopathy
F420100	Proliferative diabetic retinopathy
F420200	Preproliferative diabetic retinopathy
F420300	Advanced diabetic maculopathy
F420400	Diabetic maculopathy
F420500	Advanced diabetic retinal disease
F420600	Non proliferative diabetic retinopathy
F420700	High risk proliferative diabetic retinopathy
F420800	High risk non proliferative diabetic retinopathy
F420z00	Diabetic retinopathy NOS

F421.00	Other background retinopathy
F421.11	Microvascular retinal changes
F421000	Unspecified background retinopathy
F421800	Retinal microaneurysms NOS
F421C00	Other intraretinal microvascular abnormality
F421z00	Other background retinopathy NOS
F422.00	Other proliferative retinopathy
F422y00	Other specified other proliferative retinopathy
F422z00	Proliferative retinopathy NOS
F425900	Maculopathy
F42y900	Macular oedema
F49..00	Blindness and low vision
F49..11	Impaired vision
F49..12	Low vision
F49..13	Partial sight
F49..14	Sight impaired
F490.00	Blindness, both eyes
F490000	Unspecified blindness both eyes
F490100	Both eyes total visual impairment
F490200	Better eye: near total VI, Lesser eye: unspecified
F490300	Better eye: near total VI, Lesser eye: total VI
F490400	Better eye: near total VI, Lesser eye: near total VI
F490500	Better eye: profound VI, Lesser eye: unspecified
F490600	Better eye: profound VI, Lesser eye: total VI
F490700	Better eye: profound VI, Lesser eye: near total VI
F490800	Better eye: profound VI, Lesser eye: profound VI
F490900	Acquired blindness, both eyes
F490z00	Blindness both eyes NOS
F491.00	Better eye: low vision, Lesser eye: profound VI
F491000	One eye blind, one eye low vision
F491100	Better eye: severe VI, Lesser eye: blind, unspecified
F491200	Better eye: severe VI, Lesser eye: total VI
F491300	Better eye: severe VI, Lesser eye: near total VI
F491400	Better eye: severe VI, Lesser eye: profound VI
F491500	Better eye: moderate VI, Lesser eye: blind, unspecified
F491600	Better eye: moderate VI, Lesser eye: total VI
F491700	Better eye: moderate VI, Lesser eye: near total VI
F491800	Better eye: moderate VI, Lesser eye: profound VI
F491z00	One eye blind, one eye low vision NOS
F492.00	Low vision, both eyes
F492000	Low vision, both eyes unspecified
F492100	Better eye: severe VI, Lesser eye: low vision unspecified
F492200	Better eye: severe VI, Lesser eye: severe VI
F492300	Better eye: moderate VI, Lesser eye: low vision unspecified

F492400	Better eye: moderate VI, Lesser eye: severe VI
F492500	Better eye: moderate VI, Lesser eye: moderate VI
F492z00	Low vision, both eyes NOS
F493.00	Visual loss, both eyes unqualified
F494.00	Legal blindness USA
F495.00	Profound impairment, one eye
F495000	Blindness, one eye, unspecified
F495100	Lesser eye: total visual impairment, Better eye: unspecified
F495200	Lesser eye: total VI, Better eye: near normal vision
F495300	Lesser eye: total VI, Better eye: normal vision
F495400	Lesser eye: near total VI, Better eye: unspecified
F495500	Lesser eye: near total VI, Better eye: near normal vision
F495600	Lesser eye: near total VI, Better eye: normal vision
F495700	Lesser eye: profound VI, Better eye: unspecified
F495800	Lesser eye: profound VI, Better eye: near normal vision
F495900	Lesser eye: profound VI, Better eye: normal vision
F495A00	Acquired blindness, one eye
F495z00	Profound impairment one eye NOS
F496.00	Low vision, one eye
F496000	Low vision, one eye, unspecified
F496100	Lesser eye: severe VI, Better eye: unspecified
F496200	Lesser eye: severe VI, Better eye: near normal vision
F496300	Lesser eye: severe VI, Better eye: normal vision
F496400	Lesser eye: moderate VI, Better eye: unspecified
F496500	Lesser eye: moderate VI, Better eye: near normal vision
F496600	Lesser eye: moderate VI, Better eye: normal vision
F496z00	Low vision, one eye NOS
F497.00	Severe visual impairment, binocular
F498.00	Moderate visual impairment, binocular
F49A.00	Blindness, monocular
F49B.00	Severe visual impairment, monocular
F49C.00	Moderate visual impairment, monocular
F49D.00	Visual impairment
F49y.00	Visual loss, one eye, unqualified
F49z.00	?
F49z.11	Acquired blindness
F4H7300	Cortical blindness
F4K2800	Vitreous haemorrhage
Fy1..00	Combined visual and hearing impairment
Fy1..11	Dual sensory impairment - deafblind
Fy1..12	Deafblind
FyuF700	[X]Other proliferative retinopathy
FyuH400	[X]Vitreous haemorrhage in diseases classified elsewhere
FyuL.00	[X]Visual disturbances and blindness

medcode	description
Z6F..11	Laser therapy
Z96..00	Provision for visual and hearing impairment
Z961.00	Provision of guide help for visual and hearing impairment
Z962.00	Provision of communicator for visual and hearing impairment
Z9E1100	Provision of artificial eye
Z9E1200	Provision of removable artificial eye
Z9E2.00	Optical low vision aid provision
Z9E3.00	Provision of optical low vision aid - near
Z9E3100	Provision of magnifier low vision aid - near
Z9E3200	Provision of low vision hand magnifier
Z9E3300	Provision of low vision stand magnifier
Z9E3400	Provision of low vision headband magnifier
Z9E3500	Provision of spectacle low vision aid - near
Z9E3800	Near low vision aid - integral spectacle magnifier
Z9E3900	Near low vision aid - clip-on spectacle magnifier
Z9E3B00	Near low vision aid - integral spectacle telescope
Z9E3C00	Near low vision aid - clip-on spectacle telescope
Z9E3D00	Near low vision aid - extra cap for telescope
Z9E4.00	Provision of optical low vision aid - distance
Z9E5.00	Provision of non-optical low vision aid
Z9E5100	Provision of electronic low vision aid
Z9E5400	Provision of ancillary low vision aid
ZK74.00	Issue of local authority blind registration
ZN56800	Blind telephone user
ZN56A00	Deaf-blind telephone user
ZV41000	Problem with sight
ZV43000	[V]Has artificial eye globe
ZV43100	[V]Has artificial eye lens
ZV52200	[V]Fitting or adjustment of artificial eye

Amputations

Code	Description
14N4.00	H/O: limb amputation
14N4.11	Amputee - limb
14N4100	H/O: lower limb amputation
14N4Z00	H/O: limb amputation NOS
2G42.00	O/E - Amputated right leg
2G43.00	O/E - Amputated left leg
2G44.00	O/E - Amputated right above knee
2G45.00	O/E - Amputated left above knee
2G46.00	O/E - Amputated right below knee
2G47.00	O/E - Amputated left below knee
2G4A.00	O/E - amputated left midfoot
2G4B.00	O/E - amputated right midfoot
2G56.00	O/E - Amputated right forefoot
2G57.00	O/E - Amputated left forefoot
2G61.00	O/E - Amputated right toe
2G62.00	O/E - Amputated left toe
7L06.00	Amputation of leg
7L06000	Hindquarter amputation
7L06011	Ferre hindquarter amputation
7L06012	Gordon - Taylor hindquarter amputation
7L06013	Jaboulay hindquarter amputation
7L06014	King hindquarter amputation
7L06015	Sorrondo hindquarter amputation
7L06016	Steelquist hindquarter amputation
7L06017	Taylor hindquarter amputation
7L06100	Disarticulation of hip
7L06111	Boyd disarticulation of hip
7L06112	Fitzmaurice - Kelly disarticulation of hip
7L06200	Amputation above knee
7L06211	Kirk amputation of leg through thigh
7L06212	Amputation of leg through thigh
7L06300	Amputation through knee
7L06311	Batch disarticulation of knee
7L06312	Callander disarticulation of knee
7L06313	Disarticulation of knee
7L06314	Gritti-Stokes disarticulation of knee
7L06315	Kirk disarticulation of knee
7L06316	Mazet disarticulation of knee
7L06317	McFaddin disarticulation of knee

7L06318	Slocum disarticulation of knee
7L06319	Spittler disarticulation of knee
7L06400	Amputation below knee
7L06411	Boyd amputation of leg below knee
7L06412	Burgess amputation of leg below knee
7L06413	Guyon amputation of leg below knee
7L06y00	Other specified amputation of leg
7L06z00	Amputation of leg NOS
7L07.00	Amputation of foot
7L07000	Amputation through ankle
7L07011	Pirogoff amputation of foot through ankle
7L07012	Syme amputation of foot through ankle
7L07100	Disarticulation of tarsal bones
7L07111	Boyd amputation of hindfoot
7L07200	Disarticulation tarsometatarsal joint
7L07211	Lisfranc tarsometatarsal amputation
7L07212	Tarsometatarsal amputation
7L07300	Amputation through metatarsal bones
7L07311	Chopart midtarsal amputation
7L07312	Ray transmetatarsal amputation
7L07y00	Other specified amputation of foot
7L07z00	Amputation of foot NOS
7L07z11	Hey amputation of foot
7L08.00	Amputation of toe
7L08000	Amputation hallux
7L08011	Amputation great toe
7L08100	Amputation of phalanx of toe
7L08200	Proximal hemiphalangectomy of toe
7L08300	Amputation lesser toe
7L08400	Terminalisation of hallux
7L08500	Terminalisation of lesser toe
7L08y00	Other specified amputation of toe
7L08z00	Amputation of toe NOS
7P20000	Delivery of rehabilitation for amputation of limb
8D47600	Midfoot amputation prosthesis
N36yM00	Old amputee NOS
Z6P3100	Lower limb amputee mobility practice
Z6X2.00	Lower limb amputee transfer practice
7K12E00	Disarticulation of bone
SP16.00	Late amputation stump complication
SP16000	Late amputation stump complication, unspecified
SP16100	Neuroma of amputation stump
SP16200	Chronic infection of amputation stump
SP16300	Necrosis of amputation stump

SP16400	Bony prominence in amputation stump
SP16500	Poorly shaped amputation stump
SP16z00	Late amputation stump complication NOS
SyuKM00	[X]Other and unspecified amputation stump complications
7L07213	Disarticulation of metatarsal bones
7L08.11	Disarticulation of toe
7L08z11	Disarticulation of toe NOS
7L09.00	Operations on amputation stump
7L09000	Reamputation at higher level
7L09100	Excision of lesion of amputation stump
7L09200	Shortening of amputation stump
7L09300	Revision coverage of amputation stump
7L09400	Drainage of amputation stump
7L09500	Excision neuroma amputation stump
7L09y00	Other specified operation on amputation stump
7L09z00	Operation on amputation stump NOS
TB05.00	Amputation of limb(s) with complication, without blame
U635.00	[X]Amputat limb cause abn reac pt/lat comp no misad at time

Charcot

Code	Description
C108H00	Insulin dependent diabetes mellitus with arthropathy
C108J00	Insulin dependent diab mell with neuropathic arthropathy
C108J11	Type I diabetes mellitus with neuropathic arthropathy
C108J12	Type 1 diabetes mellitus with neuropathic arthropathy
C109H00	Non-insulin dependent d m with neuropathic arthropathy
C109H11	Type II diabetes mellitus with neuropathic arthropathy
C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
C10EJ00	Type 1 diabetes mellitus with neuropathic arthropathy
C10EJ11	Type I diabetes mellitus with neuropathic arthropathy
C10EJ12	Insulin dependent diab mell with neuropathic arthropathy
C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
C10FH11	Type II diabetes mellitus with neuropathic arthropathy
N030100	Diabetic Charcot arthropathy
N035.00	Neuropathic arthropathy
N035.11	Charcot's arthropathy
N06z700	Arthropathy NOS, of the ankle and foot
N030.00	Arthropathy associated with endocrine and metabolic disorder

C108H11	Type I diabetes mellitus with arthropathy
C108H12	Type 1 diabetes mellitus with arthropathy
C109G00	Non-insulin dependent diabetes mellitus with arthropathy
C109G11	Type II diabetes mellitus with arthropathy
C109G12	Type 2 diabetes mellitus with arthropathy
C10EH00	Type 1 diabetes mellitus with arthropathy
C10EH11	Type I diabetes mellitus with arthropathy
C10EH12	Insulin dependent diabetes mellitus with arthropathy
C10FG00	Type 2 diabetes mellitus with arthropathy
C10FG11	Type II diabetes mellitus with arthropathy
N065700	Unspecified polyarthropathy of the ankle and foot
N06y700	Other specified arthropathy of the ankle and foot

Foot

Code	Description
14F6.00	H/O: foot ulcer
14F6.00	H/O: foot ulcer
14F7.00	H/O: arterial lower limb ulcer
14F7.00	H/O: arterial lower limb ulcer
2G48.00	O/E - ankle ulcer
2G4E.00	Healed leg ulcer
2G54.00	O/E - Right foot ulcer
2G55.00	O/E - Left foot ulcer
2G5H.00	O/E - Right diabetic foot - ulcerated
2G5L.00	O/E - Left diabetic foot - ulcerated
2G5S.00	O/E - right healed foot ulcer
2G5T.00	O/E - left healed foot ulcer
2G5V.00	O/E - right chronic diabetic foot ulcer
2G5W.00	O/E - left chronic diabetic foot ulcer
2G64.00	O/E - infected toe
8CMT.00	Leg ulcer care pathway
8CS3.00	Agreeing on leg ulcer treatment plan
8CT1.00	Leg ulcer compression therapy finished
8CV2.00	Leg ulcer compression therapy started
C108500	Insulin dependent diabetes mellitus with ulcer
C108511	Type I diabetes mellitus with ulcer
C108512	Type 1 diabetes mellitus with ulcer
C109400	Non-insulin dependent diabetes mellitus with ulcer

C109411	Type II diabetes mellitus with ulcer
C109412	Type 2 diabetes mellitus with ulcer
C10E500	Type 1 diabetes mellitus with ulcer
C10E511	Type I diabetes mellitus with ulcer
C10E512	Insulin dependent diabetes mellitus with ulcer
C10F400	Type 2 diabetes mellitus with ulcer
C10F411	Type II diabetes mellitus with ulcer
M271.00	Non-pressure ulcer lower limb
M271.11	Foot ulcer
M271.12	Ischaemic leg ulcer
M271.13	Leg ulcer NOS
M271.14	Neurogenic leg ulcer
M271.15	Trophic leg ulcer
M271000	Ischaemic ulcer diabetic foot
M271100	Neuropathic diabetic ulcer - foot
M271100	Neuropathic diabetic ulcer - foot
M271200	Mixed diabetic ulcer - foot
M271300	Arterial leg ulcer
M271400	Mixed venous and arterial leg ulcer
M271700	Neuropathic foot ulcer
M271700	Neuropathic foot ulcer
M273.00	Non-healing leg ulcer
M274.00	Recurrent leg ulcer
8I3W.00	Diabetic foot examination declined
2G5G.00	O/E - Right diabetic foot at high risk
2G5K.00	O/E - Left diabetic foot at high risk
2G5E.00	O/E - Right diabetic foot at low risk
2G5I.00	O/E - Left diabetic foot at low risk
2G5d.00	O/E - Left diabetic foot at increased risk
2G5e.00	O/E - Right diabetic foot at increased risk
2G5F.00	O/E - Right diabetic foot at moderate risk
2G5J.00	O/E - Left diabetic foot at moderate risk

Gangrene

Code	Description
R054200	[D]Gangrene of toe in diabetic
R054300	[D]Widespread diabetic foot gangrene
R054200	[D]Gangrene of toe in diabetic
R054300	[D]Widespread diabetic foot gangrene
G732.	Peripheral gangrene
G7320	Gangrene of toe
G7321	Gangrene of foot
C107.11	Diabetes mellitus with gangrene
C107.12	Diabetes with gangrene
C1072	Diabetes mellitus, adult with gangrene
C1095	Non-insulin dependent diabetes mellitus with gangrene
C1086	Insulin dependent diabetes mellitus with gangrene
A3A0F	Gas gangrene-foot
G732.	Peripheral gangrene
C107.11	Diabetes mellitus with gangrene
C107.12	Diabetes with gangrene
C1072	Diabetes mellitus, adult with gangrene
C1095	Non-insulin dependent diabetes mellitus with gangrene
C1086	Insulin dependent diabetes mellitus with gangrene
R054200	[D]Gangrene of toe in diabetic
R054300	[D]Widespread diabetic foot gangrene
R054200	[D]Gangrene of toe in diabetic
R054300	[D]Widespread diabetic foot gangrene
G7320	Gangrene of toe
G7321	Gangrene of foot
A3A0F	Gas gangrene-foot

Peripheral neuropathy

Code	Description
1M8..00	Diabetic peripheral neuropathic pain
C106.12	Diabetes mellitus with neuropathy
C106.13	Diabetes mellitus with polyneuropathy
C108B00	Insulin dependent diabetes mellitus with mononeuropathy
C108B11	Type I diabetes mellitus with mononeuropathy
C108B12	Type 1 diabetes mellitus with mononeuropathy
C108C00	Insulin dependent diabetes mellitus with polyneuropathy
C108C11	Type I diabetes mellitus with polyneuropathy
C108C12	Type 1 diabetes mellitus with polyneuropathy
C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
C109A11	Type II diabetes mellitus with mononeuropathy
C109A12	Type 2 diabetes mellitus with mononeuropathy
C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
C109B11	Type II diabetes mellitus with polyneuropathy
C109B12	Type 2 diabetes mellitus with polyneuropathy
C109H00	Non-insulin dependent d m with neuropathic arthropathy
C109H11	Type II diabetes mellitus with neuropathic arthropathy
C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
C10EB00	Type 1 diabetes mellitus with mononeuropathy
C10EB11	Type I diabetes mellitus with mononeuropathy
C10EB12	Insulin dependent diabetes mellitus with mononeuropathy
C10EC00	Type 1 diabetes mellitus with polyneuropathy
C10EC11	Type I diabetes mellitus with polyneuropathy
C10EC12	Insulin dependent diabetes mellitus with polyneuropathy
C10FA00	Type 2 diabetes mellitus with mononeuropathy
C10FA11	Type II diabetes mellitus with mononeuropathy
C10FB00	Type 2 diabetes mellitus with polyneuropathy
C10FB11	Type II diabetes mellitus with polyneuropathy
F366.00	Polyneuropathy
F367.00	Peripheral neuropathy
F36y.00	Other idiopathic peripheral neuropathy
F36yz00	Other idiopathic peripheral neuropathy NOS
F372.00	Polyneuropathy in diabetes
F372.11	Diabetic polyneuropathy
F372.12	Diabetic neuropathy
F372000	Acute painful diabetic neuropathy
F372100	Chronic painful diabetic neuropathy
F372200	Asymptomatic diabetic neuropathy
F3y0.00	Diabetic mononeuropathy

Fyu6B00	[X]Other mononeuropathies of lower limb
Fyu7500	[X]Polyneuropathy/other endocrine+metabolic diseases CE
FyuAC00	[X]Autonomic neuropathy/endocrine+metabolic diseases CE
SD72200	Neuropathic foot blister
29B9.00	10g monofilament sensation R foot abnormal
29BA.00	10g monofilament sensation L foot abnormal
29B2.11	O/E - loss of touch sensation
29B8.00	10g monofilament sensation absent
29H2.00	O/E - vibration sense reduced
29H3.00	O/E - vibration sense absent
29H4.00	O/E - Vibration sense of right foot abnormal
29H6.00	O/E - Vibration sense of left foot abnormal
29H8.00	O/E - vibration sense left foot reduced
29H9.00	O/E - vibration sense right foot reduced
29HA.00	O/E - Vibration sense of right foot absent
29HB.00	O/E - Vibration sense of left foot absent
29BM.00	10g monofil sensation plantar aspect gt toe R foot absent
29BN.00	10g monofil sensation plantar aspect gt toe L foot absent
29BP.00	10g monofil sensation plantar aspect mid toe R foot absent
29BQ.00	10g monofil sensation plantar aspect mid toe L foot absent
29BR.00	10g monofil sensation plantar aspect lit toe R foot absent
29BS.00	10g monofil sensation plantar aspect lit toe L foot absent
29BT.00	10g monofil sensat plantar aspect 1st met hd R foot absent
29BV.00	10g monofil sensat plantar aspect 1st met hd L foot absent
29C2.00	O/E - tactile discrim.abnormal
29C3.00	Pin prick sensation of right foot abnormal
29C4.00	Pin prick sensation of left foot abnormal
29C7.00	Tactile discrimination right foot abnormal
29C8.00	Tactile discrimination left foot abnormal
29D2.00	O/E - deep sensation reduced
29D3.00	O/E - deep sensation absent
29E2.00	O/E - pain sensation reduced
29E3.00	O/E - analgesia present
29E4.00	On examination allodynia
29F2.00	O/E - temp. discrim. reduced
29F3.00	O/E - temp. discrim. absent
29G2.00	O/E - joint posn.sense reduced
29G3.00	O/E - joint posn.sense absent
29I2.00	O/E - stereognosis - reduced

Peripheral vascular disease

Code	Description
1M11000	Ischaemic foot pain at rest
1M11100	Ischaemic foot pain when walking
C107.12	Diabetes with gangrene
G73..00	Other peripheral vascular disease
G73..11	Peripheral ischaemic vascular disease
G73..12	Ischaemia of legs
G73..13	Peripheral ischaemia
G731.00	Thromboangiitis obliterans
G731000	Buerger's disease
G731100	Presenile gangrene
G731z00	Thromboangiitis obliterans NOS
G732.00	Peripheral gangrene
G732000	Gangrene of toe
G732100	Gangrene of foot
G732200	Gangrene of finger
G732300	Gangrene of thumb
G732400	Gangrene of hand
G733.00	Ischaemic foot
G734.00	Peripheral arterial disease
G73y.00	Other specified peripheral vascular disease
G73y000	Diabetic peripheral angiopathy
G73y100	Peripheral angiopathic disease EC NOS
G73y200	Acrocyanosis
G73yz00	Other specified peripheral vascular disease NOS
G73z.00	Peripheral vascular disease NOS
G73z000	Intermittent claudication
G73z011	Claudication
G73z012	Vascular claudication
G73z100	Spasm of peripheral artery
G73zz00	Peripheral vascular disease NOS
Gyu7400	[X]Other specified peripheral vascular diseases
R054.00	[D]Gangrene
R054000	[D]Gangrene, spreading cutaneous
R054200	[D]Gangrene of toe in diabetic
R054300	[D]Widespread diabetic foot gangrene
R054z00	[D]Gangrene NOS
24E3.00	O/E - R.femoral pulse absent
24E5.00	O/E - R.popliteal pulse absent
24E7.00	O/E - R.post.tib pulse absent

24E9.00	O/E - R.dorsalis pedis absent
24EA.00	O/E - Absent right foot pulses
24EC.00	O/E - Right dorsalis pedis abnormal
24ED.00	O/E - Right posterior tibial pulse abnormal
24EG.00	O/E right leg pulses all absent
24EH.00	Right posterior tibial pulse impalpable
24EL.00	Right dorsalis pedis pulse impalpable
24F3.00	O/E - L.femoral pulse absent
24F5.00	O/E - L.popliteal pulse absent
24F7.00	O/E - L.post.tib. pulse absent
24F9.00	O/E - L.dorsalis pedis absent
24FA.00	O/E - Absent left foot pulses
24FC.00	O/E - left dorsalis pedis abnormal
24FD.00	O/E - Left posterior tibial pulse abnormal
24FG.00	O/E left leg pulses all absent
24FJ.00	Left posterior tibial pulse impalpable
24FL.00	Left dorsalis pedis pulse impalpable
24H..00	O/E - poor tissue perfusion

Acarbose

Code	Generic name
98475997	Acarbose 100mg tablets
98475998	Acarbose 50mg tablets
98915997	Acarbose 100mg tablets
98915998	Acarbose 50mg tablets

DDP4i

Code	Generic name
26160978	Saxagliptin 5mg / dapagliflozin 10mg tablets
26161978	Saxagliptin 5mg / dapagliflozin 10mg tablets
30131978	Sitagliptin 50mg/5ml oral suspension
31126978	Sitagliptin 50mg/5ml oral solution
53004979	Saxagliptin 2.5mg / Metformin 850mg tablets
53005979	Saxagliptin 2.5mg / Metformin 850mg tablets
53006979	Saxagliptin 2.5mg / Metformin 1g tablets
53007979	Saxagliptin 2.5mg / Metformin 1g tablets
54904979	Linagliptin 2.5mg / Metformin 850mg tablets
54905979	Linagliptin 2.5mg / Metformin 850mg tablets

54906979	Linagliptin 2.5mg / Metformin 1g tablets
54907979	Linagliptin 2.5mg / Metformin 1g tablets
59371979	Sitagliptin 50mg tablets
59372979	Sitagliptin 50mg tablets
59373979	Sitagliptin 25mg tablets
59374979	Sitagliptin 25mg tablets
78723978	Alogliptin 6.25mg tablets
78724978	Alogliptin 6.25mg tablets
78725978	Alogliptin 25mg tablets
78726978	Alogliptin 25mg tablets
78727978	Alogliptin 12.5mg tablets
78728978	Alogliptin 12.5mg tablets
78729978	Alogliptin 12.5mg / Metformin 1g tablets
78730978	Alogliptin 12.5mg / Metformin 1g tablets
81159998	Linagliptin 5mg tablets
81160998	Linagliptin 5mg tablets
81513998	Saxagliptin 2.5mg tablets
81514998	Saxagliptin 2.5mg tablets
82068998	Metformin 1g / Sitagliptin 50mg tablets
82573998	Saxagliptin 5mg tablets
82575998	Saxagliptin 5mg tablets
83401998	Metformin 1g / Sitagliptin 50mg tablets
84008998	Vildagliptin 50mg / Metformin 1g tablets
84009998	Vildagliptin 50mg / Metformin 850mg tablets
84010998	Vildagliptin 50mg / Metformin 1g tablets
84011998	Vildagliptin 50mg / Metformin 850mg tablets
84338998	Vildagliptin 50mg tablets
84341998	Vildagliptin 50mg tablets
84639998	Sitagliptin 100mg tablets
84640998	Sitagliptin 100mg tablets

Glinides

Code	**Generic name**
85266998	Repaglinide 2mg tablets
85267998	Repaglinide 1mg tablets
85268998	Repaglinide 500microgram tablets
88131996	Nateglinide 180mg tablets
88131997	Nateglinide 120mg tablets
88131998	Nateglinide 60mg tablets

88132996	Nateglinide 180mg tablets
88132997	Nateglinide 120mg tablets
88132998	Nateglinide 60mg tablets
91908990	Repaglinide 500microgram tablets
91923996	Repaglinide 2mg tablets
91923997	Repaglinide 1mg tablets
91923998	Repaglinide 500microgram tablets
91924996	Repaglinide 2mg tablets
91924997	Repaglinide 1mg tablets
91924998	Repaglinide 500microgram tablets
92981979	Repaglinide 2mg tablets
92996979	Repaglinide 1mg tablets
92999979	Repaglinide 500microgram tablets
93009979	Repaglinide 500microgram tablets

Glitazones

Code	**Generic name**
47709978	Pioglitazone 30mg tablets
82196978	Pioglitazone 30mg tablets
85622998	Pioglitazone 15mg / Metformin 850mg tablets
85624998	Pioglitazone 15mg / Metformin 850mg tablets
85625998	Pioglitazone 15mg / Metformin 850mg tablets
87165998	Metformin with rosiglitazone 1000mg + 4mg tablet
87166998	Metformin with rosiglitazone 1000mg + 2mg tablet
87179998	Metformin & rosiglitazone 1g+4mg tablets
87180998	Metformin & rosiglitazone 1g+2mg tablets
87181998	Rosiglitazone 4mg / metformin 1g tablets
87182998	Rosiglitazone 2mg / metformin 1g tablets
87770998	Metformin & rosiglitazone 500mg+2mg tablets
87771998	Metformin & rosiglitazone 500mg+1mg tablets
87772998	Metformin with rosiglitazone 500mg + 2mg tablet
87773998	Rosiglitazone 2mg / metformin 500mg tablets
87774998	Metformin with rosiglitazone 500mg + 1mg tablet
87775998	Rosiglitazone 1mg / metformin 500mg tablets
87884998	Pioglitazone 45mg tablets
87885998	Pioglitazone 45mg tablets
88523996	Troglitazone 400mg tablets
88523998	Troglitazone 200mg tablets
88528996	Troglitazone 400mg tablet
88528998	Troglitazone 200mg tablet
89763996	Rosiglitazone 8mg tablets

89763997	Rosiglitazone 4mg tablets
89763998	Rosiglitazone 2mg tablet
90048996	Rosiglitazone 8mg tablets
90048997	Rosiglitazone 4mg tablets
90048998	Rosiglitazone 2mg tablet
91880990	Pioglitazone 15mg tablets
92237997	Pioglitazone 30mg tablets
92237998	Pioglitazone 15mg tablets
92238997	Pioglitazone 30mg tablets
92238998	Pioglitazone 15mg tablets

GLP1

Code	Generic name
26220978	Liraglutide 6mg/ml solution for injection 3ml pre-filled disposable devices
39144978	Albiglutide 30mg powder and solvent for solution for injection pre-filled disposable devices
52039979	Lixisenatide 20micrograms/0.2ml solution for injection 3ml pre-filled disposable devices
52040979	Lixisenatide 20micrograms/0.2ml solution for injection 3ml pre-filled disposable devices
52041979	Lixisenatide 10micrograms/0.2ml solution for injection 3ml pre-filled disposable devices
52042979	Lixisenatide 10micrograms/0.2ml solution for injection 3ml pre-filled disposable devices and Lixisenatide 20micrograms/0
52043979	Lixisenatide 10micrograms/0.2ml solution for injection 3ml pre-filled disposable devices
52044979	Lixisenatide 10micrograms/0.2ml solution for injection 3ml pre-filled disposable devices
53431978	Dulaglutide 1.5mg/0.5ml solution for injection pre-filled disposable devices
53432978	Dulaglutide 1.5mg/0.5ml solution for injection pre-filled disposable devices
53433978	Dulaglutide 0.75mg/0.5ml solution for injection pre-filled disposable devices
53434978	Dulaglutide 0.75mg/0.5ml solution for injection pre-filled disposable devices
55150978	Exenatide 2mg powder and solvent for prolonged-release suspension for injection pre-filled disposable devices
55151978	Exenatide 2mg powder and solvent for prolonged-release suspension for injection pre-filled disposable devices
55818978	Insulin degludec 100units/ml / Liraglutide 3.6mg/ml solution for injection 3ml pre-filled disposable devices
55819978	Insulin degludec 100units/ml / Liraglutide 3.6mg/ml solution for injection 3ml pre-filled disposable devices
55842978	Liraglutide 6mg/ml solution for injection 3ml pre-filled disposable devices
81305998	Exenatide 2mg injection
81307998	Exenatide 2mg powder and solvent for prolonged-release suspension for injection vials
82793998	Liraglutide 6mg/ml solution for injection 3ml pre-filled disposable devices
82794998	Liraglutide 6mg/ml solution for injection 3ml pre-filled disposable devices
84693998	Exenatide 10micrograms/0.04ml solution for injection 2.4ml pre-filled disposable devices
84694998	Exenatide 5micrograms/0.02ml solution for injection 1.2ml pre-filled disposable devices
84696998	Exenatide 10micrograms/0.04ml solution for injection 2.4ml pre-filled disposable devices
84697998	Exenatide 5micrograms/0.02ml solution for injection 1.2ml pre-filled disposable devices

Insulin

Code	Generic name
24830978	Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices
24831978	Insulin aspart 100units/ml solution for injection 3ml cartridges
24869978	Insulin aspart 100units/ml solution for injection 10ml vials
46282978	Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices
46283978	Insulin glargine 100units/ml solution for injection 3ml cartridges
46889978	Insulin glargine 300units/ml solution for injection 1.5ml pre-filled disposable devices
46890978	Insulin glargine 300units/ml solution for injection 1.5ml pre-filled disposable devices
47074978	Insulin glulisine 100units/ml solution for injection 3ml pre-filled disposable devices
51391978	Insulin lispro 200units/ml solution for injection 3ml pre-filled disposable devices
52067979	Insulin degludec 200units/ml solution for injection 3ml pre-filled disposable devices
52068979	Insulin degludec 200units/ml solution for injection 3ml pre-filled disposable devices
52069979	Insulin degludec 100units/ml solution for injection 3ml pre-filled disposable devices
52070979	Insulin degludec 100units/ml solution for injection 3ml pre-filled disposable devices
52071979	Insulin degludec 100units/ml solution for injection 3ml cartridges
52072979	Insulin degludec 100units/ml solution for injection 3ml cartridges
55553979	Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices
55818978	Insulin degludec 100units/ml / Liraglutide 3.6mg/ml solution for injection 3ml pre-filled disposable devices
55819978	Insulin degludec 100units/ml / Liraglutide 3.6mg/ml solution for injection 3ml pre-filled disposable devices
60064979	Insulin aspart 100units/ml solution for injection 3ml cartridges
62300979	Insulin human 100units/ml solution for injection 3.15ml cartridges 5 cartridge
63546979	Insulin human 500units/ml solution for injection 20ml vials
63547979	Insulin human 500units/ml solution for injection 20ml vials
64797979	Insulin human 100units/ml solution for injection 10ml vials
68748978	Insulin aspart 100units/ml solution for injection 1.6ml cartridges
68749978	Insulin aspart 100units/ml solution for injection 3ml cartridges
71799979	Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml cartridges
81164998	Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices
81426998	Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices
81687998	Insulin isophane biphasic human 15/85 100units/ml suspension for injection 3ml cartridges
81790998	Insulin isophane biphasic human 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices
81962998	Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices
81963998	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices
82096979	Insulin detemir 100units/ml solution for injection 3ml pre-filled disposable devices
82457998	Insulin lispro biphasic 25/75 100units/ml suspension for injection 10ml vials
82458998	Insulin lispro biphasic 25/75 100units/ml suspension for injection 10ml vials
83403998	Insulin lispro 100units/ml solution for injection 3ml pre-filled disposable devices
83404998	Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices
83405998	Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices
84421998	Insulin glulisine 100units/ml solution for injection 3ml pre-filled disposable devices

84422998	Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices
84779998	Insulin detemir 100units/ml solution for injection 3ml pre-filled disposable devices
85591998	Insulin glulisine 100units/ml solution for injection 3ml cartridges
86028998	Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml cartridges
86029998	Insulin lispro 100units/ml solution for injection 3ml cartridges
86044998	Human insulin 3mg unit dose blisters
86045998	Human insulin 1mg unit dose blisters
86046998	Insulin human 3mg inhalation powder blisters
86047998	Insulin human 1mg inhalation powder blisters
86077998	Insulin lispro 100units/ml solution for injection 3ml pre-filled disposable devices
86078998	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials
86080998	Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices
86081998	Insulin isophane human 100units/ml suspension for injection 10ml vials
86168998	Insulin isophane human 100units/ml suspension for injection 3ml cartridges
86169998	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml cartridges
86173998	Insulin soluble bovine 100units/ml solution for injection 10ml vials
86174998	Insulin soluble bovine 100units/ml solution for injection 3ml cartridges
86175998	Insulin soluble bovine 100units/ml solution for injection 3ml cartridges
86176998	Insulin soluble bovine 100units/ml solution for injection 10ml vials 1 vial
86177998	Isophane insulin 100iu/ml injection cartridges
86178998	Isophane insulin 100iu/ml injection
86179998	Insulin isophane bovine 100units/ml suspension for injection 3ml cartridges
86180998	Insulin isophane bovine 100units/ml suspension for injection 10ml vials
86182998	Insulin soluble porcine 100units/ml solution for injection 3ml cartridges
86183998	Insulin soluble porcine 100units/ml solution for injection 10ml vials
86184998	Insulin soluble porcine 100units/ml solution for injection 3ml cartridges 5 cartridge
86185998	Insulin soluble porcine 100units/ml solution for injection 10ml vials 1 vial
86186998	Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 3ml cartridges
86187998	Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 10ml vials
86188998	Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 3ml cartridges
86189998	Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 10ml vials
86190998	Insulin isophane porcine 100units/ml suspension for injection 3ml cartridges
86191998	Insulin isophane porcine 100units/ml suspension for injection 10ml vials
86193998	Insulin isophane porcine 100units/ml suspension for injection 3ml cartridges
86194998	Insulin isophane porcine 100units/ml suspension for injection 10ml vials
86214998	Insulin glulisine 100units/ml solution for injection 3ml pre-filled disposable devices
86215998	Insulin glulisine 100units/ml solution for injection 3ml pre-filled disposable devices
86236998	Insulin glulisine 100units/ml solution for injection 3ml cartridges
86237998	Insulin glulisine 100units/ml solution for injection 10ml vials
86238998	Insulin glargine 100units/ml solution for injection 3ml cartridges
86239998	Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices
86240998	Insulin glargine 100units/ml solution for injection 10ml vials
86241998	Insulin glargine 100units/ml solution for injection 3ml cartridges
86242998	Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices

86243998	Insulin glargine 100units/ml solution for injection 10ml vials
86245998	Insulin detemir 100units/ml solution for injection 3ml pre-filled disposable devices
86246998	Insulin detemir 100units/ml solution for injection 3ml cartridges
86247998	Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices
86248998	Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml cartridges
86249998	Insulin lispro 100units/ml solution for injection 3ml pre-filled disposable devices
86250998	Insulin lispro 100units/ml solution for injection 3ml cartridges
86251998	Insulin lispro 100units/ml solution for injection 3ml pre-filled disposable devices
86252998	Insulin lispro 100units/ml solution for injection 3ml cartridges
86253998	Insulin lispro 100units/ml solution for injection 10ml vials
86254998	Insulin lispro 100units/ml solution for injection 3ml pre-filled disposable devices
86255998	Insulin lispro 100units/ml solution for injection 3ml cartridges
86256998	Insulin lispro 100units/ml solution for injection 10ml vials
86259998	Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices
86260998	Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml cartridges
86261998	Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices
86262998	Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml cartridges
86263998	Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices
86264998	Insulin aspart 100units/ml solution for injection 3ml cartridges
86265998	Insulin aspart 100units/ml solution for injection 10ml vials
86266998	Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices
86267998	Insulin isophane human 100units/ml suspension for injection 5ml vials
86268998	Insulin isophane human 100units/ml suspension for injection 3ml cartridges
86269998	Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices
86270998	Insulin isophane human 100units/ml suspension for injection 3ml cartridges
86271998	Insulin isophane human 100units/ml suspension for injection 10ml vials
86272998	Insulin glargine 100units/ml solution for injection 3ml cartridges
86274998	Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices
86275998	Insulin isophane human 100units/ml suspension for injection 3ml cartridges
86276998	Insulin isophane human vial 100unit/ml sterile suspension injection
86278998	Insulin isophane biphasic human 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices
86279998	Insulin isophane biphasic human 25/75 100units/ml suspension for injection 3ml cartridges
86280998	Insulin isophane biphasic human 25/75 100units/ml suspension for injection 5ml vials
86281998	Insulin isophane biphasic human 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices
86282998	Insulin isophane biphasic human 25/75 100units/ml suspension for injection 3ml cartridges
86283998	Insulin isophane biphasic human 25/75 100units/ml suspension for injection 5ml vials
86284998	Insulin isophane biphasic human 15/85 100units/ml suspension for injection 3ml pre-filled disposable devices
86285998	Insulin isophane biphasic human 15/85 100units/ml suspension for injection 3ml pre-filled disposable devices
86286998	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices
86287998	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml cartridges
86288998	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices
86291998	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml cartridges
86294998	Insulin isophane biphasic human 40/60 100units/ml suspension for injection 3ml cartridges
86295998	Insulin isophane biphasic human 40/60 100units/ml suspension for injection 3ml cartridges

86298998	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices
86300998	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials
86301998	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges
86303998	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges
86304998	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices
86305998	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials
86306998	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges
86308998	Insulin isophane biphasic human 20/80 100units/ml suspension for injection 3ml cartridges
86309998	Insulin isophane biphasic human 20/80 100units/ml suspension for injection 3ml cartridges
86310998	Insulin isophane biphasic human 10/90 100units/ml suspension for injection 3ml cartridges
86311998	Insulin isophane biphasic human 10/90 100units/ml suspension for injection 3ml cartridges
86312998	Insulin soluble human 100units/ml solution for injection 10ml vials
86313998	Human insulin 100iu/ml preloaded injection pen
86314998	Insulin soluble human 100units/ml solution for injection 3ml cartridges
86315998	Insulin soluble human 100units/ml solution for injection 3ml cartridges
86316998	Insulin soluble human 100units/ml solution for injection 10ml vials
86317998	Insulin soluble human 100units/ml solution for injection 3ml cartridges
86318998	Insulin soluble human 100units/ml solution for injection 3ml pre-filled disposable devices
86319998	Insulin human 100units/ml solution for injection 10ml vials
86549998	Insulin glulisine 100units/ml solution for injection 3ml cartridges
86551998	Insulin glulisine 100units/ml solution for injection 10ml vials
86553998	Insulin glulisine 100units/ml solution for injection 10ml vials
87363979	Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml cartridges
87364979	Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml cartridges
87365979	Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices
87367979	Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices
87372979	Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices
87373979	Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices
87376979	Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices
87378979	Insulin isophane porcine 100units/ml suspension for injection 10ml vials
87379979	Insulin isophane human 100units/ml suspension for injection 5ml vials
87383979	Insulin isophane human 100units/ml suspension for injection 10ml vials
87384979	Insulin isophane human 100units/ml suspension for injection 10ml vials
87385979	Insulin isophane human 100units/ml suspension for injection 10ml vials
87387979	Isophane insulin 100iu/ml injection
87390979	Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 10ml vials
87392979	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml cartridges
87401979	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices
87402979	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges
87403979	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges
87405979	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges
87406979	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges
87407979	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges
87408979	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials

87409979	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials
87410979	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials
87411979	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 1.5ml cartridges
87416979	Insulin isophane biphasic human 20/80 100units/ml suspension for injection 1.5ml cartridges
87426979	Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices
87428979	Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices
87429979	Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml cartridges
87431979	Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml cartridges
87433979	Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml cartridges
87434979	Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices
87435979	Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices
87436979	Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices
87437979	Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices
87438979	Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices
87440979	Insulin aspart 100units/ml solution for injection 3ml cartridges
87442979	Insulin aspart 100units/ml solution for injection 3ml cartridges
87471998	Insulin detemir 100units/ml solution for injection 3ml pre-filled disposable devices
87472998	Insulin detemir 100units/ml solution for injection 3ml cartridges
87473998	Insulin detemir 100units/ml solution for injection 3ml cartridges
87967998	Insulin biphasic isophane human prb 25:75; 100 units/ml injection
88003998	Insulin soluble human 100units/ml solution for injection 3ml cartridges
88413998	Insulin soluble porcine 100units/ml solution for injection 10ml vials
88851998	Human insulin 100iu/ml preloaded injection pen
88978998	Insulin isophane biphasic Porcine 30/70 Mix 100units/ml suspension for injection 1.5ml cartridges
88995998	Insulin isophane biphasic Porcine Isophane 100units/ml suspension for injection 1.5ml cartridges
88999998	Insulin soluble porcine 100units/ml solution for injection 3ml cartridges
89554998	Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices
89555998	Insulin biphasic aspart human pyr 30:70; 100 units/ml injection 5 3ml disposable pen(s)
89639979	Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices
89640979	Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices
89643979	Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices
89659979	Insulin glargine 100units/ml solution for injection 10ml vials
89661979	Insulin glargine 100units/ml solution for injection 10ml vials
89668979	Insulin glargine 100units/ml solution for injection 3ml cartridges
89673979	Insulin glargine 100units/ml solution for injection 3ml cartridges
89888998	Insulin biphasic isophane human emp 30:70; 100 units/ml injection
89990997	Insulin biphasic lispro human prb 50:50; 100 units/ml injection 5 3ml disposable pen(s)
89990998	Insulin biphasic lispro human prb 25:75; 100 units/ml injection 5 3ml cartridge(s)
90012998	Insulin lispro 100units/ml solution for injection 1.5ml cartridges
90015998	Insulin lispro 100units/ml solution for injection 1.5ml pre-filled disposable devices
90168998	Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices
90169998	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices
90202979	Insulin soluble human 100units/ml solution for injection 3ml cartridges
90207979	Insulin soluble porcine 100units/ml solution for injection 10ml vials

90271979	Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices
90272979	Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices
90379998	Insulin aspart human pyr 100 iu/ml injection
90681996	Insulin biphasic isophane human emp 25:75; 100 units/ml injection
90682997	Insulin biphasic isophane human prb 50:50; 100 units/ml injection
90682998	Insulin biphasic isophane human prb 40:60; 100 units/ml injection
90683997	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 1.5ml cartridges
90683998	Insulin biphasic isophane human pyr 40:60; 100 units/ml injection
90684996	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials
90684997	Insulin biphasic isophane human pyr 20:80; 100 units/ml injection
90684998	Insulin biphasic isophane human pyr 10:90; 100 units/ml injection
90685998	Insulin zinc mixed human 100units/ml suspension for injection 10ml vials
90686998	Insulin isophane human 100units/ml suspension for injection 3ml cartridges
90687998	Insulin isophane human prb 100iu/ml injection
90688998	Insulin isophane human 100units/ml suspension for injection 3ml cartridges
90689998	Insulin soluble human prb 100unit/ml injection
90690998	Insulin human 100units/ml solution for injection 10ml vials
90691998	Insulin soluble human pyr 100unit/ml injection
90697996	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices
90697997	Insulin biphasic isophane human prb 20:80; 100 units/ml injection
90697998	Insulin biphasic isophane human prb 10:90; 100 units/ml injection
90698998	Insulin zinc suspension mixed bovine and porcine 100unit/ml injection
91160998	Insulin zinc suspension mixed porcine 100unit/ml injection
91273997	Insulin biphasic isophane human prb 50:50; 100 units/ml injection
91273998	Insulin biphasic isophane human prb 40:60; 100 units/ml injection
91274998	Human insulin 100iu/ml preloaded injection pen
91275996	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices
91275997	Insulin biphasic isophane human prb 20:80; 100 units/ml injection
91275998	Insulin biphasic isophane human prb 10:90; 100 units/ml injection
91276998	Human isophane insulin 100iu/ml preloaded injection pen
91289998	Insulin isophane biphasic human 15/85 100units/ml suspension for injection 5ml vials
91290996	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 10ml vials
91290997	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices
91290998	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 1.5ml cartridges
91291997	Insulin isophane biphasic human 40/60 100units/ml suspension for injection 3ml pre-filled disposable devices
91291998	Insulin biphasic isophane human pyr 40:60; 100 units/ml injection
91292996	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials
91292997	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices
91292998	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges
91293997	Insulin isophane biphasic human 20/80 100units/ml suspension for injection 3ml pre-filled disposable devices
91293998	Insulin biphasic isophane human pyr 20:80; 100 units/ml injection
91294997	Insulin isophane biphasic human 10/90 100units/ml suspension for injection 3ml pre-filled disposable devices
91294998	Insulin biphasic isophane human pyr 10:90; 100 units/ml injection
91295998	Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices

91505998	Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices
91509998	Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices
91612998	Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices
91700998	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml cartridges
91701998	Insuman comb 25 100iu/ml Injection
91758998	Insulin glargine 100units/ml solution for injection 3ml cartridges
92323998	Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices
92376996	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 5ml vials
92376997	Insulin biphasic isophane human crb 25:75; 100 units/ml injection
92555998	Insulin glargine 100units/ml solution for injection 3ml cartridges
92906998	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 1.5ml cartridges
92907998	Insulin biphasic isophane human pyr 40:60; 100 units/ml injection
92908998	Insulin biphasic isophane human pyr 20:80; 100 units/ml injection
92909998	Insulin biphasic isophane human pyr 10:90; 100 units/ml injection
92932998	Insulin biphasic isophane human pyr 30:70; 100 units/ml injection
93137992	Insulin isophane (human) 100 i/u inj
93139992	Insulin isophane 100 i/u
93467992	Insulin soluble inj i/u^2
93566979	Insulin isophane human 100units/ml suspension for injection 3ml cartridges
93567979	Insulin isophane human 100units/ml suspension for injection 3ml cartridges
93568979	Insulin isophane human 100units/ml suspension for injection 3ml cartridges
93569979	Insulin isophane human 100units/ml suspension for injection 3ml cartridges
93570979	Insulin aspart 100units/ml solution for injection 10ml vials
93572979	Insulin lispro 100units/ml solution for injection 3ml pre-filled disposable devices
93574979	Insulin lispro 100units/ml solution for injection 3ml pre-filled disposable devices
93582979	Insulin lispro 100units/ml solution for injection 10ml vials
93585979	Insulin lispro 100units/ml solution for injection 10ml vials
93586979	Insulin lispro 100units/ml solution for injection 10ml vials
93587979	Insulin lispro 100units/ml solution for injection 10ml vials
93589979	Insulin soluble human 100units/ml solution for injection 10ml vials
93590979	Insulin soluble human 100units/ml solution for injection 10ml vials
93592979	Insulin soluble human 100units/ml solution for injection 3ml cartridges
93594979	Human insulin 100iu/ml injection cartridges
94201992	Insulin zinc lente 100iu/ml injection
94202992	Insulin neusulin (neutral)(purified) 100 i/u inj
94292998	Insulin soluble human emp 100unit/ml injection
94298998	Insulin biphasic isophane human emp 25:75; 100 units/ml injection
94319998	Insulin biphasic isophane human pyr 10:90; 100 units/ml injection
94322998	Insulin isophane human 100units/ml suspension for injection 3ml cartridges
94328998	Insulin biphasic isophane human pyr 20:80; 100 units/ml injection
94337998	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices
94413998	Insulin biphasic isophane human pyr 40:60; 100 units/ml injection
94436998	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 1.5ml cartridges
94477992	Neutral insulin 100iu/ml injection

94948998	Insulin soluble porcine 100units/ml solution for injection 1.5ml cartridges 5 1.5ml cartridge(s)
95158992	INSULIN HUMAN (NEUTRAL) 40 I/U INJ
95162992	Insulin soluble human 100units/ml solution for injection 10ml vials
95163992	Isophane insulin 100iu/ml injection
95164992	Insulin zinc lente 100iu/ml injection
95168992	Insulin semitard 40 i/u inj
95846992	Insulin zinc lente 100iu/ml injection
96044992	Insulin bp 100 i/u
96045998	Isophane insulin 100iu/ml injection
96046992	Insulin humulin m4 cartridge 100 i/u
96046998	Insulin zinc mixed bovine 100units/ml suspension for injection 10ml vials
96047998	Insulin neutral human 100unit/ml injection
96048998	Insulin neutral human 100unit/ml injection
96049998	Insulin soluble porcine 100units/ml solution for injection 1.5ml cartridges
96050998	Neutral insulin bovine 100unit/ml injection 1 10ml vial(s)
96051998	Insulin protamine zinc bovine 100units/ml suspension for injection 10ml vials
96052998	Insulin isophane human 100units/ml suspension for injection 3ml cartridges
96053997	Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 1.5ml cartridges
96055998	Insulin isophane porcine 100units/ml suspension for injection 1.5ml cartridges
96056998	Insulin isophane bovine 100units/ml suspension for injection 1.5ml cartridges
96057998	Insulin zinc crystalline human 100units/ml suspension for injection 10ml vials
96058998	Insulin zinc suspension crystalline human pyr 100unit/ml long acting injection
96060998	Insulin zinc suspension mixed human pyr 100unit/ml injection
96061998	Insulin zinc mixed bovine vial 100unit/ml sterile suspension injection
96062998	Insulin biphasic 100 units/ml injection
96064992	Insulin semitard 100 i/u inj
96065998	Insulin soluble bovine 100units/ml solution for injection 10ml vials
96076992	Insulin bovine protamine zinc 100 i/u inj
96282992	Isophane insulin 100iu/ml injection
96283992	Insulin isophane (nph) 100 i/u inj
96284992	Insulin humulin m4 100 i/u inj
96285992	Insulin hypurin protamine zinc 100 i/u inj
96286992	Insulin human velosulin 100 i/u inj 0
96287992	Insulin isophane human 100units/ml suspension for injection 10ml vials
96289992	Insulin novo ultratard mc 100 i/u inj
96290992	Insulin human 100units/ml solution for injection 10ml vials
96291992	Isophane insulin 100iu/ml injection
96292992	Insulin isophane (highly purified) 100 i/u inj
96294992	Insulin zinc bovine susp 100 i/u inj
96295992	Insulin quicksol (soluble neutral) 100 i/u inj
96548992	Insulin humulin m cartridge 100 i/u
96688992	Insulin human 100units/ml solution for injection 10ml vials
96689992	Insulin zinc crystalline susp 100 i/u inj
96787992	Insulin soluble human 100units/ml solution for injection 3ml cartridges

96792992	Insulin pur-in mix 50/50 100 i/u inj
96794992	Insulin pur-in mix 15/85 100 i/u inj
96795992	Insulin pur-in isophane 100 i/u inj
97051997	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 10ml vials
97051998	Insulin biphasic isophane human prb 40:60; 100 units/ml injection
97052996	Insulin biphasic isophane human prb 30:70; 100 units/ml injection
97052997	Insulin isophane biphasic human 20/80 100units/ml suspension for injection 3ml cartridges
97052998	Insulin biphasic isophane human prb 10:90; 100 units/ml injection
97053998	Insulin zinc lente 100iu/ml injection
97244992	Insulin depo s.c.s. 5 400 i/u inj
97322997	Human insulin 100iu/ml preloaded injection pen
97322998	Human insulin 100iu/ml injection cartridges
97323998	Isophane insulin 100iu/ml injection
97524998	Insulin 100iu/ml injection
97525998	Insulin soluble bovine 100units/ml solution for injection 3ml cartridges
97526998	Isophane insulin 100iu/ml injection cartridges
97527998	Insulin zinc mixed bovine 100units/ml suspension for injection 10ml vials
97528998	Insulin protamine zinc bovine 100units/ml suspension for injection 10ml vials
97598992	Insulin isophane (nph) 40 i/u
97599992	Isophane insulin 100iu/ml injection
97600992	Insulin bovine protamine zinc 40 i/u inj
97602992	Insulin soluble 40 i/u inj
97854998	Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices
98048990	Insulin isophane bovine 100units/ml suspension for injection 1.5ml cartridges
98198998	Insulin aspart 100units/ml solution for injection 3ml cartridges
98225998	Insulin biphasic isophane human emp 50:50; 100 units/ml injection
98226998	Insulin biphasic isophane human emp 30:70; 100 units/ml injection
98227998	Neutral insulin 100iu/ml injection
98228996	Insulin isophane human 100units/ml suspension for injection 3ml cartridges
98228997	Insulin isophane human 100units/ml suspension for injection 10ml vials
98228998	Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices
98268998	Insulin zinc crystalline human 100units/ml suspension for injection 10ml vials
98474990	Insulin human 100units/ml solution for injection 10ml vials
98480998	Insulin soluble porcine 100units/ml solution for injection 1.5ml cartridges
98481997	Isophane insulin 100iu/ml injection cartridges
98481998	Isophane insulin 100iu/ml injection
98505998	Insulin zinc lente 100iu/ml injection
98525990	Insulin zinc mixed bovine 100units/ml suspension for injection 10ml vials
98817998	Insulin zinc crystalline human 100units/ml suspension for injection 10ml vials
98895998	Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices
98982998	Insulin soluble human 100units/ml solution for injection 10ml vials
99144998	Insulin zinc suspension amorphous porcine 100unit/ml injection
99196998	Insulin biphasic 100 units/ml injection
99359998	Isophane insulin 100iu/ml injection

99401998	Insulin zinc lente 100iu/ml injection
99402998	Insulin aspart 100units/ml solution for injection 10ml vials
99415998	Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 10ml vials
99480998	Insulin zinc lente 100iu/ml injection
99532998	Isophane insulin 100iu/ml injection
99533998	Isophane insulin 100iu/ml injection
99553998	Insulin soluble human 100units/ml solution for injection 3ml cartridges
99554998	Insulin isophane human prb 100iu/ml injection
99556998	Insulin zinc lente 100iu/ml injection
99557998	Insulin soluble human 100units/ml solution for injection 3ml cartridges
99976992	Insulin soluble 100 i/u inj
99977992	Insulin isophane 50%/neutral 50% 100 i/u inj
99978992	Insulin isophane (purified) 100 i/u inj

Metformin

Code	Generic name
28975978	Metformin 850mg/5ml oral solution sugar free
28977978	Metformin 1g/5ml oral solution sugar free
45821978	Empagliflozin 5mg / Metformin 850mg tablets
45822978	Empagliflozin 5mg / Metformin 850mg tablets
45823978	Empagliflozin 5mg / Metformin 1g tablets
45824978	Empagliflozin 5mg / Metformin 1g tablets
45825978	Empagliflozin 12.5mg / Metformin 850mg tablets
45826978	Empagliflozin 12.5mg / Metformin 850mg tablets
45827978	Empagliflozin 12.5mg / Metformin 1g tablets
45828978	Empagliflozin 12.5mg / Metformin 1g tablets
46249978	Metformin 1g modified-release tablets
46254978	Metformin 750mg modified-release tablets
53004979	Saxagliptin 2.5mg / Metformin 850mg tablets
53005979	Saxagliptin 2.5mg / Metformin 850mg tablets
53006979	Saxagliptin 2.5mg / Metformin 1g tablets
53007979	Saxagliptin 2.5mg / Metformin 1g tablets
54496979	Metformin 1g modified-release tablets
54786979	Metformin 500mg modified-release tablets
54904979	Linagliptin 2.5mg / Metformin 850mg tablets
54905979	Linagliptin 2.5mg / Metformin 850mg tablets
54906979	Linagliptin 2.5mg / Metformin 1g tablets
54907979	Linagliptin 2.5mg / Metformin 1g tablets
56930978	Canagliflozin 50mg / Metformin 850mg tablets
56931978	Canagliflozin 50mg / Metformin 1g tablets
56932978	Canagliflozin 50mg / Metformin 1g tablets

58558979	Metformin 500mg modified-release tablets
71281979	Metformin 500mg/5ml oral solution
74441978	Metformin 1g modified-release tablets
74453978	Metformin 500mg modified-release tablets
74454978	Metformin 500mg modified-release tablets
76199978	Metformin 1g modified-release tablets
76990978	Dapagliflozin 5mg / Metformin 850mg tablets
76991978	Dapagliflozin 5mg / Metformin 850mg tablets
76992978	Dapagliflozin 5mg / Metformin 1g tablets
76993978	Dapagliflozin 5mg / Metformin 1g tablets
78729978	Alogliptin 12.5mg / Metformin 1g tablets
78730978	Alogliptin 12.5mg / Metformin 1g tablets
79508979	Metformin 850mg/5ml oral suspension
79510979	Metformin 850mg/5ml oral solution
79512979	Metformin 500mg/5ml oral solution
81158998	Metformin 500mg modified-release tablets
81344998	Metformin 1g modified-release tablets
81701998	Metformin 500mg modified-release tablets
82068998	Metformin 1g / Sitagliptin 50mg tablets
82916998	Metformin hydrochloride 1g sachets
82917998	Metformin hydrochloride 500mg sachets
82918998	Metformin 1g oral powder sachets sugar free
82919998	Metformin 500mg oral powder sachets sugar free
83031998	Metformin 1g modified-release tablets
83032998	Metformin 1g modified-release tablets
83401998	Metformin 1g / Sitagliptin 50mg tablets
83619998	Metformin 500mg modified-release tablets
83732998	Metformin 750mg modified-release tablets
83733998	Metformin 750mg modified-release tablets
84008998	Vildagliptin 50mg / Metformin 1g tablets
84009998	Vildagliptin 50mg / Metformin 850mg tablets
84010998	Vildagliptin 50mg / Metformin 1g tablets
84011998	Vildagliptin 50mg / Metformin 850mg tablets
84268978	Metformin 1g modified-release tablets
85554998	Metformin 850mg capsules
85555998	Metformin oral solution
85622998	Pioglitazone 15mg / Metformin 850mg tablets
85624998	Pioglitazone 15mg / Metformin 850mg tablets
85625998	Pioglitazone 15mg / Metformin 850mg tablets
85673998	Metformin 500mg/5ml oral solution sugar free
85674998	Metformin 500mg/5ml oral solution
87053998	Metformin 500mg modified-release tablets
87054998	Metformin 500mg modified-release tablets
87165998	Metformin with rosiglitazone 1000mg + 4mg tablet

87166998	Metformin with rosiglitazone 1000mg + 2mg tablet
87179998	Metformin & rosiglitazone 1g+4mg tablets
87180998	Metformin & rosiglitazone 1g+2mg tablets
87181998	Rosiglitazone 4mg / metformin 1g tablets
87182998	Rosiglitazone 2mg / metformin 1g tablets
87536998	Metformin 500mg/5ml oral solution
87770998	Metformin & rosiglitazone 500mg+2mg tablets
87771998	Metformin & rosiglitazone 500mg+1mg tablets
87772998	Metformin with rosiglitazone 500mg + 2mg tablet
87773998	Rosiglitazone 2mg / metformin 500mg tablets
87774998	Metformin with rosiglitazone 500mg + 1mg tablet
87775998	Rosiglitazone 1mg / metformin 500mg tablets
87883998	Metformin 500mg modified-release tablets
89128979	Metformin 1g modified-release tablets
89129979	Metformin 1g modified-release tablets
89188979	Metformin 500mg/5ml oral solution
89868979	Metformin 500mg modified-release tablets
89870979	Metformin 500mg modified-release tablets
89871979	Metformin 500mg modified-release tablets
91221997	Metformin hydrochloride 850mg tablets
91221998	Metformin hydrochloride 500mg tablets
91686990	Metformin 500mg/5ml oral solution
92983990	Metformin 500mg/5ml oral solution
93167990	Metformin 500mg/5ml oral solution
93459979	Metformin 850mg tablets
93462979	Metformin 500mg tablets
93469979	Metformin 500mg tablets
94235992	Metformin 500mg tablets
94248990	Metformin 500mg tablets
95270992	Metformin 800 mg tab
95271992	Metformin 850mg tablets
95272992	Metformin 250 mg tab
95600990	Metformin 500mg tablets
95880998	Metformin 500mg modified-release tablets
96111990	Metformin 500mg tablets
96270990	Metformin 500mg tablets
96850990	Metformin 500mg tablets
97087997	Metformin 850mg tablets
97087998	Metformin 500mg tablets
97110989	Metformin 850mg tablets
97110990	Metformin 500mg tablets
98125989	Metformin 850mg tablets
98125990	Metformin 500mg tablets
98493989	Metformin 500mg tablets

98493990	Metformin 850mg tablets
98654989	Metformin 500mg tablets
98654990	Metformin 850mg tablets
99149990	Metformin 500mg tablets
99513989	Metformin 850mg tablets
99513990	Metformin 500mg tablets
99514989	Metformin 850mg tablets
99514990	Metformin 500mg tablets
99590997	Metformin 850mg tablets
99590998	Metformin 500mg tablets

SGLT2i

Code	Generic name
26160978	Saxagliptin 5mg / dapagliflozin 10mg tablets
26161978	Saxagliptin 5mg / dapagliflozin 10mg tablets
45821978	Empagliflozin 5mg / Metformin 850mg tablets
45822978	Empagliflozin 5mg / Metformin 850mg tablets
45823978	Empagliflozin 5mg / Metformin 1g tablets
45824978	Empagliflozin 5mg / Metformin 1g tablets
45825978	Empagliflozin 12.5mg / Metformin 850mg tablets
45826978	Empagliflozin 12.5mg / Metformin 850mg tablets
45827978	Empagliflozin 12.5mg / Metformin 1g tablets
45828978	Empagliflozin 12.5mg / Metformin 1g tablets
53325979	Dapagliflozin 5mg tablets
53326979	Dapagliflozin 5mg tablets
53327979	Dapagliflozin 10mg tablets
53328979	Dapagliflozin 10mg tablets
56930978	Canagliflozin 50mg / Metformin 850mg tablets
56931978	Canagliflozin 50mg / Metformin 1g tablets
56932978	Canagliflozin 50mg / Metformin 1g tablets
70445978	Empagliflozin 25mg tablets
70446978	Empagliflozin 25mg tablets
70447978	Empagliflozin 10mg tablets
70448978	Empagliflozin 10mg tablets
76399978	Canagliflozin 300mg tablets
76400978	Canagliflozin 300mg tablets
76401978	Canagliflozin 100mg tablets
76402978	Canagliflozin 100mg tablets
76980978	Canagliflozin 100mg tablets
76981978	Canagliflozin 100mg tablets
76990978	Dapagliflozin 5mg / Metformin 850mg tablets

76991978	Dapagliflozin 5mg / Metformin 850mg tablets
76992978	Dapagliflozin 5mg / Metformin 1g tablets
76993978	Dapagliflozin 5mg / Metformin 1g tablets

Sulphonylurea

Code	Generic name
39422978	Gliclazide 60mg modified-release tablets
39755978	Gliclazide 30mg modified-release tablets
55225978	Gliclazide 60mg modified-release tablets
55773978	Gliclazide 30mg modified-release tablets
62836979	Gliclazide 40mg tablets
68690978	Gliclazide 30mg modified-release tablets
69061979	Gliclazide 120mg/5ml oral suspension
80004979	Gliclazide 160mg/5ml oral suspension
81260998	Gliclazide 80mg/5ml oral suspension
82136998	Gliclazide 40mg tablets
82137998	Gliclazide 40mg tablets
82304998	Gliclazide 30mg modified-release tablets
82989998	Gliclazide 30mg modified-release tablets
83916998	Gliclazide 30mg modified-release tablets
83949998	Gliclazide 30mg modified-release tablets
84493978	Gliclazide 60mg modified-release tablets
84494978	Gliclazide 60mg modified-release tablets
85003998	Gliclazide oral solution
85547978	Gliclazide 30mg modified-release tablets
85901998	Glibenclamide 5mg/5ml oral suspension
86018998	Gliclazide 40mg/5ml oral suspension
88135998	Gliclazide 80mg tablets
88334998	Glimepiride 4mg tablets
88355998	Glimepiride 4mg tablets
88447996	Glimepiride 3mg tablets
88447997	Glimepiride 1mg tablets
88447998	Glimepiride 2mg tablets
88449996	Glimepiride 3mg tablets
88449997	Glimepiride 1mg tablets
88449998	Glimepiride 2mg tablets
91407998	Gliclazide 30mg modified-release tablets
91559998	Glibornuride 25mg tablet
92831990	Gliclazide 30mg modified-release tablets
93483979	Glimepiride 4mg tablets
93509979	Glimepiride 1mg tablets

93528979	Glimepiride 2mg tablets
93545979	Gliclazide 80mg tablets
93546979	Gliclazide 80mg tablets
93556979	Glibenclamide 5mg tablets
93564990	Glimepiride 1mg tablets
94371992	Tolbutamide 100 mg tab
94470992	Glymidine 500mg tablets
95025990	Gliclazide 80mg tablets
95148998	Tolbutamide 50mg/ml injection
95149997	Tolazamide 250mg tablets
95149998	Tolazamide 100mg tablets
95150997	Tolazamide 250mg tablets
95150998	Tolazamide 100mg tablet
95672992	Tolbutamide 1 gm tab
95674992	Tolbutamide 250 mg tab
95870992	Butamide cap
95898990	Gliclazide 80mg tablets
96220990	Glibenclamide 5mg tablets
96264998	Glymidine sodium 500mg tablet
96280998	Gliquidone 30mg tablets
96281998	Glipizide 2.5mg tablets
96282997	Glipizide 5mg tablets
96282998	Glipizide 2.5mg tablets
96283997	Gliclazide 30mg modified-release tablets
96283998	Gliclazide 80mg tablets
96427990	Gliclazide 80mg tablets
96495990	Gliclazide 80mg tablets
96687998	Chlorpropamide 250mg tablets
96755997	Chlorpropamide 250mg tablets
96755998	Chlorpropamide 100mg tablets
96893990	Glipizide 5mg tablets
96981998	Acetohexamide 500mg tablets
97026990	Gliclazide 80mg tablets
97032990	Gliclazide 80mg tablets
97057997	Glibenclamide 2.5mg tablets
97057998	Glibenclamide 5mg tablets
97089998	Tolbutamide 500mg tablets
97097997	Glibenclamide 5mg tablets
97109998	Tolbutamide 500mg tablets
97127997	Glibenclamide 5mg tablets
97127998	Glibenclamide 2.5mg tablets
97133992	Chlorpropamide 500 mg tab
97146990	Glipizide 5mg tablets
97154990	Gliclazide 80mg tablets

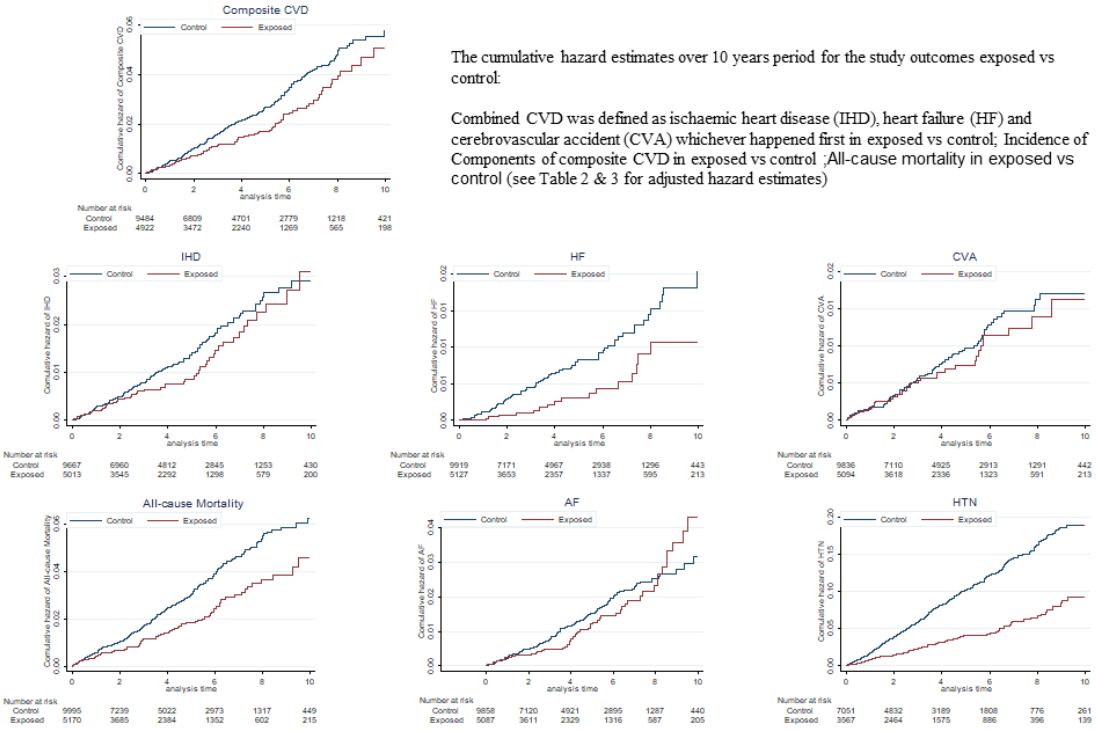
97166990	Gliclazide 80mg tablets
97202990	Glipizide 5mg tablets
97236992	Daonil 10 mg tab
97303998	Gliclazide 80mg tablets
97537997	Glibenclamide 5mg tablets
97537998	Glibenclamide 2.5mg tablets
97538990	Gliclazide 80mg tablets
97552990	Glibenclamide 2.5mg tablets
97583997	Glibenclamide 5mg tablets
97583998	Glibenclamide 2.5mg tablets
97590990	Gliclazide 80mg tablets
97834990	Glipizide 5mg tablets
97889990	Gliclazide 80mg tablets
97938990	Gliclazide 80mg tablets
98053990	Tolbutamide 500mg tablets
98133990	Gliclazide 80mg tablets
98188989	Chlorpropamide 250mg tablets
98664989	Glibenclamide 2.5mg tablets
98664990	Glibenclamide 5mg tablets
99145998	Glibenclamide 2.5mg tablets
99195998	Tolbutamide 500mg tablets
99246990	Chlorpropamide 100mg tablets
99247989	Chlorpropamide 250mg tablets
99347990	Tolbutamide 500mg tablets
99349990	Tolbutamide 500mg tablets
99419998	Glipizide 5mg tablets
99580989	Glibenclamide 2.5mg tablets
99580990	Glibenclamide 5mg tablets
99582989	Glibenclamide 2.5mg tablets
99582990	Glibenclamide 5mg tablets
99588998	Glibornuride 25mg tablets
99589998	Gliquidone 30mg tablets
99591998	Glipizide 5mg tablets
99668997	Glibenclamide 5mg tablets
99668998	Glibenclamide 2.5mg tablets
99754998	Acetohexamide 500mg tablets
99764997	Chlorpropamide 250mg tablets
99764998	Chlorpropamide 100mg tablets
99787998	Glibenclamide 5mg tablets

Appendices for Chapter 3

Appendices for manuscript 1

Supplementary Figure S1: Unadjusted Nelson–Aalen cumulative hazard estimates for cardiovascular disease and mortality

eFigure 1: Unadjusted Nelson-Aalen cumulative hazard estimates for cardiovascular diseases and mortality



The cumulative hazard estimates over 10 years period for the study outcomes exposed vs control:

Combined CVD was defined as ischaemic heart disease (IHD), heart failure (HF) and cerebrovascular accident (CVA) whichever happened first in exposed vs control; Incidence of Components of composite CVD in exposed vs control ;All-cause mortality in exposed vs control (see Table 2 & 3 for adjusted hazard estimates)

Supplementary Table S1: Impact of bariatric surgery on cardiovascular outcomes in participants with and without type 2 diabetes mellitus

Type 2 DM		Hypertension		Atrial fibrillation		Combined Cardiovascular event	
		Exposed	Control	Exposed	Control	Exposed	Control
		518	854	1148	2032	1060	1821
Outcome events, n (%)		19 (3.7)	81 (9.5)	16 (1.4)	54 (2.7)	34 (3.2)	85 (4.7)
Person-years		1913.3	2962.1	4416.3	8158.2	4005.7	7241.1
Crude Incidence Rate*		9.93	27.35	3.62	6.62	8.49	11.74
Follow-up years, Median (IQR)		3.2 (1.5- 5.4)	3.1 (1.4- 5.2)	3.4 (1.6- 5.5)	3.7 (1.8- 5.9)	3.3 (1.5-5.5)	3.6 (1.7- 5.8)
HR (95% CI), p value	**Unadjusted**	0.37 (0.22-0.60), <0.001		0.55 (0.32-0.96), 0.037		0.72 (0.49-1.08), 0.113	
	Adjusted Model 1	0.33 (0.2-0.56), <0.001		0.57 (0.32-1.01), 0.053		0.78 (0.52-1.18), 0.239	
	Adjusted Model 3	0.34 (0.20-0.56), <0.001		0.58 (0.33-1.02), 0.060		0.77 (0.51-1.16) 0.204	
No Type 2 DM		**Hypertension**		**Atrial fibrillation**		**Combined Cardiovascular event**	
		3049	6197	3939	7826	3862	7663
Outcome events, n (%)		99 (3.3)	486 (7.8)	43 (1.1)	76 (1.0)	53 (1.4)	145 (1.9)
Person-years		12383.9	25611.6	16595.4	34895.4	16236.5	33965.0
Crude Incidence Rate*		7.99	18.98	2.59	2.18	3.26	4.27
Follow-up years, Median (IQR)		3.5 (1.6- 6.1)	3.7 (1.6- 6.2)	3.7 (1.7- 6.2)	4.1 (1.8- 6.7)	3.7 (1.7- 6.2)	4.1 (1.8- 6.6)
HR (95% CI), p value	**Unadjusted**	0.42 (0.34-0.52), <0.001		1.21 (0.83-1.76), 0.316		0.77 (0.57-1.06), 0.112	
	Adjusted Model 1	0.41 (0.33-0.51), <0.001		1.24 (0.85-1.81), 0.271		0.80 (0.59-1.11), 0.182	
Type 2 DM		**Ischaemic Heart disease**		**Heart Failure**		**Cerebrovascular accident**	
		1096	1905	1157	2039	1142	2020
Outcome events, n (%)		22 (2.0)	50 (2.6)	9 (0.8)	33 (1.62)	11 (1.0)	35 (1.73)
Person-years		4179.1	7629.8	4467.0	8255.7	4403.1	8168.1
Crude Incidence Rate*		5.26	6.55	2.01	4.0	2.50	4.29
Follow-up years, Median (IQR)		3.3 (1.6- 5.5)	3.7 (1.7- 5.9)	3.4 (1.6- 5.6)	3.7 (1.8- 5.9)	3.4 (1.6- 5.6)	3.7 (1.8- 5.9)
HR (95% CI), p value	**Unadjusted**	0.81 (0.49-1.33), 0.406		0.50 (0.24-1.05), 0.069		0.59 (0.3-1.15), 0.121	
	Adjusted Model 1	0.89 (0.53-1.50), 0.674		0.55 (0.26-1.19), 0.128		0.67 (0.34-1.34), 0.260	
	Adjusted Model 3	0.87 (0.52-1.47), 0.610		0.57 (0.26-1.22) 0.147		0.66 (0.33-1.31) 0.235	
No Type 2 DM		**Ischaemic Heart disease**		**Heart Failure**		**Cerebrovascular accident**	
		3917	7762	3970	7880	3952	7816
Outcome events, n (%)		27 (0.7)	73 (0.9)	10 (0.3)	39 (0.5)	26 (0.7)	48 (0.6)
Person-years		16502	34496.2	16814.1	35162.8	16699	34896.6
Crude Incidence Rate*		1.64	2.12	0.59	1.11	1.56	1.38
Follow-up years, Median (IQR)		3.7 (1.7- 6.3)	4.1 (1.8- 6.6)	3.7 (1.8- 6.3)	4.1 (1.8- 6.7)	3.7 (1.7- 6.3)	4.1 (1.8- 6.7)
HR (95% CI), p value	**Unadjusted**	0.78 (0.50-1.21), 0.272		0.54 (0.27-1.09), 0.087		1.14 (0.71-1.84), 0.582	
	Adjusted Model 1	0.82 (0.53-1.28), 0.385		0.58 (0.29-1.16), 0.124		1.22 (0.75-1.97), 0.425	

*Rate per 1000 person years. HR: Hazard rate

Adjusted Model 1: Adjusted for age, sex, BMI, smoking status, alcohol consumption, Townsend deprivation quintile, ethnicity, baseline hypertension.

Adjusted Model 3: Adjusted for age, sex, BMI, smoking status, alcohol consumption, Townsend deprivation quintile, ethnicity, baseline hypertension, DM duration.

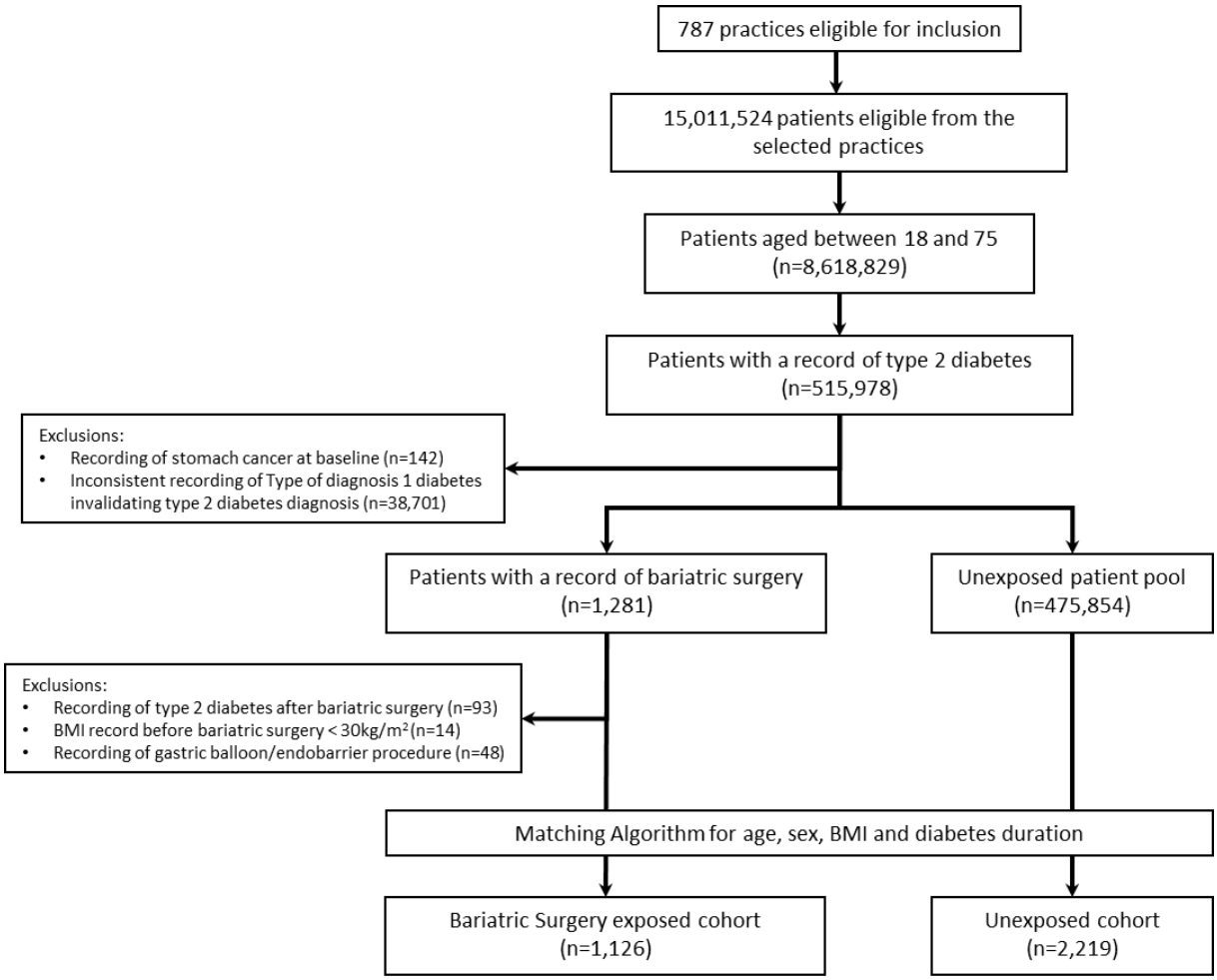
Supplementary Table S2: Impact of bariatric surgery on mortality in participants with and without type 2 diabetes mellitus

Mortality		Type 2 DM		No Type 2 DM	
		Exposed	Control	Exposed	Control
		1176	2089	3994	7906
Outcome events, n(%)		36 (3.1)	120 (5.7)	54 (1.4)	158 (2.0)
Person-years		4567.3	8517.1	16924.0	35346.5
Crude Incidence Rate/1000 person years		7.88	14.09	3.19	4.47
Follow-up years, Median(IQR)		3.4 (1.6- 5.6)	3.8 (1.8- 5.9)	3.7 (1.8- 6.3)	4.1 (1.8- 6.7)
HR ratio (95% CI), p value	**Unadjusted**	0.56 (0.39-0.82), 0.002		0.72 (0.53-0.98), 0.037	
	Adjusted Model 1	0.62 (0.42-0.91), 0.016		0.75 (0.55-1.03), 0.073	
	Adjusted Model 2	0.64 (0.44-0.95), 0.026		0.73 (0.53-1.00), 0.050	
	Adjusted Model 3	0.65 (0.44- 0.96), 0.030			

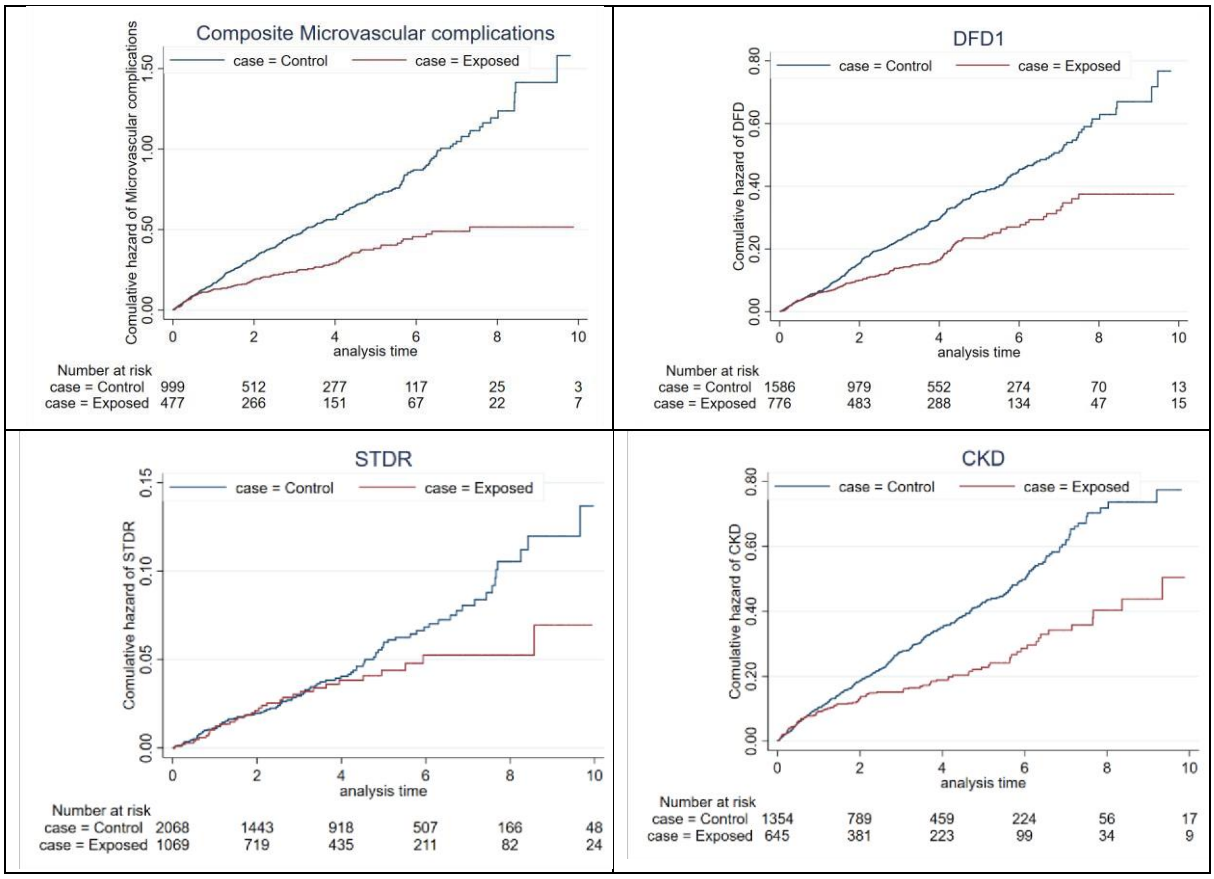
*Rate per 1000 person years
HR = Hazard rate
Adjusted Model 1: Adjusted for age, sex, BMI, smoking status, alcohol consumption, Townsend deprivation quintile, ethnicity, baseline hypertension.
Adjusted Model 2: Adjusted for age, sex, BMI, smoking status, alcohol consumption, Townsend deprivation quintile, ethnicity, baseline hypertension, Charlson co morbidity index
Adjusted Model 3: Adjusted for age, sex, BMI, smoking status, alcohol consumption, Townsend deprivation quintile, ethnicity, baseline hypertension, Charlson co morbidity index and T2DM duration.

Appendices for Chapter 5

Appendices for manuscript 2



Supplementary Figure 1: Flowchart showing participant selection



Supplement Figure 2: Unadjusted Nelson-Aalen cumulative hazard estimates for composite microvascular complications, DFD1, STDR and CKD

Appendices for Chapter 7

Appendices for manuscript 4

Supplementary Table 1: Search strategy used in Embase

1. exp *Diabetes Mellitus, Type 2/ or exp *DIABETES MELLITUS/ or diabetes.mp.
2. exp *REMISSION, SPONTANEOUS/ or exp *REMISSION INDUCTION/ or remission.mp.
3. reversal.mp.
4. cure*.mp.
5. resolv*.mp.
6. treat*.mp.
7. 2 or 3 or 4 or 5 or 6
8. bariatric.mp. or exp *BARIATRICS/
9. gastric band*.mp.
10. exp *Gastric Bypass/ or roux en y.mp. or exp *Anastomosis, Roux-en-Y/
11. gastrectomy.mp. or exp *GASTRECTOMY/
12. exp *Gastrectomy/ or sleeve gastrectomy.mp. or exp *Gastroplasty/
13. exp *Biliopancreatic Diversion/ or duodenal switch.mp.
14. metabolic surgery.mp. or exp *Bariatric Surgery/
15. 8 or 9 or 10 or 11 or 12 or 13 or 14
16. (Stratification or ROC curve or discrimination or discriminate or c-statistic or c statistic or area or area under the curve or AUC or calibration or indices or algorithm$).mp. or multivariable.ti,ab. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
17. Validat$.mp. or Predict$.ti. or Rule$.mp. or (Predict$ and (Outcome$ or Risk$ or Model$)).mp. or ((History or Variable$ or Criteria or Scor$ or Characteristic$ or Finding$ or Factor$) and (Predict$ or Model$ or Decision$ or Identif$ or Prognos$)).mp. or (Decision$.mp. and ((Model$ or Clinical$).mp. or Logistic Models/)) or (Prognostic and

(History or Variable$ or Criteria or Scor$ or Characteristic$ or Finding$ or Factor$ or Model$)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 18. predict*.mp.

19. exp *Observer Variation/ or exp *"Reproducibility of Results"/ or observ*.mp.
20. exp *Algorithms/ or validat*.mp. or exp *"Sensitivity and Specificity"/
21. ((prognos* or predict*) adj3 model).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 22. scor*.mp.
23. exp *ROC CURVE/ or ROC.mp.

24. AUC.mp. or exp *Area Under Curve/
25. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 1 and 7 and 15 and 25
27. limit 26 to (english language and last 15 years)

Supplementary Table 2: Papers excluded on full-text

Paper ID	Reasons for exclusion
Bhasker (2018) Bhasker AG, Dixon JB, Lakdawala M. Selection of Bypass vs Sleeve for the Management of Type-2 Diabetes in Severely Obese: Could Ethnicity Play a Role? Obesity surgery. 2018;28(10):3073-9	No model development or validation. Used the prediction score as adjusting variable to choose the appropriate type of bariatric surgery
Haruta (2017) Haruta H, Kasama K, Ohta M, Sasaki A, Yamamoto H, Miyazaki Y, et al. Long-Term Outcomes of Bariatric and Metabolic Surgery in Japan: Results of a Multi-Institutional Survey. Obesity surgery. 2017;27(3):754-62	No model development or validation. Remission rate for type 2 diabetes mellitus at 3 years after surgery stratified by prediction model
Wood (2016) G. Craig Wood MTM, PhD2; Christopher D. Still, DO1; et alAnnemarie G. Hirsch, PhD, MPH3. Association of DiaRem Score With Cure of Type 2 Diabetes Following Bariatric Surgery Author Affiliations. JAMA Surg. 2016(151(8):779-781. doi:10.1001/jamasurg.2016.0251).	Population (P)-Used the same population as was used to develop the model
Park J Y et al (2015) Park Ji Y, Kim Yong J. Prediction of Diabetes Remission in Morbidly Obese Patients After Roux-en-Y Gastric Bypass. Obesity surgery. 2016;26(4):749-56.	Outcome (O)- Definition of diabetes remission not fulfilled. Mean follow-up was 12.3±8.0 with IQR of 1.0 months to 41.3months
Panunzi Simona (2016) Panunzi S, Carlsson L, De Gaetano A, Peltonen M, Rice T, Sjostrom L, et al. Determinants of Diabetes Remission and Glycemic Control After Bariatric Surgery. Diabetes care. 2016;39(1):166-74LID.	Outcome (O)- Definition of diabetes remission not fulfilled. Diabetes remission was defined without mention of HbA1c or follow up duration

Ha Jane et al (2019) Ha J, Kwon Y, Kim Nam H, Park S, Menzo Emanuele L, Rosenthal Raul J. Discordance in prediction for prognosis of type 2 diabetes after metabolic surgery: comparison of the ABCD, DiaRem, and individualized metabolic surgery models. Annals of surgical treatment and research. 2019;97(6):309-18	No model development or validation. Evaluated discordance between prediction models
Sjoholm K et al (2020)	No model development or validation. Evaluated diabetes relapse rate
Sjoholm K, Svensson PA, Taube M, Jacobson P, Andersson-Assarsson JC, Carlsson LMS, et al. Evaluation of Prediction Models for Type 2 Diabetes Relapse After Post-bariatric Surgery Remission: a Post hoc Analysis of 15-Year Follow-up Data from the Swedish Obese Subjects (SOS) Study. Obesity Surgery. 2020	
Sohal D S et al (2020) Sohal DS, Nain PS, Singh P, Ahuja A, Singh A. ABCD score of > 6 predicts diabetes remission following bariatric surgery. International Journal of Diabetes in Developing Countries. 2020	Outcome (O)- Definition of diabetes remission not fulfilled. Follow up of period of 6 month
Ceperuelo-Mallafre Victoria et al (2019) Ceperuelo-Mallafre V, Llaurado G, Keiran N, Benaiges E, Astiarraga B, Martinez L, et al. Preoperative Circulating Succinate Levels as a Biomarker for Diabetes Remission After Bariatric Surgery. Diabetes care. 2019;42(10):1956-65.	Outcome (O)- Definition of diabetes remission not fulfilled. Focussed on identifying single predictor, small number of outcomes (<30)

Supplementary Table 3: Data collection questionnaire

Characteristic of study	Types of Study
	Ref id
	Publication Reference
	Aim/Objective
	Number of participants?
	Type of study
Source	Source of data?
	Country
	Centres -> Single/ multiple

	Study Date (start)
	Study Date (end)
	Number of outcome/events
	Number of outcomes/events in relation to the number of candidate predictors (Events Per Variable)
	Number of participants with any missing value (include predictors and outcomes) -> Lost to follow up/ died/ no information
	Handling of missing data -> Others
Participants	Age Mean (SD)
	Males
	Females
	Diabete Duration
	Body mass index mean (SD)
	HbA1c Mean (SD)
	Inclusion Criteria
	Exclusion Criteria
	Types of Surgery -> Gastric Band/ Gastric bypass/ Sleeve gastrectomy/ duodenal switch
Outcomes	Definition for measurement of outcome
	Method for measurement of outcome
	Was the same outcome definition (and method for measurement) used in all patients?
	Type of outcome
	Was the outcome assessed without knowledge of the candidate predictors (i.e., blinded)?
	Were candidate predictors part of the outcome (e.g., in panel or consensus diagnosis)?
	Time of outcome occurrence or summary of duration of study - Follow-up
Predictors	Number of variables
	Types of variables (Number and type of predictors (e.g., demographics, patient history, physical examination, additional testing, disease characteristics)
	Definition for measurement of candidate predictors
	Method for measurement of candidate predictors
	Timing of predictor measurement -> Patient Presentation/ at diagnosis/ treatment initiation/ post operatively
	Handling of predictors in the modelling -> Continuous/ linear/ categorised
Analysis	Modelling method -> Logistic regression
	Method for selection of predictors for inclusion in multivariable modelling (e.g., all candidate predictors, pre-selection based on unadjusted association with the outcome)

	Method for selection of predictors during multivariable modelling (e.g., full model approach, backward or forward selection) and criteria used (e.g., p-value, Akaike Information Criterion)
	Shrinkage of predictor weights or regression coefficients (e.g., no shrinkage, uniform shrinkage, penalized estimation)
Performance	Calibration (calibration plot, calibration slope, Hosmer-Lemeshow test) and Discrimination (C-statistic, D-statistic, log-rank) measures with confidence intervals
	Classification measures (e.g., sensitivity, specificity, predictive values, net reclassification improvement) and whether a-priori cut points were used
	Method used for testing model performance: development dataset only (random split of data, resampling methods e.g. bootstrap or cross-validation, none) or separate external validation (e.g. temporal, geographical, different setting, different investigators)
	In case of poor validation, whether model was adjusted or updated (e.g., intercept recalibrated, predictor effects adjusted, or new predictors added)
	Final and other multivariable models (e.g., basic, extended, simplified) presented, including predictor weights or regression coefficients, intercept, baseline survival, model performance measures (with standard errors or confidence intervals)
	Any alternative presentation of the final prediction models, e.g., sum score, nomogram, score chart, predictions for specific risk subgroups with performance
	Comparison of the distribution of predictors (including missing data) for development and validation datasets
	Interpretation of presented models (confirmatory, i.e., model useful for practice versus exploratory, i.e., more research needed)
	Comparison with other studies, discussion of generalizability, strengths and limitations.

Supplementary Table 4: PROBAST data collection questionnaire

Participants	Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?
	Were all inclusions and exclusions of participants appropriate?
Predictors	Were predictors defined and assessed in a similar way for all participants?
	Were predictor assessments made without knowledge of outcome data?
	Are all predictors available at the time the model is intended to be used?
Outcome	Was the outcome determined appropriately?

	Was a pre-specified or standard outcome definition used?
	Were predictors excluded from the outcome definition?
	Was the outcome defined and determined in a similar way for all participants?
	Was the outcome determined without knowledge of predictor information?
	Was the time interval between predictor assessment and outcome determination appropriate?
Analysis	Were there a reasonable number of participants with the outcome?
	Were continuous and categorical predictors handled appropriately?
	Were all enrolled participants included in the analysis?
	Were participants with missing data handled appropriately?
	Was selection of predictors based on univariable analysis avoided?
	Were complexities in the data (e.g. censoring, competing risks, sampling of controls) accounted for appropriately?
	Were relevant model performance measures evaluated appropriately?
	Were model overfitting and optimism in model performance accounted for?
	Do predictors and their assigned weights in the final model correspond to the results from multivariable analysis?

Supplementary Table 5: Risk of bias assessment and applicability for model development studies

	Risk of Bias					Applicability			
	Participants	Predictors	Outcome	Analysis	Overall	Participants	Predictors	Outcome	Overall
ABCD; Lee et al; 2013 (16)	L	L	L	H	H	L	L	L	L
DiaRem ;Still et al; 2014 (17)	L	L	L	L	L	L	L	L	L
Robert et.al; 2013 (31)	L	L	L	H	H	L	L	L	L
DRS; Ugale S; 2014 (33)	L	L	L	H	H	L	L	L	L
ADDiaRem; Aron-Wisnewsky et.al; 2017 (34)	L	L	L	L	L	L	L	L	L
DiaBetter; Pucci et.al; 2017 (35)	UC	L	L	H	H	L	L	L	L
IMS; Aminian et.al; 2017 (18)	L	L	L	H	H	L	L	L	L
DiaRem 2; Still et al; 2018 (36)	UC	UC	L	H	H	L	L	L	L
Hayes et.al; 2011 (40)	UC	L	L	H	H	L	L	L	L
Dixon el.al; 2013 (13)	L	L	L	UC	UC	L	L	L	L
5 models; Ana et al; 2014 (41)	UC	UC	L	H	H	L	L	L	L
Cotillard et al; 2015 (42)	UC	L	L	H	H	L	L	L	L
Stallard et al; 2016 (43)	UC	L	L	H	H	L	L	L	L
5y-DR, 2018 (37)	UC	L	L	H	H	L	L	L	L
MDR, 2020 (38)	L	L	L	H	H	L	L	L	L
Umemura, 2020 (39)	UC	L	L	H	H	L	L	L	L

L= low risk, UC = unclear, H = high risk

Supplementary Table 6: Risk of bias assessment and applicability for external validation studies

	Risk of Bias					Applicability			
	Participants	Predictors	Outcome	Analysis	Overall	Participants	Predictors	Outcome	Overall Applicability
Lee et al 2015 (44)	L	L	L	UC	UC	L	L	L	L
Lee MH et al 2015 (45)	L	L	L	H	H	L	L	L	L
Lee et al 2015 (46)	L	L	L	UC	UC	L	L	L	L
Sampaio-Neto Jose, et al 2015 (47)	UC	L	L	UC	UC	L	L	L	L
Lee et al 2016 (48)	L	L	L	UC	UC	L	L	L	L
Lee et al 2017 (49)	L	L	L	UC	UC	L	L	L	L
Mehaffey et al 2017 (50)	UC	L	L	H	H	L	L	L	L
Honarmand K, et al 2017 (51)	UC	L	L	UC	UC	L	L	L	L
Tharkan, 2017 (52)	UC	L	L	UC	UC	L	L	L	L
Raj et al, 2017 (53)	L	L	L	H	H	L	L	L	L
Seki et al. 2018 (54)	UC	L	L	UC	UC	L	L	L	L
Shen et al 2018 (55)	L	L	L	UC	UC	L	L	L	L
Naitoh et al 2018 (56)	UC	L	L	UC	UC	L	L	L	L
Ahuja et al 2018 (57)	L	L	L	UC	UC	L	L	L	L
Almalki et al 2018 (58)	L	L	L	UC	UC	L	L	L	L
Chen et al 2018 (59)	L	L	L	UC	UC	L	L	L	L
Wood et al 2018 (60)	L	L	L	UC	UC	L	L	L	L
Dicker et al 2019 (61)	L	L	L	UC	UC	L	L	L	L
Kam et al, 2020 (62)	UC	L	L	UC	UC	L	L	L	L
Park et al, 2020 (63)	L	L	L	UC	UC	L	L	L	L
Lee et al, 2020 (64)	L	L	L	UC	UC	L	L	L	L
Guerron et al, 2020 (65)	L	L	L	L	L	L	L	L	L

L= low risk, UC = unclear, H = high risk

Supplementary Material 7: Example of AUC analysis
Model development studies Predicting success of metabolic surgery: age, body mass index, C-peptide, and duration score.

Lee et al 2013 (16)
From table:

Table: pop = population achieving diabetes remission; disease: 0 = no diabetes remission, 1 = diabetes remission

score	pop	disease
0	2	0
0	1	1
1	6	0
1	3	1
2	17	0
2	13	1
3	13	0
3	11	1
4	10	0
4	7	1
5	6	0
5	8	1
6	4	0
6	20	1
7	3	0
7	20	1
8	0	0
8	15	1
9	0	0
9	13	1
10	0	0
10	4	1

Analysis: *roctab disease score*
[fweight= pop]

	ROC		-Asymptotic Normal--	
Obs	Area	Std. Err.	[95% Conf. Interval]	
176	0.7909	0.0329	0.72636	0.85539

A probability score for preoperative prediction of type 2 diabetes remission following RYGB surgery. Still CD, Wood GC, Benotti P, Petrick AT, Gabrielsen J, Strodel WE, et al. Lancet Diabetes Endocrinol. 2014 score (17)
From table S6 DiaRem score:

Table: pop = population achieving diabetes remission; disease: 0 = no diabetes remission, 1 = diabetes remission

scoring	class	pop	disease
0-2	5	3	0
0-2	5	20	1
3- 7	4	27	0
3- 7	4	48	1
8- 12	3	42	0
8- 12	3	12	1
13- 17	2	133	0
13- 17	2	17	1
18- 22	1	52	0
18- 22	1	1	1

roctab disease class [fweight=pop]

ROC		-Asymptotic Normal--	
Obs	Area	Std. Err.	[95% Conf. Interval]
355	0.8404	0.0231	0.79522 0.88560

Prognostic factors and a new preliminary scoring system for remission of type 2 diabetes mellitus after laparoscopic sleeve gastrectomy; Akira Umemura (39)

Table: pop = population achieving diabetes remission; disease: 0 = no diabetes remission, 1 = diabetes remission

score range	score	disease	pop
Poor	1	0	8
Poor	1	1	7
Moderate	2	0	3
Moderate	2	1	5
Good	3	0	0
Good	3	1	26

roctab disease score [fweight= pop], graph summary

ROC		-Asymptotic Normal--	
Obs	Area	Std. Err.	[95% Conf. Interval]
49	0.8648	0.0456	0.77538 0.95428

Validation studies Preoperative Prediction of Type 2 Diabetes Remission After Gastric Bypass Surgery:

A Comparison of DiaRem Scores and ABCD Scores. Lee et al (48)

Validation of ABCD score From

Table 4:

Table: pop1 = population achieving diabetes remission defined as hba1c of 6.0%, pop2 = population achieving diabetes remission defined as hba1c of 6.5%, disease: 0 = no diabetes remission, 1 = diabetes remission

score	pop1	pop2	disease
0	2	1	0
0	0	1	1
1	13	11	0
1	1	3	1
2	25	20	0
2	3	8	1
3	25	19	0
3	16	22	1
4	25	17	0
4	17	25	1
5	10	4	0
5	19	25	1
6	10	3	0
6	23	30	1
7	4	3	0
7	23	24	1
8	1	0	0
8	16	17	1
9	0	0	0
9	11	11	1
10	0	0	0
10	1	1	1

Complete remission roctab disease score [fweight= pop1]

	ROC	-Asymptotic Normal--	
Obs	Area	Std. Err.	[95% Conf. Interval]
245	0.8198	0.0258	0.76918 0.87048

Partial remission. roctab disease score [fweight= pop2]

	ROC	-Asymptotic Normal--	
Obs	Area	Std. Err.	[95% Conf. Interval]
245	0.8176	0.0274	0.76389 0.87123

Validating DiaRem score

Table: pop = population achieving diabetes remission defined as hbA1c of 6.5%; disease: 0 = no diabetes remission, 1 = diabetes remission

score	score	pop	disease
0-2	5	0	0
0-2	5	5	1
3-7	4	10	0
3-7	4	58	1
8-12	3	61	0
8-12	3	47	1
13-17	2	13	0
13-17	2	8	1
18-22	1	31	0
18-22	1	12	1

Complete and partial remission. roctab disease score [fweight= pop]

	ROC		-Asymptotic Normal--	
Obs	Area	Std. Err.	[95% Conf.	Interval]
245	0.7319	0.0296	0.67393	0.78995

Predictors of long-term diabetes remission after metabolic surgery; Lee MH et al (45)

From Table 6:

Table: pop1 = CR = population achieving diabetes remission defined as hba1c of 6.0%; pop2 = PR= population achieving diabetes remission defined as hba1c of 6.5%; disease: 0 = no diabetes remission, 1= diabetes remission

	CR	PR	
score	pop1	pop2	disease
1	4	3	0
1	0	1	1
2	1	1	0
2	0	0	1
3	7	5	0
3	1	3	1
4	9	6	0
4	4	7	1
5	10	5	0
5	5	10	1

6	3	2	0
6	11	12	1
7	12	3	0
7	16	25	1
8	6	2	0
8	18	22	1
9	5	3	0
9	25	27	1
10	3	3	0
10	17	17	1

Complete remission. roctab disease score [fweight= pop1]

	ROC		-Asymptotic Normal--	
Obs	Area	Std. Err.	[95% Conf. Interval]	
157	0.7631	0.0398	0.68507	0.84105

Partial remission disease score [fweight= pop2]

	ROC		-Asymptotic Normal--	
Obs	Area	Std. Err.	[95% Conf. Interval]	
157	0.7323	0.0572	0.62012	0.84445

The Effect and Predictive Score of Gastric Bypass and Sleeve Gastrectomy on Type 2 Diabetes Mellitus Patients with BMI <30 kg/m^2 (46)

From Table 6:

Table: pop1 = CR = population achieving diabetes remission defined as hba1c of 6.0%; pop2 = PR = population achieving diabetes remission defined as hba1c of 6.5%; disease: 0 = no diabetes remission, 1 = diabetes remission

	CR	PR	
Score	pop1	pop2	disease
0	3	2	0
0	0	1	1
1	12	9	0
1	0	3	1
2	19	14	0
2	2	7	1
3	12	8	0
3	5	9	1
4	9	6	0
4	4	7	1
5	3	2	0
5	5	6	1

6	2	0	0
6	3	5	1
7	0	0	0
7	1	1	1

Complete remission roctab disease score [fweight= pop1]

	ROC		-Asymptotic Normal--	
Obs	Area	Std. Err.	[95% Conf. Interval]	
80	0.8087	0.0509	0.70903	0.90847

Partial remission. roctab disease score [fweight= pop2]

	ROC		-Asymptotic Normal--	
Obs	Area	Std. Err.	[95% Conf. Interval]	
80	0.7164	0.0564	0.60575	0.82702

Metabolic Surgery for Diabetes Treatment: Sleeve Gastrectomy or Gastric Bypass World journal of surgery. 2017;41(1):216-23. Lee W-J, Chong K, Aung L, Chen S-C, Ser K-H, Lee Y-C (49)

From tables 6 and 7 of Lee et al (49):

Table: pop1 = population achieving diabetes remission in SG at 1 yr; pop2 = population achieving diabetes remission in gastric bypass at 1 year; pop3 = population achieving diabetes remission in SG at 5 years; pop4 = population achieving diabetes remission in gastric bypass at 5 years; disease: 0 = no diabetes remission, 1 = diabetes remission

			SG 1yr	GB 1yr	SG 5 yr	GB 5 yr
score range	score	disease	pop1	pop2	pop3	pop4
2-0	1	0	5	57	3	15
2-0	1	1	0	9	0	3
4-3	2	0	12	70	9	22
4-3	2	1	4	61	0	6
6-5	3	0	16	27	10	5
6-5	3	1	16	84	0	17
8-7	4	0	13	5	0	4
8-7	4	1	26	79	9	22
10-9	5	0	2	1	0	0
10 -9	5	1	15	67	3	15
			109	460	34	109

SG at 1 year, roctab disease score [fweight= pop1]

	ROC		-Asymptotic Normal--	
Obs	Area	Std. Err.	[95% Conf. Interval]	
109	0.7432	0.0450	0.65501	0.83133

RYGB at 1 year, roctab disease score [fweight= pop2]

	ROC		-Asymptotic Normal--	
Obs	Area	Std. Err.	[95% Conf. Interval]	
460	0.8483	0.0171	0.81484	0.88185

SG at 5 year, roctab disease score [fweight= pop3]

ROC		-Asymptotic Normal--		
Obs	Area	Std. Err.	[95% Conf. Interval]	
34	1.0000	0.0000	1.00000	1.00000

RYGB at 5 year roctab disease score [fweight= pop4]

	ROC		-Asymptotic Normal--	
Obs	Area	Std. Err.	[95% Conf. Interval]	
109	0.8654	0.0344	0.79796	0.93289

Do Bariatric Surgery-Related Type 2 Diabetes Remission Predictors Add Clinical Value? A Study on Asian Indian Obese Diabetics; Raj et al (53)

From table 6:

Table: pop1= total = population achieving diabetes remission irrespective of type of surgery; pop2 = PR = population achieving diabetes remission in SG; pop3 = PR = population achieving diabetes remission in RYGB; disease: 0 = no diabetes remission, 1 = diabetes remission

			total	SG	RYGB
score range	score	disease	pop1	pop2	pop3
1-5	1	0	5	3	2
1-5	1	1	15	6	9
6-7	2	0	5	4	1
6-7	2	1	22	18	4
>7	3	0	0	0	0
>7	3	1	6	4	2
			53	35	18

Total roctab disease score [fweight= pop1]

	ROC		-Asymptotic Normal--	
Obs	Area	Std. Err.	[95% Conf. Interval]	
53	0.6105	0.0834	0.44693	0.77400

SG roctab disease score [fweight= pop2]

	ROC		-Asymptotic Normal--	
Obs	Area	Std. Err.	[95% Conf. Interval]	
35	0.6480	0.0987	0.45443	0.84149

RYGB roctab disease score [fweight= pop3]

	ROC		-Asymptotic Normal--	
Obs	Area	Std. Err.	[95% Conf. Interval]	
18	0.5556	0.1623	0.23751	0.87360

The Effects of Laparoscopic Sleeve Gastrectomy with Duodenojejunal Bypass on Japanese Patients with BMI < 35 kg/m2 on Type 2 Diabetes Mellitus and the Prediction of Successful Glycemic Contro; Seki et al (54)

From table 6:

Table: pop1 = CR = population achieving diabetes remission defined as hba1c of 6.0%; pop2 = PR = population achieving diabetes remission defined as hba1c of 6.5%; disease: 0 = no diabetes remission, 1 = diabetes remission

	CR	PR	
score	pop1	pop2	disease
1	6	5	0
1	0	1	1
2	16	13	0
2	0	3	1
3	15	9	0
3	6	12	1
4	4	3	0
4	5	6	1
5	3	2	0
5	6	7	1
6	1	1	0
6	1	1	1
7	0	0	0
7	2	2	1
	65	65	

Complete remission, roctab disease score [fweight= pop1]

	ROC		-Asymptotic Normal--	
Obs	Area	Std. Err.	[95% Conf. Interval]	
65	0.8461	0.0451	0.75767	0.93455

Partial remission roctab disease score [fweight= pop2]

	ROC	-Asymptotic Normal--		
Obs	Area	Std. Err.	[95% Conf. Interval]	
65	0.7514	0.0592	0.63544	0.86740

Predicting remission of diabetes post metabolic surgery: a comparison of ABCD, diarem, and DRS scores; Ahuja et al (57)

From table 3:

Score range1 = ABCD score, score range 2 = DiaRem score, score range 3 = DRS score pop1 = CR = population achieving diabetes remission in ABCD scoring; pop2 = PR = population achieving diabetes remission defined as hba1c of 6.5%; disease: 0 = no diabetes remission, 1 = diabetes remission

ABCD				DiaRem			DRS			
score range 1	score 1	pop 1	disease	score range 2	score 2	pop 2	score range3	score 3	pop3	disease 3
2-0	1	7	0	18-22	1	10	severe	1	0	0
2-0	1	3	1	18-22	1	3	severe	1	0	1
4-3	2	10	0	13-17	2	10	Moderate	2	17	0
4-3	2	4	1	13-17	2	3	Moderate	2	9	1
6-5	3	9	0	8-12	3	3	Mild	3	12	0
6-5	3	29	1	8-12	3	10	Mild	3	64	1
8-7	4	4	0	3-7	4	7				
8-7	4	32	1	3-7	4	40				
10-9	5	0	0	0-2	5	0				
10-9	5	4	1	0-2	5	16				

ABCD roctab disease score1 [fweight= pop1]

	ROC	-Asymptotic Normal--		
Obs	Area	Std. Err.	[95% Conf. Interval]	
102	0.7861	0.0488	0.69048	0.88174

DiaRem roctab disease score2 [fweight= pop2]

	ROC	-Asymptotic Normal--		
Obs	Area	Std. Err.	[95% Conf. Interval]	
102	0.8403	0.0415	0.75898	0.92158

DRS roctab disease3 score3 [fweight= pop3]

	ROC	-Asymptotic Normal--		
Obs	Area	Std. Err.	[95% Conf. Interval]	
102	0.7315	0.0504	0.63266	0.83026

Laparoscopic gastric bypass for the treatment of type 2 diabetes: a comparison of Roux-en-Y versus single anastomosis gastric bypass. 2018;14(4); Almalki et al (58)
From table 7:

In RYGB

Table: pop = population achieving diabetes remission; disease: 0 = no diabetes remission, 1 = diabetes remission

RYGB				In RYGB with single anastomosis		
score range	score	pop	disease	score range	score	pop
2-0	1	28	0	2-0	1	14
2-0	1	3	1	2-0	1	5
4-3	2	28	0	4-3	2	17
4-3	2	18	1	4-3	2	30
6-5	3	10	0	6-5	3	11
6-5	3	28	1	6-5	3	46
8-7	4	4	0	8-7	4	3
8-7	4	26	1	8-7	4	70
10-9	5	0	0	10-9	5	0
10-9	5	12	1	10-9	5	53

roctab disease score [fweight= pop]

	ROC		-Asymptotic Normal--	
Obs	Area	Std. Err.	[95% Conf. Interval]	
157	0.8397	0.0301	0.78084	0.89864

In RYGB with single anastomosis, roctab disease score [fweight= pop]

	ROC		-Asymptotic Normal--	
Obs	Area	Std. Err.	[95% Conf. Interval]	
249	0.8517	0.0269	0.79903	0.90446

References

1. Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Leccesi L, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. The New England journal of medicine. 2012;366(17):1577-85.
2. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Aminian A, Brethauer SA, et al. Bariatric Surgery versus Intensive Medical Therapy for Diabetes - 5-Year Outcomes. N Engl J Med. 2017;376(7):641-51.
3. P M, V C, P S, CW lR, AA T, R S. Changes in glycaemic control, blood pressure and lipids 5 years following laparoscopic adjustable gastric banding combined with medical care in patients with type 2 diabetes: a longitudinal analysis. Clinical obesity. 2018;8(3).
4. Avenell A, Robertson C, Skea Z, Jacobsen E, Boyers D, Cooper D, et al. Bariatric surgery, lifestyle interventions and orlistat for severe obesity: the REBALANCE mixed-methods systematic review and economic evaluation. 2018.
5. SinghP, SubramaniaA, AdderleyN, GokhaleK, SinghalR, BellaryS, et al. Impact of Bariatric Surgery on Cardiovascular Outcomes and Mortality: A Population-Based Cohort Study. The British journal of surgery. 2020;107(4):432- 42.
6. Singh P, Adderley N, Subramanian A, Gokhale K, Singhal R, Toulis KA, et al. The Impact of Bariatric Surgery on Incident Microvascular Complications in Patients With Type 2 Diabetes: A Matched Controlled Population-Based Retrospective Cohort Study. Diabetes Care 2021. 2021;44 (1):116-24.
7. Brethauer SA, Aminian A, Romero-Talamas H, Batayyah E, Mackey J, Kennedy L, et al. Can diabetes be surgically cured? Long-term metabolic effects of bariatric surgery in obese patients with type 2 diabetes mellitus. Annals of surgery. 2013;258(4):628-36; discussion 36.
8. Schauer PR, Mingrone G, Ikramuddin S, Wolfe B. Clinical Outcomes of Metabolic Surgery: Efficacy of Glycemic Control, Weight Loss, and Remission of Diabetes. Diabetes Care. 2016;39(6):902-11.
9. Mingrone G, Guidone C, Iaconelli A, Nanni G, Castagneto M, Panunzi S, et al. Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 Year follow-up of an open-label, single-centre, randomised controlled trial. The Lancet. 2015;386(9997):964-73.
10. F R, DM N, RH E, PR S, KG A, PZ Z, et al. Metabolic Surgery in the Treatment Algorithm for Type 2 Diabetes: A Joint Statement by International Diabetes Organizations. Diabetes care. 2016;39(6).
11. Mahmood F, Munasinghe A, MacAno C, Sharples A, Etumnu N, Katreddy V, et al. Factors predicting remission or improvement of type 2 diabetes after gastric bypass. 33rd American Society for Metabolic Surgery Annual Meeting, ASMBS 2016 United States. 2016;12(7 Supplement 1):S165-S6.
12. Panunzi S, Carlsson L, De Gaetano A, Peltonen M, Rice T, Sjostrom L, et al. Determinants of Diabetes Remission and Glycemic Control After Bariatric Surgery. Diabetes care. 2016;39(1):166-74LID.
13. Dixon JB, Chuang LM, Chong K, Chen SC, Lambert GW, Straznicky NE, et al. Predicting the glycemic response to gastric bypass surgery in patients with type 2 diabetes. Diabetes care. 2013;36(1):20-6LID.
14. Blackstone R, Bunt JC, Cortes MC, Sugerman HJ. Type 2 diabetes after gastric bypass: remission in five models using HbA1c, fasting blood glucose, and medication status. Surgery for obesity and related diseases: official journal of the American Society for Bariatric Surgery. 2012;8(5):548-55LID.

15. Park JY. Prediction of Diabetes Remission after Bariatric or Metabolic Surgery. 2018.
16. Lee W-J, Hur Kyung Y, Lakadawala M, Kasama K, Wong Simon KH, Chen S-C, et al. Predicting success of metabolic surgery: age, body mass index, C-peptide, and duration score. Surgery for obesity and related diseases: official journal of the American Society for Bariatric Surgery. 2013;9(3):379-84.
17. Still CD, Wood GC, Benotti P, Petrick AT, Gabrielsen J, Strodel WE, et al. A probability score for preoperative prediction of type 2 diabetes remission following RYGB surgery. Lancet Diabetes Endocrinol. 2014;2(1):38-45.
18. Aminian A, Brethauer SA, Andalib A, Nowacki AS, Jimenez A, Corcelles R, et al. Individualized Metabolic Surgery Score: Procedure Selection Based on Diabetes Severity. Annals of surgery. 2017;266(4):650-7LID.
19. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and metaanalyses: the PRISMA statement. 2009.
20. Geersing GJ, Bouwmeester W, Zuithoff P, Spijker R, Leeflang M, Moons KG. Search filters for finding prognostic and diagnostic prediction studies in Medline to enhance systematic reviews. PLoS One. 2012;7(2):e32844.
21. EPPI-Reviewer 4: systematic review software 2017 [Available from: http://eppi.ioe.ac.uk/cms/Default.aspx?alias=eppi.ioe.ac.uk/cms/er4.
22. DistillerSR. DistillerSR 2020 [Available from: https://www.evidencepartners.com/products/distillersrsystematic-review-software/.
23. Karel G. M. Moons JAHdG, Walter Bouwmeester, Yvonne Vergouwe,. Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies: The CHARMS Checklist. 2014 October.
24. Wolff RF, Kleijnen Systematic Reviews Y, United Kingdom (R.F.W., M.W.), Moons KGM, Julius Center for Health Sciences and Primary Care and Cochrane Netherlands UMCU, Utrecht University, Utrecht, the Netherlands (K.G.M., J.B.R.), Riley RD, Centre for Prognosis Research RIfPCaHS, Keele University, Keele, United Kingdom (R.D.R.), et al. PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies. Annals of Internal Medicine. 2019;170(1):51-8.
25. Moons KG, Altman DG, Vergouwe Y, Royston P. Prognosis and prognostic research: application and impact of prognostic models in clinical practice. BMJ (Clinical research ed). 2009;338:b606.
26. Moons KG, Kengne AP, Woodward M, Royston P, Vergouwe Y, Altman DG, et al. Risk prediction models: I. Development, internal validation, and assessing the incremental value of a new (bio)marker. Heart. 2012;98(9):68390.
27. Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Gonen M, Obuchowski N, et al. Assessing the performance of prediction models: a framework for some traditional and novel measures. Epidemiology. 2010;21(1):128-38. 28. Mandrekar JN. Receiver operating characteristic curve in diagnostic test assessment. J Thorac Oncol. 2010;5(9):1315-6.
29. Zhang R, Borisenko O, Telegina I, Hargreaves J, Ahmed AR, Sanchez Santos R, et al. Systematic review of risk prediction models for diabetes after bariatric surgery. The British journal of surgery. 2016;103(11):1420-7.
30. Hanson RK. Assessing the Calibration of Actuarial Risk Scales: A Primer on the E/O Index. http://dxdoiorg/101177/0093854816683956. 2016.
31. Robert M, Ferrand-Gaillard C, Disse E, Espalieu P, Simon C, Laville M, et al. Predictive factors of type 2 diabetes remission 1 year after bariatric surgery: impact of surgical techniques. Obes Surg. 2013;23(6):770-5.

32. Still Christopher D, Wood GC, Benotti P, Petrick Anthony T, Gabrielsen J, Strodel William E, et al. Preoperative prediction of type 2 diabetes remission after Roux-en-Y gastric bypass surgery: a retrospective cohort study. The lancet Diabetes & endocrinology. 2014;2(1):38-45.
33. Ugale S, Gupta N, Modi KD, Kota SK, Satwalekar V, Naik V, et al. Prediction of remission after metabolic surgery using a novel scoring system in type 2 diabetes – a retrospective cohort study. Journal of Diabetes & Metabolic Disorders. 2014;13(1):89.
34. Aron-Wisnewsky J, Sokolovska N, Liu Y, Comaneshter DS, Vinker S, Pecht T, et al. The advanced-DiaRem score improves prediction of diabetes remission 1 year post-Roux-en-Y gastric bypass. Diabetologia. 2017;60(10):1892-902.
35. Pucci A, Tymoszuk U, Cheung WH, Makaronidis JM, Scholes S, Tharakan G, et al. Type 2 diabetes remission 2 years post Roux-en-Y gastric bypass and sleeve gastrectomy: The role of the weight loss and comparison of DiaRem and DiaBetter scores. Diabetic Medicine. 2017.
36. CD S, P B, T M, A C, GC W. DiaRem2: Incorporating Duration of Diabetes to Improve Prediction of Diabetes Remission After Metabolic Surgery. Surgery for obesity and related diseases: official journal of the American Society for Bariatric Surgery. 2019;15(5).
37. Debedat J, Sokolovska N, Coupaye M, Panunzi S, Chakaroun R, Genser L, et al. Long-term Relapse of Type 2 Diabetes After Roux-en-Y Gastric Bypass: Prediction and Clinical Relevance. Diabetes Care. 2018;41(10):2086-95.
38. Moh Mei C, Cheng A, Tan Chun H, Lim Boon K, Tan Bo C, Ng D, et al. Metabolic Surgery Diabetes Remission (MDR) Score: a New Preoperative Scoring System for Predicting Type 2 Diabetes Remission at 1 Year After Metabolic Surgery in the Singapore Multi-ethnic Asian Setting. Obesity surgery. 2020;30(9):3387-93.
39. Umemura A, Sasaki A, Nitta H, Nikai H, Baba S, Takahara T, et al. Prognostic factors and a new preliminary scoring system for remission of type 2 diabetes mellitus after laparoscopic sleeve gastrectomy. Surgery Today. 2020.
40. Hayes MT, Hunt LA, Foo J, Tychinskaya Y, Stubbs RS. A model for predicting the resolution of type 2 diabetes in severely obese subjects following Roux-en Y gastric bypass surgery. Obes Surg. 2011;21(7):910-6.
41. Ramos-Levi AM, Matia P, Cabrerizo L, Barabash A, Sanchez-Pernaute A, Calle-Pascual AL, et al. Statistical models to predict type 2 diabetes remission after bariatric surgery. Journal of diabetes. 2014;6(5):472-7LID.
42. Cotillard A, Poitou C, Duchateau-Nguyen G, Aron-Wisnewsky J, Bouillot JL, Schindler T, et al. Type 2 Diabetes Remission After Gastric Bypass: What Is the Best Prediction Tool for Clinicians? Obesity surgery. 2015;25(7):112832LID.
43. Stallard R, Sahai V, Drover JW, Chun S, Keresztes C. Defining and Using Preoperative Predictors of Diabetic Remission Following Bariatric Surgery. JPEN J Parenter Enteral Nutr. 2016;42(3):573-80.
44. Lee W-J, Almulaifi A, Tsou JJ, Ser K-H, Lee Y-C, Chen S-C. Laparoscopic sleeve gastrectomy for type 2 diabetes mellitus: predicting the success by ABCD score. Surgery for obesity and related diseases: official journal of the American Society for Bariatric Surgery. 2015;11(5):991-6.
45. Lee MH, Lee W-J, Chong K, Chen J-C, Ser K-H, Lee Y-C, et al. Predictors of long-term diabetes remission after metabolic surgery. Journal of gastrointestinal surgery: official journal of the Society for Surgery of the Alimentary Tract. 2015;19(6):1015-21.
46. Lee W-J, Almulaifi A, Chong K, Chen S-C, Tsou JJ, Ser K-H, et al. The Effect and Predictive Score of Gastric Bypass and Sleeve Gastrectomy on Type 2 Diabetes Mellitus Patients with BMI<30 kg/m(2). Obesity surgery. 2015;25(10):1772-8.

47. Sampaio-Neto J, Nassif LS, Branco-Filho AJ, Bolfarini LA, Loro LS, de SM, et al. EXTERNAL VALIDATION OF THE DIAREM SCORE AS REMISSION PREDICTOR OF DIABETES MELLITUS TYPE 2 IN OBESE PATIENTS UNDERGOING ROUXEN-Y GASTRIC BYPASS. Arq Bras Cir Dig. 2015;28(Suppl 1):19-22.
48. Lee W-J, Chong K, Chen S-C, Zachariah J, Ser K-H, Lee Y-C, et al. Preoperative Prediction of Type 2 Diabetes Remission After Gastric Bypass Surgery: a Comparison of DiaRem Scores and ABCD Scores. Obesity surgery. 2016;26(10):2418-24.
49. Lee W-J, Chong K, Aung L, Chen S-C, Ser K-H, Lee Y-C. Metabolic Surgery for Diabetes Treatment: Sleeve Gastrectomy or Gastric Bypass? World journal of surgery. 2017;41(1):216-23.
50. Mehaffey JH, Mullen MG, Mehaffey RL, Turrentine FE, Malin SK, Kirby JL, et al. Type 2 diabetes remission following gastric bypass: does diarem stand the test of time? Surgical endoscopy. 2017;31(2):538-42LID.
51. Honarmand K, Chetty K, Vanniyasingam T, Anvari M, Chetty VT. Type 2 diabetes remission rates 1-year postRoux-en-Y gastric bypass and validation of the DiaRem score: the Ontario Bariatric Network experience. Clinical obesity. 2017;7(3):176-82LID.
52. Tharakan G, Scott R, Szepietowski O, Miras AD, Blakemore AI, Purkayastha S, et al. Limitations of the DiaRem Score in Predicting Remission of Diabetes Following Roux-En-Y Gastric Bypass (RYGB) in an ethnically Diverse Population from a Single Institution in the UK. Obesity surgery. 2017;27(3):782-6LID.
53. Praveen Raj P, Bhattacharya S, Saravana Kumar S, Sabnis SC, Parthasarathi R, Swamy PDK, et al. Do Bariatric Surgery-Related Type 2 Diabetes Remission Predictors Add Clinical Value? A Study on Asian Indian Obese Diabetics. Obesity surgery. 2017;27(8):2113-9LID.
54. Seki Y, Kasama K, Yasuda K, Yokoyama R, Porciuncula JP, Kurokawa Y. The Effects of Laparoscopic Sleeve Gastrectomy with Duodenojejunal Bypass on Japanese Patients with BMI < 35 kg/m2 on Type 2 Diabetes Mellitus and the Prediction of Successful Glycemic Control. Obesity surgery. 2018;28(8):2429-38.
55. Shen SC, Wang W, Tam KW, Chen HA, Lin YK, Wang SY, et al. Validating Risk Prediction Models of Diabetes Remission After Sleeve Gastrectomy. Obes Surg. 2018.
56. Naitoh T, Kasama K, Seki Y, Ohta M, Oshiro T, Sasaki A, et al. Efficacy of Sleeve Gastrectomy with DuodenalJejunal Bypass for the Treatment of Obese Severe Diabetes Patients in Japan: a Retrospective Multicenter Study. Obesity Surgery. 2018;28(2):497-505.
57. Ahuja A, Tantia O, Chaudhuri T, Khanna S, Seetharamaiah S, Majumdar K, et al. Predicting remission of diabetes post metabolic surgery: a comparison of ABCD, diarem, and DRS scores. Obesity Surgery. 2018:1-7.
58. Almalki OM, Lee W-J, Chong K, Ser K-H, Lee Y-C, Chen S-C. Laparoscopic gastric bypass for the treatment of type 2 diabetes: a comparison of Roux-en-Y versus single anastomosis gastric bypass. Surgery for obesity and related diseases: official journal of the American Society for Bariatric Surgery. 2018;14(4):509-15.
59. Chen J-C, Hsu N-Y, Lee W-J, Chen S-C, Ser K-H, Lee Y-C. Prediction of type 2 diabetes remission after metabolic surgery: a comparison of the individualized metabolic surgery score and the ABCD score. Surgery for obesity and related diseases: official journal of the American Society for Bariatric Surgery. 2018;14(5):640-5.
60. Craig Wood G, Horwitz D, Still CD, Mirshahi T, Benotti P, Parikh M, et al. Performance of the DiaRem Score for Predicting Diabetes Remission in Two Health Systems Following Bariatric Surgery Procedures in Hispanic and nonHispanic White Patients. Obesity Surgery. 2018;28(1):61-8.

61. Dicker D, Golan R, Aron-Wisnewsky J, Zucker JD, Sokolowska N, Comaneshter DS, et al. Prediction of LongTerm Diabetes Remission After RYGB, Sleeve Gastrectomy, and Adjustable Gastric Banding Using DiaRem and Advanced-DiaRem Scores. Obes Surg. 2019;29(3):796-804.
62. Kam H, Tu Y, Pan J, Han J, Zhang P, Bao Y, et al. Comparison of Four Risk Prediction Models for Diabetes Remission after Roux-en-Y Gastric Bypass Surgery in Obese Chinese Patients with Type 2 Diabetes Mellitus. Obesity surgery. 2020;30(6):2147-57.
63. Park DG CY, Kim SH, Kim YJ. Diabetes Remission Rate after Sleeve Gastrectomy or Roux-en-Y Gastric Bypass; Utilizing Individualized Metabolic Surgery Score for Korean Patients. J Metab Bariatr Surg. 2020;9:13-8.
64. Lee MH, Almalki OM, Lee WJ, Chen SC, Chen JC, Wu CC. Laparoscopic Sleeve Gastrectomy for Type 2 Diabetes Mellitus: Long-Term Result and Recurrence of Diabetes. Obesity Surgery. 2020.
65. Guerron AD, Perez JE, Risoli T, Lee HJ, Portenier D, Corsino L. Performance and improvement of the DiaRem score in diabetes remission prediction: a study with diverse procedure types. Surgery for Obesity and Related Diseases. 2020.
66. Mehaffey JH, Mullen MG, Mehaffey RL, Turrentine FE, Malin SK, Schirmer B, et al. Diabetes remission following gastric bypass: Does diarem stand the test of time? 2016 Scientific Session of the Society of American Gastrointestinal and Endoscopic Surgeons, SAGES 2016 Boston, MA United States. 2016;30(SUPPL. 1):S461.
67. S F, P R, K C, A D, E R, A F. Top ten research priorities for type 2 diabetes: results from the Diabetes UK-James Lind Alliance Priority Setting Partnership. The lancet Diabetes & endocrinology. 2017;5(12).
68. A J, I N, J O, E S, E N, E S. Duration of type 2 diabetes and remission rates after bariatric surgery in Sweden 2007-2015: A registry-based cohort study. PLoS medicine. 2019;16(11).
69. Sjostrom L, Peltonen M, Jacobson P, Ahlin S, Andersson-Assarsson J, Anveden A, et al. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. JAMA. 2014;311(22):2297-304LID.
70. Arterburn DE, Bogart A, Sherwood NE, Sidney S, Coleman KJ, Haneuse S, et al. A multisite study of long-term remission and relapse of type 2 diabetes mellitus following gastric bypass. Obesity surgery. 2013;23(1):93-102LID. 71. Dogan K, Gadiot RP, Aarts EO, Betzel B, van Laarhoven CJ, Biter LU, et al. Effectiveness and Safety of Sleeve Gastrectomy, Gastric Bypass, and Adjustable Gastric Banding in Morbidly Obese Patients: a Multicenter, Retrospective, Matched Cohort Study. Obes Surg. 2015;25(7):1110-8.
72. L D, Y F, H L, Y Z, D Q, S T, et al. Comparative Effectiveness of Bariatric Surgeries in Patients With Obesity and Type 2 Diabetes Mellitus: A Network Meta-Analysis of Randomized Controlled Trials. Obesity reviews: an official journal of the International Association for the Study of Obesity. 2020.
73. Leighton E, Sainsbury CA, Jones GC. A Practical Review of C-Peptide Testing in Diabetes. Diabetes Ther. 82017. p. 475-87.
74. M P, RR R, T L, SE S, FJ S, DR M, et al. Resistance to Insulin Therapy Among Patients and Providers: Results of the Cross-National Diabetes Attitudes, Wishes, and Needs (DAWN) Study. Diabetes care. 2005;28(11).