Obesity and Weight-Loss Treatment: Long-Term Outcomes and Predictors of Treatment Response

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Gothenburg 2026

Cover illustration: Pathways by Ala Jelil

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ISBN 978-91-8115-703-1 (PRINT)
ISBN 978-91-8115-704-8 (PDF)

Printed in Borås, Sweden 2026
Printed by Stema Specialtryck AB

To my family

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ABSTRACT

Background and aim

Metabolic bariatric surgery, including Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) is an effective treatment for sustained weight loss in individuals with obesity. However, the benefits and risks of surgical treatment vary significantly between individuals and evidence of long-term effectiveness remains limited, particularly among individuals with obesity and type 2 diabetes. This thesis examines underlying risk profiles and long-term clinical outcomes in individuals undergoing metabolic bariatric surgery, with a focus on those with type 2 diabetes.

Methods

This thesis comprises four observational studies using real-world data on individuals with obesity. *Study I* assessed health-related quality of life (HRQoL) and disease burden in individuals accepted for weight-loss treatment and compared them with those of the general population. *Study II* assessed vitamin D deficiency before and two years after RYGB and SG, compared with individuals on a very low-energy diet (VLED) and the general population. Study III compares long-term outcomes of RYGB and SG in individuals with type 2 diabetes with matched unexposed individuals. *Study IV* used machine learning to explore predictors of a multidimensional clinical benefit five years after RYGB and SG in individuals with type 2 diabetes.

Results

Study I: Individuals with obesity (n=1120) seeking weight-loss treatment reported worse general, physical and mental HRQoL than individuals from the general population (n=414). They also experienced a higher burden of disease. *Study II:* Two years after treatment, vitamin D levels improved with a low prevalence of vitamin D deficiency (<3%). Vitamin D levels were similar between RYGB (n=297) and SG (n=160) but higher than those in VLED (n=256). Compared to the general population, individuals with obesity had lower vitamin D levels. *Study III:* RYGB (n=7294) was associated with sustained reductions in all-cause mortality and obesity-related comorbidities in individuals with type 2 diabetes, but the risk of malabsorption and micronutrient deficiency, alcohol use disorder and gastrointestinal complications was markedly increased. In contrast, SG (n=1105) showed no significant effects on mortality or comorbidities compared with unexposed individuals, but had a higher risk of malabsorption and micronutrient deficiency. *Study IV:* Across machine learning models, the most consistent predictors of long-term clinical outcome after RYGB and SG reflected psychiatric and somatic disease burden, metabolic and renal function, and sociodemographic characteristics. However, overall discrimination was modest, underscoring the limited predictive capability of registry-based preoperative data.

Conclusion

Individuals seeking weight-loss treatment are more likely to have impaired HRQoL, higher disease burden and poorer vitamin D status than the general population, which should be taken into account when planning treatment. Vitamin D status improves with weight-loss treatment and adequate supplementation, but the risk of micronutrient deficiency persists over time after metabolic bariatric surgery, highlighting the need for lifelong monitoring. In individuals with type 2 diabetes, RYGB, rather than SG, remains an effective treatment option for achieving mortality and cardiometabolic benefits. However, following RYGB, individuals experience worse psychiatric health, nutrient status, and gastrointestinal complications. A more complex psychosomatic and metabolic profile before surgery constitutes a high-risk group for long-term harm.

Keywords: obesity, type 2 diabetes mellitus, weight-loss, long-term, metabolic bariatric surgery, Roux-en-Y gastric bypass, sleeve gastrectomy, HRQoL, nutritional deficiency, mortality, cardiovascular disease, psychiatric disorders

ISBN 978-91-629-703-1 (PRINT)
ISBN 978-91-629-704-8 (PDF)

SAMMANFATTNING PÅ SVENSKA

Bakgrund och syfte

Metabol bariatrisk kirurgi (kirurgi mot obesitas), där Roux-en-Y gastric bypass (RYGB) och sleeve gastrektomi (SG) är de vanligaste metoderna, är en allmänt erkänd och effektiv behandling för att uppnå betydande och varaktig viktnedgång. Samtidigt är utfallet efter kirurgi inte enhetligt, där vissa har en mer begränsad effekt eller drabbas av komplikationer, näringsbrist och psykisk ohälsa. Kunskapen om långsiktiga effekter och risker är fortfarande begränsad, särskilt hos personer med typ 2-diabetes mellitus. Det övergripande syftet med denna avhandling är att fördjupa kunskapen om individer som söker viktreducerande behandling samt att utvärdera den kliniska nyttan med RYGB och SG på lång sikt.

Metoder

Delarbete I och II baseras på data från en pågående prospektiv behandlingsstudie i Region Västra Götaland. Delarbete III och IV baseras på nationella registerdata från det Nationella Diabetesregistret och det skandinaviska kvalitetsregistret för obesitaskirurgi.

Delarbete I undersökte hälsorelaterad livskvalitet och sjukdomsbörda hos personer med obesitas som accepteras för viktreducerande behandling och jämförde dessa med en referensgrupp från den allmäna befolkningen.

Delarbete II analyserade D-vitaminbrist och -insufficiens före och två år efter RYGB och SG. Resultaten jämfördes med en livsstilsintervention baserad på mycket lågkaloridiet (VLED) och med en referensgrupp från den allmäna befolkningen.

Delarbete III analyserade långtidseffekter upp till 14 år efter RYGB och SG hos personer med obesitas och typ 2-diabetes mellitus, i jämförelse med individer med obesitas och typ 2-diabetes mellitus som inte genomgått obesitaskirurgi.

Delarbete IV använde avancerade maskininlärningsmetoder för att undersöka möjligheten att identifiera preoperativa prediktorer för optimal viktnedgång och avsaknad av kliniskt betydelsefulla komplikationer fem år efter RYGB och SG hos personer med obesitas och typ 2-diabetes mellitus.

Resultat

Delarbete I: Generell, fysisk och psykisk hälsorelaterad livskvalitet var sämre hos personer med obesitas som sökte viktreducerande behandling jämfört med referensgruppen. De hade även högre sjukdomsbörda.

Delarbete II: Hos personer med obesitas ökade D-vitaminnivåerna efter samtliga interventioner vid två års uppföljning och förekomsten av D-vitaminbrist var generellt låg. Däremot var D-vitamininsufficiens högre efter VLED än efter RYGB och SG. Ingen skillnad sågs mellan RYGB och SG. Vid baslinjen var D-vitaminbrist och -insufficiens vanligare hos personer med obesitas.

Delarbete III: Trots likartad viktnedgång efter RYGB och SG var endast RYGB associerad med en långvarig minskning av totalmortalitet och obesitasrelaterade samsjukligheter jämfört med icke-kirurgiskt behandlade individer. Båda ingreppen var samtidigt förenade med en kvarstående ökad risk för malabsorption och mikronutrientbrister. RYGB var dessutom associerat med en nästan trefaldig ökad risk för alkoholberoende och för andra mag-tarmrelaterade komplikationer.

Delarbete IV: Preoperativa prediktorer för optimal viktnedgång och frånvaro av kliniskt betydelsefulla komplikationer på lång sikt speglade psykiatrisk och somatisk sjukdomsbörda, metabol funktion samt sociodemografiska faktorer. Den övergripande diskriminativa förmågan var dock måttlig, vilket understryker begränsningarna i att förutsäka långsiktiga effekter med enbart preoperativa registerdata.

Betydelse

Personer med obesitas har oftare högre sjuklighet, sämre hälsorelaterad livskvalitet och lägre D-vitaminnivåer, vilket bör beaktas vid val av behandling och uppföljning. Även om D-vitaminnivåer förbättras vid viktnedgång och genom vitamintillskott är det viktigt med långtidsmonitorering eftersom riskerna för brist kvarstår. För personer med typ 2-diabetes mellitus är RYGB på lång sikt kopplad till tydliga förbättringar i mortalitet och kardiometabola tillstånd, medan dessa fördelar inte kan visas för SG. Däremot är RYGB förknippad med ökad psykiatrisk sjukdomsbörda, alkoholberoende, näringsbrist och mag-tarmrelaterade komplikationer. Personer med typ 2-diabetes med en mer uttalad psykosomatisk och metabol belastning före operation kan vara särskilt sårbara för ogynnsamma långtidseffekter. Dessa fynd understryker tillsammans behovet av individanpassade behandlingar och ett strukturerat, livslångt uppföljningsstöd från flera professioner.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. **Mejaddam A,** Krantz E, Höskuldsdóttir G, Fändriks L, Mossberg K, Eliasson B, Trimpou P, Landin-Wilhelmsen K. Comorbidity and quality of life in obesity - a comparative study with the general population in Gothenburg, Sweden. PLoS One. 2022 Oct 4;17(10):e0273553.

II. **Mejaddam A,** Höskuldsdóttir G, Lenér F, Wallenius V, Trimpou P, Fändriks L, Mossberg K, Eliasson B, Landin-Wilhelmsen K. Effects of medical and surgical treatment on vitamin D levels in obesity. PLoS One. 2023 Dec 22;18(12):e0292780.

III. **Mejaddam A,** Carlsen HK, Larsson I, Eeg-Olofsson K, Lugner M, Ottosson J, Stenberg E, Höskuldsdóttir G, Eliasson B. Long-term effects of gastric bypass and sleeve gastrectomy in type 2 diabetes: a matched retrospective cohort study from Sweden. Lancet Reg Health Eur. 2025 Aug 30;58:101430.

IV. **Mejaddam A,** Lugner M, Carlsen HK, Rawshani A, Larsson I, Ottosson J, Stenberg E, Eeg-Olofsson K, Höskuldsdóttir G, Landin-Wilhelmsen K, Eliasson B. Exploring predictors for long-term clinical benefit after gastric bypass and sleeve gastrectomy in type 2 diabetes: A Machine Learning Approach. (*Under revision, Metabologia*)

CONTENTS

ABBREVIATIONS

aHR	Adjusted hazard ratio
ATC	Anatomical therapeutic chemical classification
ANOVA	Analysis of variance
BMI	Body mass index
BASUN	BAriatric surgery SUbstitution and Nutrition study
CI	Confidence interval
EQ-5D	EuroQol research foundation 5-dimension questionnaire
GLP-1	Glucagon-like peptide-1
GIP	Glucose-dependent insulinotropic polypeptide
HR	Hazard ratio
HRQoL	Health-related quality of life
IWQOL	Impact of weight on quality of life
ICD-10	International classification of diseases, tenth revision
IU	International units
L1	Least absolute deviations regularisation
L2	Least squares regularisation
LASSO	Least absolute shrinkage and selection operator
LDL	Low-density lipoprotein
LightGBM	Light gradient boosting model
LISA	Longitudinal integrated database for health insurance and labour market studies
ML	Machine learning
MONICA	Multinational monitoring of trends and determinants in cardiovascular disease study

NDR	National diabetes register
NPR	National patient register
PTH	Parathyroid hormone
PR-AUC	Precision recall area under the curve
RCT	Randomised controlled trial
RFC	Random forest classifier
ROC-AUC	Area under the receiver operating characteristic curve
RYGB	Roux-en-Y gastric bypass
SF-36	Medical outcome short form 36
S-25(OH)D	Serum 25-hydroxyvitamin D
SG	Sleeve gastrectomy
SHAP	Shapley additive explanations
SMD	Standardised mean difference
SOReg	Scandinavian obesity surgery registry
VAS	Visual analogue scale
VLED	Very low energy diet
WHO	World Health Organization
XGB	Extreme gradient boosting

INTRODUCTION

Obesity has become one of the most powerful drivers of chronic disease worldwide, shaping the epidemiology of type 2 diabetes, cardiovascular disease, and premature mortality.[1,2] The World Health Organization (WHO) has described obesity as "the defining health challenge of our time".[1] In medicine, this has led to substantial advances in therapeutic strategies targeting obesity, with metabolic bariatric surgery emerging as one of the most effective treatments for sustained weight loss and durable metabolic improvements.[3] Yet, as the use of metabolic bariatric surgery has increased and follow-up periods have lengthened, data have revealed a more nuanced pattern of late outcomes. Given that obesity reflects diverse environmental, behavioural, and biological drivers, long-term responses are unlikely to be uniform, and sustained benefit cannot be assumed for all individuals.

In this context, the aim of this thesis was to examine the long-term benefits and harms of metabolic bariatric surgery and to explore whether baseline characteristics can predict long-term clinical trajectories.

OBESITY AS A GLOBAL AND CLINICAL HEALTH BURDEN

Despite rising awareness about obesity and its role in chronic disease, body mass index (BMI) has continued to increase consistently across all continents over the past three decades, affecting people of all ages and both sexes.[2] In 2021, approximately 2 billion adults worldwide were overweight or had obesity.[2] If current systemic drivers persist, the number of adults living with overweight and obesity may reach nearly 4 billion in 2050, of whom almost 2 billion could have obesity.[2] The global rise in obesity has also paralleled increases in several obesity-related diseases, particularly type 2 diabetes, which is projected to affect more than 1.3 billion people worldwide by 2050.[4] Geographical variations exist, with prevalence estimates for overweight and obesity of 30-40% or more in parts of central and eastern Europe and the Middle East, compared with less than 20% in Sweden.[2,5] Although the prevalence in Sweden remains lower, it is also increasing, albeit at a slower rate.[5]

The clinical significance of obesity extends beyond its prevalence, as it is increasingly recognised as a chronic, relapsing condition associated with clear pathophysiological mechanisms, elevated risk of other chronic diseases, and a tendency toward recurrence despite treatment.[6,7] As a consequence of its chronic course and high prevalence, obesity imposes a substantial and growing burden on healthcare systems and society. BMI is among the leading risk factors of premature death, primarily through cardiovascular disease, and contributes substantially to years lived with disability, and increasing societal and healthcare costs.[8,9]

MULTIFACTORIAL ORIGINS OF OBESITY

In a recent report by the Global Burden of Disease collaborators, obesity was identified as having surpassed underweight in most countries as the leading weight- and nutrition-related contributor to disease burden.[10] Several reasons for this global evolution have been proposed, encompassing interacting drivers that range from systemic structures to individual biological susceptibility. Obesity is not simply a matter of individual willpower but reflects modern living conditions that promote a chronic imbalance by which energy intake exceeds energy expenditure.[10,11] Global economic and technological changes have altered both food environments and physical activity patterns, increasing reliance on commercially produced, energy-dense foods while reducing occupational and transport-related energy expenditure, and increasing sedentary leisure activities.[2,10] Yet exposure to obesogenic environments does not uniformly result in obesity, underscoring the role of genetic predisposition and explaining the substantial variation in risk both between and within populations.[11,12] Multiple genetic variants and epigenetic modifications have been described as contributors to heterogeneity in obesity phenotypes and susceptibility to environmental influences.[12]
Part of this heterogeneity is mediated through the neuroendocrine systems regulating energy balance, including several entero-pancreatic and adipose-tissue hormones, such as insulin, ghrelin, leptin, and the incretins glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).[3,13] Genetic variability in the expression and regulation of these pathways influences appetite, energy expenditure, and resistance to weight loss, thereby contributing to differences in weight trajectories and treatment response.[14,15] These neurohormonal mechanisms therefore play a central role not only in the development of obesity but also in long-term weight regulation and represent key therapeutic targets of the emerging pharmacological treatments.

Growing evidence also implicates the gut microbiome in the pathogenesis of obesity.[16] Individuals with obesity are more likely to exhibit dysbiosis, characterised by reduced microbial diversity, which may influence energy homeostasis.[16]

METABOLIC EFFECTS AND TYPE 2 DIABETES

Obesity is not merely a state of excess adiposity that functions as a fuel reserve for the body. Adipose tissue is also an active endocrine organ that contributes directly to metabolic disturbances and adverse outcomes related to obesity.[17] Obesity, particularly when characterised by central or visceral adipose distribution, is linked to increased release of free fatty acids, chronic low-grade inflammation, leptin resistance, and deposition of lipid intermediates in non-adipose tissues, as well as mechanical effects related to excess adipose tissue mass.[3,17,18] These mechanisms underlie the hypertensive, dyslipidaemia and insulin-resistant states that are present or can eventually develop in individuals with obesity.[17,19] In parallel, the progressive beta cell dysfunction further elevates the risk of developing type 2 diabetes.[17] Epidemiological data indicate that individuals with obesity have an up to nine-fold increased risk of developing type 2 diabetes compared to normal-weight individuals.[20]

Beyond diabetes, obesity-related alterations in adipose tissue metabolism and inflammation exert direct effects on the cardiovascular systems, kidneys, and liver, promoting disease that is partly independent of overt type 2 diabetes and hypertension.[3,21] Mechanical overload from excess adiposity also contributes to disease in the airways and the musculoskeletal system.[3] Accordingly, individuals seeking help with weight loss differ not only in their BMI but also in underlying metabolic burden and organ involvement.

PSYCHIATRIC AND PSYCHOSOCIAL DIMENSIONS

Beyond metabolic variation, psychiatric and psychosocial factors also influence the clinical expression of obesity and its long-term trajectories.[22] In contrast to the relatively well-defined metabolic pathway linking obesity to cardiometabolic disease, the relationship between obesity and psychiatric disorders such as depression is less clear. Evidence supports a bidirectional association, with each condition increasing the risk of the other.[23]

Several of the mechanistic processes underlying the development of obesity, including genetic and epigenetic patterns, leptin dysregulation, insulin resistance and gut microbiome dysbiosis, have also been implicated in the development of depression, although the direction of causality remains uncertain.[24] Some studies suggest that obesity and the risk of depressive symptoms are partly dependent on metabolic health and propose that low-grade inflammation associated with excess adiposity is a mediator.[24] Conversely, other longitudinal studies indicate that depression is more likely to precede and increase the risk of obesity, particularly among females.[23] Social and behavioural pathways, including social stigma, the higher risk of unhealthy eating behaviours and sedentary lifestyles associated with depression and anxiety, have been proposed as mediators of this directionality.[23-25] Eating disorders in individuals with obesity are furthermore associated with high rates of suboptimal results following weight-loss treatment and an increased risk of metabolic and cardiovascular comorbidities.[14,26] This multifaceted relationship between obesity and depression illustrates how mental health may modify both metabolic risk and treatment response with variations in both weight-loss and psychiatric outcomes following weight-loss interventions.[27,28]

NUTRITIONAL VULNERABILITY

The complexity of obesity is also reflected in variations in nutritional status. Clinical assessment of individuals undergoing metabolic bariatric surgery has demonstrated that obesity itself is frequently accompanied by deficiencies in several micronutrients.[29,30] Vitamin D deficiency is the most consistently observed abnormality among individuals with obesity, and several underlying mechanisms have been proposed, relating to lifestyle and eating behaviours as well as excess adiposity itself. [31] Limited sun exposure and low dietary intake may contribute, but volumetric dilution due to increased body mass and sequestration of fat-soluble vitamin D in adipose tissue appear to be central pathways for reduced circulating serum 25-hydroxyvitamin D (S-25(OH)D) concentrations.[32,33] Impaired hepatic hydroxylation in the context of metabolic-associated steatotic liver disease has also been suggested as a contributing factor.[34]

Vitamin D deficiency is also common in individuals with type 2 diabetes and has been independently associated with insulin resistance, dyslipidaemia and cardiovascular disease.[35] Thiamine and iron deficiency also appear more prevalent in individuals with obesity, possibly reflecting suboptimal dietary intake or chronic low-grade inflammation.[29,36] Thiamine deficiency has, similar to vitamin D, been implicated in the pathogenesis of type 2 diabetes and cardiovascular disease.[36,37]

TREATMENT OF OBESITY

Given the status of obesity as one of the defining health challenges of our time, there is increasing recognition that it requires structured, long-term management. The goal of treatment should include sustained weight reduction, amelioration or remission of cardiometabolic risk factors and other clinical manifestations of obesity, as well as improvement in health-related quality of life (HRQoL).[7,38]

Evidence indicates that a weight reduction of at least 5% is associated with measurable improvements in several cardiometabolic risk indicators.[3,39] Greater weight loss, in the range of 10-20% of baseline weight, appears necessary to influence cardiovascular disease.[39,40] In metabolic bariatric surgery, a 20% total weight loss is often used as a threshold for optimal clinical response.[41,42]

Assessment of HRQoL has become an integral component of both clinical and scientific practice when evaluating the overall impact of illness and its treatment.[43] There is evidence that obesity is associated with impairments in the physical, mental, and social domains of well-being.[44-46] The relationship between weight loss and HRQoL is more ambiguous.[44,47] Greater weight reductions seem to be associated with larger improvements in physical health-related quality of life, whereas associations with social and mental well-being are weaker and more variable.[44,48]

Obesity treatment comprises three principal modalities today, namely lifestyle intervention, pharmacotherapy, and surgically induced weight loss. These are discussed in more detail below.

LIFESTYLE INTERVENTION AND PHARMACOTHERAPY

Sustained weight loss through lifestyle intervention alone has been challenging. In two large randomised controlled trials (RCTs), the Look AHEAD (Action for Health in Diabetes) and the Diabetes Remission Clinical (DiRECT) trials, the majority of participants were able to maintain a weight loss of ≥5% through intensive lifestyle intervention, but many experienced significant weight regain.[39,49] In the DiRECT trial, remission of type 2 diabetes was closely linked to substantial and sustained weight loss, and only one-third of participants maintained remission in the longer term.[50] In the Look Ahead trial, there was no reduction in cardiovascular morbidity and mortality.[39] For greater weight loss and its maintenance over time, lifestyle interventions likely require additional therapeutic support, such as pharmacotherapy.[3,51]

Until recently, few pharmacological agents were approved for weight management, and most produced moderate effects, with mean weight reductions of 5-8% at one year.[3] Advances in understanding of the neurohormonal gut-brain axis have led to the development of agents targeting the different entero-pancreatic hormones, with promising results. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) were initially introduced for the treatment of type 2 diabetes and were subsequently shown to induce significant weight loss alongside improved glycaemic control.[52] Over the years, incretin-based therapies have expanded, demonstrating greater weight reductions and cardiovascular benefits in individuals with obesity.[53-55] Nonetheless, weight loss responses vary, and individuals with type 2 diabetes tend to achieve smaller reductions than those without diabetes.[56] Furthermore, discontinuation of pharmacological treatments is frequently followed by substantial weight regain, suggesting that long-term treatment may be necessary for weight management, similar to the management of hypertension and dyslipidaemia.[56,57]

Although pharmacological agents have broadened the therapeutic landscape in obesity management, the magnitude and durability of weight loss remain generally lower than those achieved with metabolic bariatric surgery.[58]

SURGICAL WEIGHT LOSS MANAGEMENT

Metabolic bariatric surgery remains a benchmark for durable weight loss and metabolic improvement. It is defined in this thesis as gastrointestinal surgery performed to induce weight loss and improve metabolic control.[59] In the Swedish Obesity Subjects' study (SOS), a pioneering long-term observational trial of surgical weight loss, bariatric surgery in individuals with obesity was shown not only to be superior to usual care for sustained weight loss but also associated with a significant reduction in mortality and cardiovascular risk factors.[60,61] The SOS trial also demonstrated higher remission rates for type 2 diabetes compared with usual care; however, most participants did not undergo the two most common procedures today, Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG).[62]

In a subsequent RCT, the Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial, RYGB and SG were superior to intensive medical therapy alone in achieving sustained weight loss and diabetes remission in individuals with type 2 diabetes up to five years after surgery.[63] Since then, studies have consistently demonstrated that both procedures achieve weight loss of 25% or more, improve hypertension and dyslipidaemia, as well as glycaemic control.[64-66] These findings have led to the inclusion of metabolic bariatric surgery in guidelines for the management of type 2 diabetes in individuals with severe obesity.[67]

Although RYGB and SG have produced comparable effects on weight and glycaemic control, RYGB has, in several analyses, demonstrated greater long-term weight and metabolic benefits.[65,66,68] RYGB has long been regarded as a standard bariatric procedure, whereas SG has gained popularity over the past decade due to its technical simplicity and a promise of a lower risk of complications compared with RYGB.[69,70] By the end of the last decade, the annual number of RYGB and SG procedures performed in Sweden was similar. [71] RYGB combines restrictive and malabsorptive techniques, creating a bypass of the stomach, duodenum, and most of the jejunum.[70,72] In contrast, SG primarily involves restriction through resection of a large portion of the stomach (**Figure 1**).[70,73]

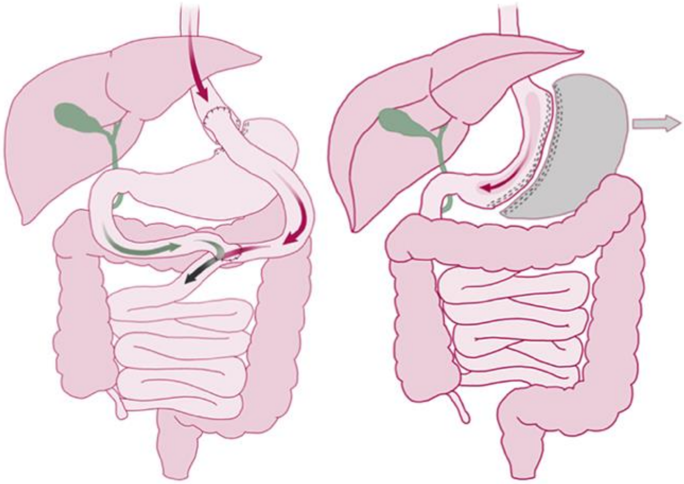

Figure 1. Schematic illustration of Roux-en-Y gastric bypass (left) and sleeve gastrectomy (right), two of the most common performed metabolic bariatric procedures. *Reprinted from Contemporary Clinical Trials, Vol. 84, Hedberg S, Olbers T, Peltonen M, et al. BEST: Bypass equipoise sleeve trial; rationale and design of a randomized, registry-based, multicenter trial comparing Roux-en-Y gastric bypass with sleeve gastrectomy. Copyright (2019), with permission from Elsevier*

Both procedures are associated with low perioperative morbidity and mortality. However, the long-term surgical complication profiles can differ between the two.[74,75] Pooled data from the SLEEVEPASS (the Finnish Sleeve versus bypass Study) and SM-BOSS (Swiss Multicentre Bypass or Sleeve Study) randomised trials with five-year follow-up showed higher complication rates after RYGB, mainly due to internal herniation and severe dumping, whereas SG was frequently associated with gastro-oesophageal reflux disease (GERD). [65] SG has also been linked to a higher risk of revisional surgery, either because of suboptimal clinical response or refractory GERD.[76,77]

Furthermore, both procedures increase the risk of nutritional deficiencies, with higher rates following RYGB due to the malabsorptive component of the surgery.[78] RYGB has additionally been associated with a higher risk of alcohol and substance use disorder in previous studies.[79,80] Regarding mental health, many experience an improvement in depressive symptoms in the early postoperative period; however, there are indications of deterioration and new-onset depressive disorders in the long term, as well as a higher risk of self-harm and suicide attempts.[81,82]

Although average benefits are well documented, the long-term balance between effectiveness and safety in individuals with type 2 diabetes remains less well defined. There are indications that individuals with type 2 diabetes may experience less favourable postoperative cardiovascular and renal outcomes after metabolic bariatric surgery compared with those without diabetes.[83,84] Furthermore, long-term safety data in individuals with type 2 diabetes remain limited, particularly for SG, leaving gaps in understanding the long-term benefits and harms in this population.

CHALLENGES IN TREATMENT ALLOCATION

Gaps in long-term outcome data following metabolic bariatric surgery can create uncertainty in treatment allocation in clinical practice. Decisions regarding metabolic bariatric surgery continue to rely largely on BMI thresholds and average treatment effects rather than on individual-level benefits and risks. [7] Given the biological and clinical heterogeneity described previously, treatment efficacy can vary considerably between individuals, and no single intervention is universally effective for achieving optimal weight loss, long-term risk reduction, and improved quality of life.[38,85] A more detailed understanding of how environmental, behavioural, and clinical factors influence long-term outcomes across groups and individuals would support a more personalised approach to treatment selection.[86] Artificial intelligence has emerged as a potential tool to facilitate this, as machine learning (ML) can detect complex, non-linear patterns in high-dimensional clinical data beyond the capacity of traditional statistical methods.[87] Although the application of artificial intelligence in metabolic bariatric surgery, such as the prediction of weight loss and surgical complications, has increased, most studies focus on short-term endpoints and are constrained by limited high-dimensional data.[86,88]

AIM

This thesis aims to expand existing knowledge of which individuals are most likely to benefit from metabolic bariatric surgery and on its long-term consequences across diverse populations, using real-world data. Specifically, it examines individuals with obesity seeking weight-loss treatment and whether their clinical characteristics, beyond body mass index, differ from those of the general population. The thesis further evaluates the meaningful long-term benefits and harms following metabolic bariatric surgery compared with lifestyle intervention or no treatment, and investigates whether preoperative characteristics can predict long-term outcomes to guide treatment decisions.

The specific aims of each study are as follows:

I. To describe HRQoL and disease burden in individuals with obesity accepted for weight-loss treatment in specialist services for obesity management, compared to the general population in the same region. The hypotheses were that individuals with obesity had a lower physical and mental HRQoL and a higher disease burden than the general population.

II. To assess the effects of RYGB, SG, and non-surgical lifestyle intervention on vitamin D status two years after treatment in individuals with obesity. The hypothesis was that RYGB, in particular, would be associated with a higher prevalence of vitamin D deficiency.

III. To evaluate the long-term effects of RYGB and SG on mortality, obesity-related comorbidities and surgical complications in individuals with type 2 diabetes and obesity, compared with a matched control population.

IV. To identify important predictors of individuals at risk of suboptimal weight loss and of high risk of postoperative complications among individuals with type 2 diabetes and obesity undergoing metabolic bariatric surgery.

PATIENTS AND METHODS

OVERALL STUDY FRAMEWORK

This dissertation comprises four original studies of individuals with obesity, addressing different aspects of health among those seeking and undergoing surgical weight-loss treatment. All four studies are observational and derive data from other sources. In Papers I and II, individuals were included from two other projects: one a prospective, clinically recruited cohort of individuals with obesity seeking weight-loss treatment in Region Västra Götaland (VGR), Sweden, and the other a population-based cohort drawn from the general adult population in Gothenburg, Sweden.[30,89] Papers III and IV were also observational but explicitly focused on individuals with obesity and type 2 diabetes, sourcing data from two national quality registries.[90] For all studies, the WHO definition of obesity is used. The definition is based on BMI, with a BMI≥ 30 kg/m^2 used as the cutoff.[91]

Table 1 provides an overview of all four studies and their designs.

Table 1. Overview of study design, populations, main outcomes and statistical analyses for each paper in this thesis.

	Paper I	Paper II	Paper III	Paper IV
Main data source	BASUN and WHO MONICA	BASUN and WHO MONICA	SOReg and NDR	SOReg and NDR
Study period	2015-2017	2015-2019	2007-2021	2007-2021
Number of participants	1536	1385	16798	8399
Target population	Obesity: Seeking weight loss treatment with reference population	Obesity: RYGB, SG or lifestyle intervention with reference population	Obesity and type 2 diabetes: RYGB or SG with matched unexposed controls	Obesity and type 2 diabetes: RYGB or SG
Subgroups	Treatment seeking – 1122 Reference – 414	RYGB – 388 SG – 201 VLED – 382 Reference – 414	RYGB – 7294 SG – 1105 Controls – 8399	RYGB – 7294 SG – 1105
Primary outcome	HRQoL	Vitamin D deficiency defined as S-25(OH)D <25nmol/L	All-cause mortality, obesity-related comorbidities, surgical complications	Composite outcome of optimal clinical response and absence of certain complications
Statistical methods	Linear regression	ANOVA, random forest classifier	Kaplan-Meier analysis, Cox regression	Machine learning model (XGB)

Abbreviations: BASUN, BAriatric surgery Substitution and Nutrition study; WHO MONICA, World Health Organisation MONItoring of Trends and Determinants in CArdiovascular disease project; SOReg, Scandinavian Obesity Surgery Registry; NDR, Swedish National Diabetes Register; RYGB, Roux-en-Y gastric bypass; SG, Sleeve gastrectomy; VLED, Very low-energy diet; HRQoL, Health-related quality of life; ANOVA, analysis of variance; XGB, Extreme gradient boosting.

DATA SOURCES

THE BARIATRIC SURGERY SUBSTITUTION AND NUTRITION (BASUN) STUDY

In papers I and II, individuals from the BASUN project served as the study population. BASUN is a 10-year, ongoing, non-randomised, prospective intervention trial that recruited individuals in VGR, Sweden, seeking help with weight loss.[92] The overall aims of BASUN were to assess the long-term effectiveness of bariatric surgery (RYGB and SG) and of non-surgical treatment with a very low-energy diet (VLED) for obesity.

All individuals were initially referred to the Regional Obesity Centre (ROC) at the Sahlgrenska University Hospital in Gothenburg. The centre is responsible for coordinating and assessing all referrals for surgical or intensive medical weight-loss treatments in VGR.[92] Recruitment for the study through the ROC began in May 2015 and concluded in November 2017. All individuals were assigned to RYGB or SG based on their preferences and clinical eligibility criteria, in accordance with international bariatric surgery guidelines.[93] Individuals with a BMI ≥35 kg/m^2 who were either not interested in or eligible for surgery were offered a 12-month programme with VLED.[92] The VLED regimen was initiated with a caloric intake of 450-800 kcal/day for 12 to 20 weeks, depending on baseline BMI. During this phase, participants attended nurse-led follow-up visits at 2, 5, 8, and 12 weeks. This was followed by 12 weeks of gradual food reintroduction and finally monthly controls under the supervision of a clinical nutritionist.[92] Physician consultations were scheduled at 6 and 12 months to evaluate the need for pharmacological reinforcement for weight loss with orlistat, bupropion/naltrexone, sodium-glucose co-transporter-2 inhibitors, or GLP-1 receptor agonists.[92] During this time, GLP-1 agonists were not subsidised by the government, which affected the number of individuals treated with these agents.

A sample size estimation was performed assuming a statistical power of 80% and a 20% dropout rate, resulting in 1400 individuals.[94] Ionised calcium was selected for the power analysis because it was considered the outcome requiring the largest sample size to detect a clinically meaningful difference. Individuals who did not understand Swedish were excluded due to difficulties obtaining informed consent.

There were 2260 individuals deemed eligible for participation, of whom 1122 provided informed consent and underwent baseline assessment. Baseline evaluation included, among other things, blood biochemical markers, anthropometric measurements, HRQoL and physical activity questionnaires, and self-reported use of prescription drugs and vitamin supplements.[92]

Following baseline assessments, 971 individuals initiated treatment, with 388 undergoing RYGB, 201 undergoing SG, and 382 receiving VLED.[30,92]

THE WORLD HEALTH ORGANISATION MONITORING OF TRENDS AND DETERMINANTS IN CARDIOVASCULAR DISEASE (WHO MONICA) PROJECT

In Papers I and II of this thesis, participants from the WHO MONICA project served as the reference population. WHO MONICA was a multinational initiative designed to monitor trends in cardiovascular risk through independent cross-sectional random sample population surveys conducted between 1985 and 1995 in 38 countries worldwide.[91,95] A study centre in Gothenburg, Sweden, participated in the project.[95]

In the third and final screening, 2,563 individuals were randomly selected from the 1995 Gothenburg city population register, which is continuously maintained and updated with a maximum delay of 14 days.[95] 1618 individuals consented to participate (participation rate 63%), and among them, a subset with every fourth individual and all women aged 45-64 years (n=662) underwent additional hormonal assessments focused on sex and bone health. In 2008, 608 individuals from this subset were alive and reinvited for a follow-up examination using a similar protocol for physical examination, hormonal markers, and questionnaires regarding HRQoL. The reexamination was completed in 414 individuals (participation rate 68%).[96]

THE SCANDINAVIAN OBESITY SURGERY REGISTRY (SOREG)

SOReg is a national quality registry that monitors outcomes of bariatric surgery in Sweden. Since its establishment in the early 2000s, it has become one of the most comprehensive databases on bariatric surgery worldwide, covering more than 99% of all operations performed in Sweden.[97] Through the systematic collection of detailed data on clinical characteristics, including biochemical markers, risk factors, surgical procedures, peri- and postoperative outcomes and complications, the registry has enabled high-quality research, improved clinical care, and contributed to new knowledge on obesity and its treatment.[98,99]

Data are prospectively collected at 1, 2, 5, 10, and 15 years after surgery and routinely cross-matched with national registries on causes of death and inpatient care, and randomly compared with clinical records. These audits indicate high validity, with rates above 98%.[100]

THE SWEDISH NATIONAL DIABETES REGISTER (NDR)

Another well-recognised high-quality register is the NDR, which was established in 1996 to improve diabetes care in Sweden.[101] Since then, the implementation of guidelines for diabetes care has been closely monitored by the NDR, which includes a comprehensive set of variables related to glycemic control, risk factors and complications. As for SOReg, the NDR has contributed to excellent research, advances in understanding disease trajectories and associated comorbidities, and holistic improvements in care.[102,103]

In the NDR, which includes more than 90% of all individuals living with type 2 diabetes in Sweden, the diagnosis of type 2 diabetes is defined epidemiologically as individuals treated with diet alone or in combination with oral antihyperglycaemic drugs. Individuals on insulin who are older than 40 years are also classified as having type 2 diabetes.[90,104] When information for this definition was missing, individuals were classified through clinical assessment.

OTHER REGISTERS

In Sweden, there are several national registers that cover all residents and are maintained by government institutions, including the National Board of Health and Welfare and Statistics Sweden. For papers II and III, demographic and socioeconomic variables were obtained from Statistics Sweden's Longitudinal Integration for Health Insurance and Labour Market Studies (LISA) database.[105] The National Board of Health and Welfare maintains the National Cause of Death register, the National Patient Register (NPR), the National Cancer register, and the National Prescribed Drug register, all of which have high validity and were used in papers III and IV.[106-110]

STUDY POPULATIONS AND DESIGN

All individuals with obesity included in this thesis underwent weight-loss treatment in Sweden, of whom the majority underwent surgical treatment with either RYGB or SG, provided in accordance with internationally recognised guidelines.[92,97] According to these guidelines, surgery should be considered for all individuals with a BMI ≥ 40 kg/m², or with a BMI ≥ 35 kg/m² in the presence of obesity-related comorbidities. Recommended contraindications for surgery are mainly high operative risk related to severe somatic disease, cancer in the past 5 years, active substance abuse or other severe psychiatric disorders.

PAPER I

This study was designed as a cross-sectional cohort study with a reference population. For the primary outcome, physical and mental well-being were assessed using generic HRQoL instruments: the RAND-36 Item Health Survey, the Medical Outcome Short Form 36 (SF-36) and the Visual Analogue Scale (VAS) for self-rated health from the 1990 edition of the five-dimensional questionnaire™ of the EuroQol Research Foundation (EQ-5D).[111-113] The RAND-36, used in BASUN, and the SF-36, used in WHO MONICA, comprise the same questions and yield the same eight domains (**Figure 2**).

Figure 2. The eight domains of the generic RAND/SF-36 health-related quality of life instrument.

The results were, therefore, considered comparable across cohorts, except for the summary scores, which were derived using different algorithms.[89,112,114] Across all scales, the range was 0-100, with higher scores representing a greater functional health and well-being.[111,113] For the secondary outcome, self-reported use of prescription medications for hypertension, diabetes, high cholesterol, depression, anxiety, and pain served as an indicator for each condition, and were used as a proxy for disease burden. Individuals under 18 years were excluded from the analysis.

PAPER II

This study was designed as a longitudinal observational cohort study. For the primary outcome, vitamin D deficiency was defined as S-25(OH)D < 25 nmol/L. Vitamin D insufficiency was also assessed and defined as S-25(OH)D between 25 and 50 nmol/L.[115] Levels of parathyroid hormone (S-PTH; pmol/L) and serum ionised calcium (mmol/L) were also measured, with secondary hyperparathyroidism defined as S-PTH > 6.9 pmol/L.[30] In both cohorts, S-25(OH)D was measured using a 125i radioimmunoassay kit (DiaSorin, Stillwater, MN, USA), with a coefficient of variation of 6.2%.[30] PTH was measured using an immunoradiometric assay (Roche Cobas, Rotkreutz, Switzerland).[30] Blood samples from both the BASUN and WHO MONICA studies were analysed at the accredited Clinical Chemistry laboratory at the Sahlgrenska University Hospital.[30]

Furthermore, self-reported use of vitamin D and calcium supplements was assessed. In BASUN, individuals undergoing RYGB or SG received specific recommendations for 400-800 IU of cholecalciferol and 500 mg of calcium carbonate twice daily.[30] These recommendations were consistent with the Scandinavian bariatric surgery guidelines on nutritional supplementation, updated in 2015.[116]

In BASUN and WHO MONICA, all examinations were conducted according to a strictly standardised protocol and conducted by the same trained clinical personnel.[92,96] Fasting blood samples were obtained, height and weight were measured to the nearest 1 cm and 0.1 kg, and questionnaires were completed in the same order for all participants.[92,96] BMI was calculated as weight divided by height squared. Furthermore, self-reported demographic and social variables were collected and used in both studies, including age, sex, educational level, civil status, smoking habits, and physical activity. All self-reported prescription-based medications were defined and coded according to the Anatomical Therapeutic Chemical (ATC) classification system.

PAPER III

This was a nationwide, prospective, observational study encompassing all Swedes with type 2 diabetes who underwent metabolic bariatric surgery with RYGB or SG.[90] The study was based on data from SOReg and the NDR.

In Sweden, the unique personal identification number assigned to every citizen enables studies to draw on data from multiple nationwide registries, creating comprehensive datasets.[90,102] In study III, individuals from SOReg who had undergone surgery with RYGB or SG between January 1, 2007 and December 31, 2020, were cross-matched with the NDR to determine whether they had a diagnosis of type 2 diabetes before surgery. Those with type 2 diabetes before surgery were included and further matched with unexposed individuals from the NDR, consisting of people with type 2 diabetes and obesity who had not undergone surgical treatment at the time of matching.

Several outcomes were assessed, such as the incidence of all-cause mortality, cardiovascular mortality, cardiovascular diseases, chronic kidney disease, cancer, diabetes-related microvascular complications, mental health disorders, malabsorption and micronutrient deficiency, and surgical-related complications.[90] All outcomes were retrieved from the NPR and defined using the International Classification of Diseases, version 10 (ICD-10). For the complete list of study endpoints, including their ICD codes, refer to Tables 2 and 3, and the supplementary appendix in the accompanying documentation for Paper III. Postoperative data on BMI and glycated haemoglobin (HbA1c) were retrieved from NDR, and data on prescribed drugs were identified through the ATC classification system in the National Prescribed Drug Register.

All participants were followed until death, another outcome event, emigration, or until December 31, 2021, whichever occurred first.

PAPER IV

This study was designed to explore associations between preoperative register-based characteristics and a multidimensional long-term outcome following metabolic bariatric surgery. The study included the same cross-matched individuals with type 2 diabetes and obesity from SOReg and the NDR as in Paper III, all of whom had undergone RYGB or SG. There was no control group in this study.

The primary outcome was defined as a composite binary endpoint comprising optimal weight response at five years, defined as more than 20% total weight loss, and absence of hospital-recorded adverse events requiring specialist care during the same period. These events included malabsorption and micronutrient deficiencies (iron and vitamins), psychiatric disorders, including depression, anxiety, and substance and alcohol abuse, and gastrointestinal reflux and ulceration, bowel obstruction, and gastrointestinal leakage. The diagnoses, as in Paper III, were identified through the NPR and defined according to ICD-10.

All available body weight measurements recorded in the NDR and SOReg between four and six years postoperatively were used to assess the optimal weight response at five years. Only participants with body weight data were included in the analysis of the primary endpoint.

Secondary endpoints included separate analyses of optimal weight response, a composite of malabsorption and micronutrient deficiencies (iron and vitamins), a composite of depression and anxiety disorders, and a composite of alcohol and other drug use disorders five years after RYGB and SG.

STATISTICAL ANALYSIS

This thesis employed a range of statistical analyses tailored to the specific aims and challenges of each study. The diversity of study designs and populations, along with the use of reference groups, contributed to an overall robust methodological framework.

Across all papers, conventional descriptive and inferential statistics were used to describe baseline population characteristics. Continuous variables were reported as means with standard deviations, or medians with interquartile ranges. Counts and percentages were used to describe nominal data. Group comparisons at baseline were performed using Pearson's chi-squared test or Fisher's exact test for nominal data, and Student's t-test or Wilcoxon rank sum test for continuous data. The standardised mean difference (SMD) was also used to evaluate covariate balance in Papers I-IV, serving as the primary and only analysis of baseline group differences in Papers II and III. SMD is a measure of effect size, and values>0.1 are considered statistically significant. SMD has previously been used for both categorical and continuous variables.[117]

In all studies, hypothesis tests were two-sided, and statistical significance was defined as $\alpha = 0.05$. All statistical analyses were performed in R Studio (version 4.0.3 in Papers I and II, version 2024.12.0+467 in Paper III, and version 2025.09.2+418 in Paper IV, R Foundation for Statistical Computing, Vienna, Austria).

STATISTICAL METHODS PAPER I

SMD was used to estimate effect sizes, and a multivariate linear regression model, adjusted for age and number of medications, was developed to quantify the difference in HRQoL between the BASUN study population and the reference population (WHO MONICA). The same model was also used to compare HRQoL between individuals with a BMI ≥40 kg/m^2 and those with a lower BMI within the BASUN population. Results from the regression models were presented as beta coefficients with 95% confidence intervals (CI).

STATISTICAL METHODS PAPER II

At the two-year follow-up, a separate one-way analysis of variance (ANOVA) was conducted to compare vitamin D deficiency and insufficiency across the RYGB, SG, and VLED cohorts, with a Tukey-Kramer post hoc test applied if significant differences were observed. Changes in body weight, BMI, S-25(OH)D, S-PTH and S-ionised calcium from baseline to follow-up were analysed using a multivariate linear regression model adjusted for age, sex, and their baseline values. Results were reported as estimated means with 95% CI.

Furthermore, a supervised ML model was used to explore associations between all baseline features and vitamin D deficiency at 2 years. For this purpose, a decision tree-based random forest classifier (RFC) was trained, and the input variables were then ranked by predictive performance using a conditional permutation scheme.[118]

In the multivariate linear regression and random forest analyses, missing data were treated as missing at random and handled using multiple imputation with a chained equations algorithm.

STATISTICAL METHODS PAPER III

Individuals with type 2 diabetes and obesity who had undergone either RYGB or SG were matched with unexposed individuals by sex, age in whole years, BMI to 1 decimal place, and the surgery date of the exposed individuals, all of which were considered clinically meaningful. Matching on surgery date was deemed sufficient to control for secular trends during the study period.

For all study participants, follow-up began at the time of surgery for the exposed individuals. Incidence rates were calculated and reported as events per 10,000 person-years. Unadjusted cumulative hazard estimates were calculated and visualised using Kaplan-Meier survival curves (1-Kaplan-Meier). Multivariate Cox proportional hazards regression models were then used to estimate adjusted hazard ratios (aHR) with 95% CIs for each outcome. All Cox-regression models were adjusted for sex, BMI, diabetes duration at inclusion, marital status, educational level, income quartile, smoking status, level of physical activity, and the presence of each outcome at baseline. [90] The proportional hazard assumption was evaluated using the Grambsch-Therneau test, Schoenfeld's residual plots and smooth hazard plots. Risks were calculated separately for each surgery group, RYGB and SG, compared to their matched unexposed individuals.[90]

The income data variable was the only one with significant missing values, and the last observation carried forward method was used to impute them.

STATISTICAL METHODS PAPER IV

In this study, a supervised ML approach with a Shapley Additive exPlanations (SHAP) method was employed to explore features associated with the multidimensional composite outcome. The outcome was operationalised as a binary target, with the two levels defined as favourable and unfavourable. Initially, six models appropriate for binary classification were evaluated. These included ensemble tree algorithms, including Extreme Gradient Boosting (XGB), Light Gradient Boosting Machine (LightGBM), and a RFC. The other three models included a standard logistic regression model and two regularised logistic regression models employing L1 (Least Absolute Shrinkage and Selection Operator, LASSO) and L2 (Least Squares/Ridge) penalisation.[119-121] Model development involved preprocessing input variables and internal validation using a training-testing split with five-fold cross-validation. Missing data were imputed in the training dataset to avoid information leakage to the test set. Variables with more than 70% missing data were excluded a priori.

All models were trained with their default hyperparameters and evaluated using the area under the receiver operating characteristic curve (ROC-AUC). Of these six models, XGB was selected for further development and underwent more rigorous hyperparameter optimisation based on ROC-AUC. SHAP values were then used to determine which input features were most influential in the prediction. SHAP values have been shown to better capture and explain how each feature contributes to predictions, particularly in tree-based models.[122,123] SHAP values were visualised using summary and dependence plots. Final model performance was assessed on new data from the test set using measures of discrimination and calibration, including ROC-AUC and Brier score, which is a measure of overall predictive accuracy. The final model was also audited for fairness in terms of sex. The same model development for XGB was applied to the separate secondary endpoints.

ETHICAL CONSIDERATIONS

All studies were conducted and published in accordance with the Declaration of Helsinki, national statutory requirements, and relevant data-reporting protocols. The research procedures included in this dissertation were reviewed and approved by the Swedish Ethical Review Authority.

- BASUN study: 2014 reference number 673-14

- WHO MONICA: 2006 reference number 088-06 with addendum Ad 088-06, T 282-11 (approved 2011)

- NDR and SOReg-based studies: 2020 reference number 2020-05410

Participants in the BASUN and WHO MONICA studies provided written informed consent prior to participation and for publication. Confidentiality and data protection were ensured through de-identification, with each participant assigned a unique study code accessible only to the principal investigator. Data were handled in secure environments by authorised personnel, and all analyses and publications were at the group level, minimising the risk of individual identification. In the BASUN study, care was provided in accordance with standard clinical practice for weight-loss treatment, with no coercive or inappropriate interventions. Additional blood sampling and questionnaires conducted for research purposes may have caused discomfort; however, participants were informed of the rationale for data collection and retained the right to decline participation at any stage without providing a reason, after which their data would not be used. Participants in the WHO MONICA study received no intervention other than blood sampling and questionnaires, and they could also decline participation at any stage.

For studies III and IV, data were obtained from several national and quality registries, with approval from the registry holders. Cross-matching was conducted by the National Board of Health and Welfare. All data were de-identified before submission to the research group for processing and analysis. Both NDR and SOReg operate under an “opt-out” system, in which individuals receive prior information about data collection for the registry and its use for research, but can “opt out” at any time. Individuals are not informed of the details of each research project utilising registry data. However, NDR and SOReg publish publicly available annual reports detailing studies that have used their data and the contributions of these data to advances in medical care quality and disease knowledge.

In Study IV, ML models were used to explore predictors. While ML models can enhance decision-making, they also raise ethical concerns. An important concern is the “black-box” nature of many algorithms, making it difficult to understand how predictions and associations are made, which could limit their application in clinical contexts. Model fairness across demographic groups has also attracted increased attention in recent years, and refers to whether model performance differs systematically across subgroups, potentially discriminating against individuals or groups based on sex, age, ethnicity or race. Updated reporting guidelines for prediction model studies, irrespective of whether regression or machine learning methods are used, are currently available to promote accurate, transparent, and fair reporting.[124]

RESULTS AND COMMENTS

This chapter summarises the main results and provides commentary on each original study included in this thesis. Detailed results are available in the articles and their supplementary material.

PAPER I

RESULTS

The BASUN cohort of 1122 individuals with baseline assessments was included in the study and compared with the reference cohort from the general population (WHO MONICA). There was no difference in sex distribution between the groups ($p = 0.30$ and $SMD = 0.1$). However, the reference cohort was significantly older and had a lower BMI than the BASUN cohort (62.8 ± 9.4 vs 43.9 ± 12.9 years and 26.8 ± 4.7 vs 42.0 ± 5.0 kg/m^2; $p < 0.001$ and $SMD > 0.1$).

HRQOL AND COMORBIDITY

Individuals from BASUN rated their overall HRQoL significantly lower than the reference population on the SRH-VAS (53.4 ± 20.1 vs 75.7 ± 20.4; *adjusted* $p < 0.001$ and $SMD > 0.1$) and on the general health domain of RAND-36/SF-36, even after adjusting for age and number of medications. Lower scores were also reported on the RAND-36/SF-36 for the domains of physical and social functioning, vitality, and mental health (*adjusted* $p < 0.001$; $SMD > 0.1$). Use of antidepressants, glucose-lowering and analgesic agents was higher in the BASUN cohort than in the reference population (*adjusted* $p < 0.001$; $SMD > 0.1$).

Within the BASUN cohort, after adjusting for age and number of medications, only the RAND-36 mental health domain showed a significant difference between participants with a BMI >40 kg/m^2 and those with a lower BMI.

COMMENTS ON PAPER I

In recent years, obesity has consistently been shown to negatively affect HRQoL, particularly in physical health domains, whereas findings for mental well-being are more heterogeneous.[46,125] In previous systematic reviews and meta-analyses, mental health domains were found to be less associated with body weight and more strongly influenced by other factors, such as somatic and psychiatric comorbidities.[45,126] Furthermore, individuals with obesity and metabolic comorbidities reported even lower HRQoL than metabolically healthy individuals with obesity.[45,127]

Against this background, the main findings of Study I, demonstrating decreased HRQoL across most domains among weight-loss-treatment-seeking individuals with obesity compared with the population-based reference cohort, are likely attributable to several factors, and not only differences in body weight. The higher use of antidepressants and glucose-lowering agents, despite being significantly younger, may have influenced the association between obesity and perceived health. However, this should be interpreted with caution, as self-reported medication use is an imperfect surrogate for comorbidity, severity and untreated conditions. In addition, the analyses were not adjusted for specific drug classes, such as antidepressants, analgesics, and glucose-lowering agents.

Furthermore, given that the WHO MONICA reference cohort was not concurrent with the BASUN study group, confounding factors, such as temporal mismatches in societal behaviours and systems, and medical practice, such as changes in prescribing patterns and diagnostic thresholds, could have influenced the results.[44] That said, because impairments in physical and general HRQoL, as well as comorbidities, are also associated with older age, this is unlikely to lead to an overestimation of clinically meaningful differences.[43]

Another important methodological consideration is the choice of instruments to assess HRQoL. The RAND-36 and SF-36 remain among the most widely used generic instruments to assess HRQoL in individuals with obesity.[46] Obesity-specific HRQoL instruments, such as the Impact of Weight on Quality of Life-Lite (IWQOL-lite) questionnaire, are inherently more sensitive to weight-related health concerns than generic instruments.[44] However, relying solely on a disease-specific instrument risks underrepresenting other important determinants of HRQoL in individuals with obesity. In a large meta-analysis, impairments in SF-36 domains, but not IQWOL-lite, persisted after accounting for body weight, particularly for mental health.[126] These findings suggest that the limitations in daily life experienced by individuals with obesity, especially regarding mental health, are not solely due to body weight.[128,129] The lack of differences in HRQoL across BMI categories in the BASUN cohort, except in the mental health domain, may support the interpretation that other factors, such as sex, comorbidities, and psychosocial factors, could affect HRQoL.[128,130] However, the absence of differences may also reflect the limited sensitivity of generic instruments to HRQoL impairments associated with severe obesity.

Finally, the cohort's treatment-seeking nature and the cross-sectional design shape both the clinical generalisability and the limitations of the findings in Study I. Nevertheless, a strength is the magnitude of the differences, with large standardised mean differences across several HRQoL domains, suggesting clinically meaningful impairment rather than solely statistically significant effects. SMD, like Cohen's d, provides a more clinically relevant interpretation of group differences alongside p-values.[112,131] In addition to the methodological considerations of the HRQoL instruments discussed above, the use of self-reported HRQoL and the manner in which they were collected may introduce information and context biases, as the interpretation of HRQoL items could vary across settings, expectations, mood, and disease context.[132] However, study protocols were strictly standardised, and questionnaires were given in the same order within each cohort.

Other considerations include a lack of data on attempts to lose weight, which could influence HRQoL. Socioeconomic status and physical activity were not adjusted for and may also independently affect HRQoL. The cohort was predominantly female, and although sex distribution was similar across cohorts and to previous studies, the overrepresentation of women may limit applicability to men with obesity. A substantial proportion of eligible individuals declined to participate in BASUN, for which no data were collected, potentially introducing selection bias toward individuals with better HRQoL or other confounders related to health-seeking behaviours. Individuals who did not understand Swedish were also excluded, affecting the generalisability to certain minority groups.

PAPER II

RESULTS

Only individuals who had undergone RYGB (n=388), SG (n=201), or VLED (n=382) treatment within the BASUN project were included in this study. Those who chose not to continue with treatment after inclusion were excluded (n=149). Sex distribution was similar across the three treatment groups, but those treated with VLED were older (*SMD* > 0.1).

At baseline, the entire cohort was compared with the same reference cohort from the general population as in Study I.

VITAMIN D IN INDIVIDUALS WITH OBESITY

Before treatment, 5.2% of individuals with obesity had vitamin D deficiency, which was significantly higher than the sample from the general population (*SMD* >0.1). The mean S-25(OH)D levels were 53.4 nmol/L in BASUN and 63.6 nmol/L in WHO MONICA despite no difference in vitamin D supplement use.

VITAMIN D AFTER WEIGHT-LOSS TREATMENT

At the two-year follow-up, only 713 individuals had blood tests for vitamin D, calcium, and PTH. Of these, 297 had undergone RYGB, 160 had SG, and 256 had received VLED treatment. Individuals who had undergone surgery with either RYGB or SG experienced greater weight loss at two years than those treated with VLED (BMI at two years: RYGB, 28.4 ± 4.1 kg/m^2; SG, 30.5 ± 4.7 kg/m^2; VLED, 36.6 ± 5.7 kg/m^2; *adjusted p* < 0.001 and *SMD* > 0.1).

Very few individuals had vitamin D deficiency after treatment, with no differences among RYGB, SG, and VLED (p = 0.29; *SMD* = 0.11). All treatment groups showed an increase in S-25(OH)D levels compared with baseline, but individuals treated with VLED had lower S-25(OH)D levels two years after treatment than those treated surgically (*adjusted p* < 0.001 and *SMD* > 0.1). The VLED cohort also demonstrated significantly higher rates of vitamin D insufficiency (37.1%; p < 0.001 and *SMD* > 0.1). Regarding supplements, only 16% of individuals on VLED reported taking a vitamin D supplement, compared with 81% and 71% in RYGB and SG, respectively.

PREDICTORS OF VITAMIN D DEFICIENCY

In the RFC model for vitamin D deficiency, the top three domains identified as most important for predicting risk included anthropometric features, vitamin and mineral biomarkers, and comorbidities. The most important individual predictors were postoperative BMI, hospitalisation, and postoperative serum iron levels, followed by baseline S-25(OH)D and S-PTH levels.

COMMENTS ON PAPER II

The main finding was that, although all treatment groups showed improvements in serum 25-hydroxyvitamin D concentrations, with corresponding reductions in vitamin D deficiency, insufficiency, and secondary hyperparathyroidism, individuals undergoing RYGB or SG achieved significantly higher vitamin D levels than those with VLED. This difference likely reflects greater weight loss after surgery, regular post-operative follow-ups, and the supplementation guidelines that accompany bariatric procedures.[116]

In previous studies, volumetric dilution and adipose sequestration have been associated with lower vitamin D status in individuals with obesity, which would explain the observations in the present study with increased levels after weight loss.[32,33] This may also explain the RFC results, in which follow-up weight indicators were the most important predictors of vitamin D deficiency.

Yet increases attributable to weight loss alone are often modest and insufficient to achieve recommended vitamin D target levels, especially in the long term.[133] Vitamin supplementation, therefore, plays a major role in increasing and maintaining these levels over time.[134] In the present study, none achieved a mean 25(OH)D concentration exceeding 75 nmol/L, a level often considered the threshold for vitamin D to exert positive effects beyond skeletal health.[135] This pattern has been reported across a wide range of bariatric studies, regardless of population characteristics and follow-up duration, suggesting that achieving higher vitamin D targets remains challenging in this context.[136] This can be attributed to both the lower vitamin D status associated with obesity and the malabsorptive or restrictive nature of the surgeries, which may necessitate higher supplementation doses.[133] The 2015 Swedish guidelines, which recommended daily intakes of up to 800 IU of cholecalciferol and at least 500 mg of calcium carbonate, were therefore likely insufficient to meet the needs of the study population in Paper II.[116,133] These guidelines have since been revised, and in 2024, a daily intake of 3000 IU of vitamin D and >1200-1500 mg of calcium was recommended.[137] Studies have also shown that the malabsorptive component of RYGB does not necessarily result in poorer vitamin D status compared to SG when supplementation is adequate, consistent with the findings in Paper II.[134,138]

Nevertheless, adherence to supplementation over time remains a challenge. In Study II, reported supplement use declined by 24 months, and if not addressed, the risk of late nutritional complications has been shown to increase.[139] In recently published long-term data from the SLEEVEPASS RCT, micronutrient deficiencies were low after RYGB and SG among individuals who remained adherent to vitamin supplements.[134]

The observed prevalence of vitamin D deficiency in the current study also warrants further discussion. In the present study, the prevalence of vitamin D deficiency was below 3% across all three treatment groups. This was lower than reported in many previous studies, both in cohorts with and without reported supplement use.[140] One important explanation for this discrepancy is the definition of vitamin D deficiency used in the current analysis, S-25(OH)D < 25 nmol/L. This cut-off is commonly applied in Sweden and is strongly associated with clinically overt skeletal disease, including osteomalacia and nutritional rickets.[115,141] According to the Institute of Medicine, 25(OH)D levels below 50 nmol/L are associated with reduced calcium absorption and adverse effects on extraskeletal tissues, which is why this definition is also widely used for deficiency (in the present study, this was defined as insufficiency).[115,142]

Although the optimal threshold for defining vitamin D deficiency remains a subject of debate, the choice of cutoff primarily affects the estimated prevalence rather than the underlying pathophysiology or the consequences of deficiency. In the present study, rates of insufficiency were comparable to those reported in previous studies with the same cut-off. This supports the validity of the present findings and indicates that the low prevalence of deficiency primarily reflects the strict cutoff applied rather than an absence of clinically relevant vitamin D disturbance.

There are other methodological considerations to be acknowledged. The lack of detailed information on dietary vitamin D intake and sunlight exposure is a limitation of the present study and should be considered when interpreting the results at the two-year follow-up. However, in WHO MONICA, blood samples were not collected from June through August, and in BASUN, fewer than 10% were collected during these months at follow-up.[30]

The use of a reference group for baseline analyses strengthens the conclusion, and the WHO MONICA cohort was considered a suitable reference, as it includes a comprehensive set of hormonal and bone health analyses.[96] As discussed for Paper I, the lack of temporal concurrence could, nonetheless, introduce a historical bias. Although similar assays were used, measurements in the BASUN and WHO MONICA cohorts were obtained years apart, which could introduce systematic bias if protocols changed over time.

There was also a significant age difference between the groups, and although this was adjusted for, residual confounding may remain. Age is a known risk factor for vitamin D deficiency and is typically associated with higher PTH.[143] However, the older reference group in Study I did not show lower vitamin D or higher PTH concentrations, suggesting that age is unlikely to have contributed to an overestimation of differences.

Regarding missing data, characteristics were similar between completers and those lost to follow-up. However, the latter may differ in unmeasured ways, such as dietary preferences, treatment dissatisfaction, and supplement adherence, which could influence the nutritional outcome.

PAPER III

RESULTS

The main analyses included 8399 individuals with type 2 diabetes and obesity who underwent surgical treatment, matched with 8399 unexposed individuals with type 2 diabetes and obesity. Of those treated surgically, 7294 had RYGB and 1105 underwent SG. There were no differences in mean age (49 years) or mean BMI (41 kg/m^2) across the two surgical cohorts and the matched unexposed groups. The prevalence of baseline comorbidities was similar between RYGB, SG, and their matched unexposed individuals, except for hypertension, which was more common in the surgical cohorts. The median follow-up was 9 years for the RYGB cohort and 4 years for the SG cohort. For a full overview of all baseline characteristics of the study, refer to Table 1 and Supplementary Table S3 in the accompanying documentation for Paper III.

In the first two years, total weight loss was greater and HbA1c levels were lower after RYGB and SG than in matched unexposed individuals (*SMD* >0.1). However, over the longer follow-up, there was a slight increase in body weight and a rise in HbA1c in both surgical cohorts.

LONG-TERM OUTCOMES AFTER ROUX-EN-Y GASTRIC BYPASS

Following RYGB, the incidence rates of all-cause mortality, cardiovascular death, cardiovascular disease, chronic kidney disease, diabetic microvascular complications, and cancer were significantly lower than in unexposed individuals. The relative risk reduction for these events ranged from 38% for all-cause mortality (aHR 0.62; 95% CI 0.51–0.71, *adjusted p* < 0.001) to 51% for heart failure (aHR 0.49; 95% CI 0.42–0.57, *adjusted p* < 0.001) (**Figure 3**).

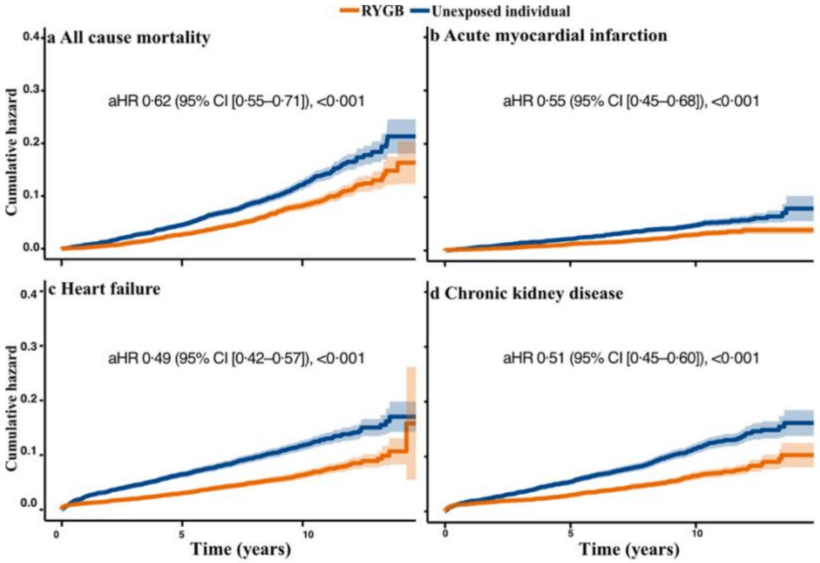

Figure 3. Kaplan-Meier curves for cumulative incidence of outcomes in individuals with type 2 diabetes and obesity undergoing Roux-en-Y gastric bypass (RYGB) compared with matched unexposed individuals. (A) All-cause mortality. (B) Acute myocardial infarction. (C) Heart failure. (D) Chronic kidney disease. Shaded areas represent 95% confidence intervals (CI). Adjusted hazard ratios (aHR) were estimated using Cox proportional hazards models. *Reproduced from Mejaddam A et al., 2025, licensed under CC BY.*

The risk of malabsorption and micronutrient deficiency was twice that of unexposed individuals (aHR 2.00; 95% CI 1.76–2.28, *adjusted* $p < 0.001$). The risk of alcohol use disorder was almost three times higher after RYGB, with an adjusted HR of 2.82 (95% CI 2.37–3.36, *adjusted* $p < 0.001$) (**Figure 4**).

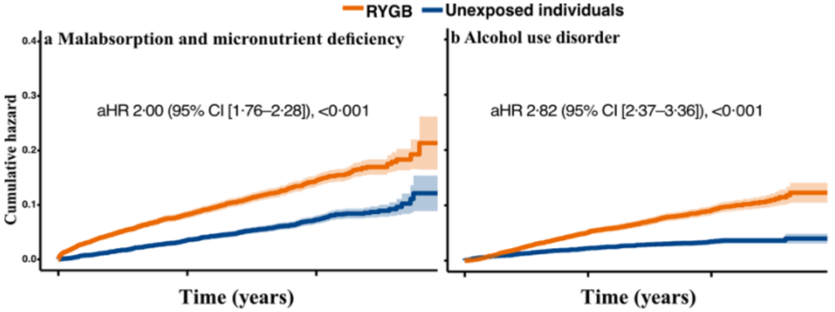

Figure 4. Kaplan–Meier curves for cumulative incidence of malabsorption and micronutrient deficiency and alcohol use disorder in individuals with type 2 diabetes and obesity undergoing Roux-en-Y gastric bypass (RYGB) compared with matched unexposed individuals. (A) Malabsorption and micronutrient deficiency. (B) Alcohol use disorder. Shaded areas represent 95% confidence intervals (CI). Adjusted hazard ratios were estimated using Cox proportional hazards models.*Reproduced from Mejaddam et al., 2025, under CC BY.*

The incidence of specialised care for depressive and anxiety disorders, gastrointestinal disorders and surgical complications was also significantly higher after RYGB (*p<0.001)*. The corresponding number-at-risk is presented in the supplementary material of Paper III.

LONG-TERM OUTCOMES AFTER SLEEVE GASTRECTOMY

Regarding overall mortality, cardiovascular disease and renal health, no risk reduction was observed following SG compared with unexposed individuals (**Figure 5**). There was, however, a lower risk of diabetic microvascular complications (aHR 0.66; 95% CI 0.51-0.84; *adjusted p* < 0.001) and hypertension (aHR 0.66; 95% CI 0.54-0.79; *adjusted p* <0.001) following SG.

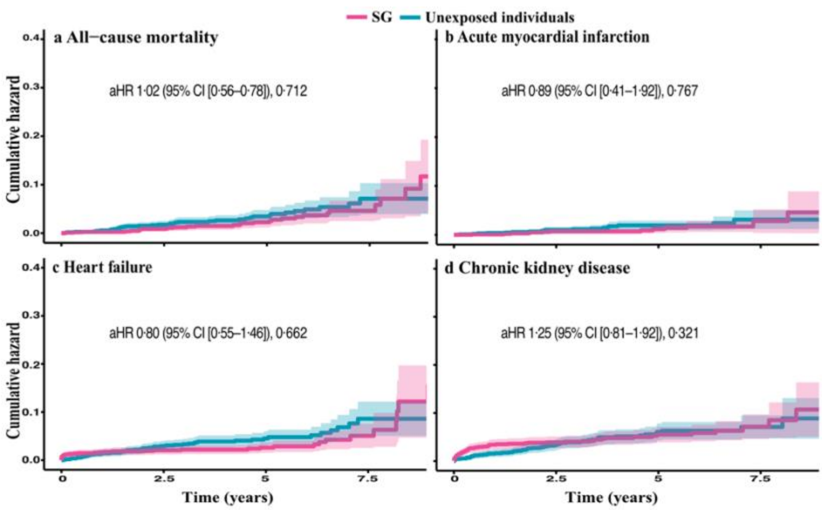

Figure 5. Kaplan–Meier curves for cumulative incidence of outcomes in individuals with type 2 diabetes and obesity undergoing sleeve gastrectomy (SG) compared with matched unexposed individuals. (A) All-cause mortality. (B) Acute myocardial infarction. (C) Heart failure. (D) Chronic kidney disease. Shaded areas represent 95% confidence intervals (CI). Adjusted hazard ratios (aHR) were estimated using Cox proportional hazards models. *Reproduced from Mejaddam et al., 2025, under CC BY.*

Similar to RYGB, the risk of malabsorption and micronutrient deficiency was twice that of unexposed individuals (aHR 2.36; 95% CI 1.37–4.08; *adjusted p* < 0.001) (**Figure 6**). However, SG did not increase the long-term risk of alcohol use disorders or depression compared with unexposed individuals. In relation to gastrointestinal disorders and surgical complications, only the risk of specialist care for abdominal pain was significantly higher after SG (aHR 1.59; 95% CI 1.22-2.08; *adjusted p* < 0.001). The corresponding number-at-risk is presented in the supplementary material of Paper III.

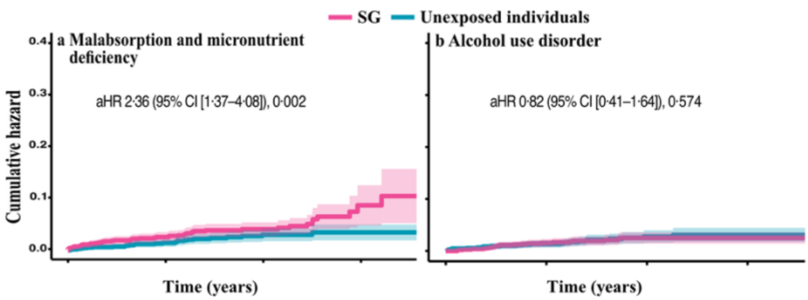

Figure 6. Kaplan–Meier curves for cumulative incidence of selected adverse outcomes in individuals with type 2 diabetes and obesity undergoing sleeve gastrectomy (SG) compared with matched unexposed individuals. (A) Malabsorption and micronutrient deficiency. (B) Alcohol use disorder. Shaded areas represent 95% confidence intervals (CI). Adjusted hazard ratios (aHR) were estimated using Cox proportional hazards models. *Reproduced from Mejaddam A et al., 2025, licensed under CC BY.*

COMMENTS ON PAPER III

According to the second Diabetes Surgery Summit, RYGB and SG are considered viable options for achieving long-term weight and glycaemic control and for reducing the risk of microvascular complications and cardiovascular disease; however, reservations remained due to the limited availability of long-term studies on the efficacy of SG.[59] In this large, nationwide matched study, only RYGB, and not SG, was associated with sustained reductions in overall mortality, cardiovascular mortality, and adverse cardiovascular and metabolic events during up to 14 years of follow-up. This was observed despite similar reductions in weight and HbA1c for RYGB and SG within 2-5 years. However, the benefits associated with RYGB must be weighed against the associated higher long-term burden of nutritional, psychiatric and gastrointestinal disorders.

To contextualise these findings, several methodological considerations should be acknowledged. The ability to study large, well-defined populations over extended follow-up periods, including a comprehensive set of individual-level parameters, would not have been possible without the Swedish national and quality registries. Nevertheless, the registries can lack granular clinical information essential for disease-specific interpretations.

Surgical selection can be influenced by factors not always captured in registries, such as clinical judgment, frailty, individual preference and motivation, all of which could affect comparative outcomes. Matching on BMI, age, and sex does not equate to matching on overall health burden and cannot fully address residual confounding. Previous studies have shown that individuals seeking weight-loss treatment more often report a lower quality of life than weight-matched populations, which may also influence subsequent outcomes.[44,47] In contrast, surgically treated individuals in the present study exhibited several indicators of higher health literacy, such as higher income, higher education, and higher rates of civil partnership. Although these factors were adjusted for, residual confounding and a potential healthy-adherer effect may still have influenced outcomes such as mortality, cardiovascular or metabolic disorders.

From an analytical perspective, relying exclusively on baseline values does not account for temporal changes in covariates and how they may relate to survival outcomes.[144] For example, weight loss or regain, diabetes remission or relapse, and changes in pharmacotherapies (e.g., statins, antihypertensive treatment, incretin-based therapies) may occur during follow-up and act as mediators of long-term outcomes. Although sparse observations at the end of follow-up were considered a likely contributor to violations of the proportional hazards assumption in some models, time-varying covariates could also have influenced the results and the interpretation of the effects of RYGB and SG on the different outcomes.

SG was more commonly performed in later calendar years, which may have coincided with advances in diabetes and cardiovascular care, including increased use of SGLT-2 inhibitors and GLP-1 analogues among individuals with type 2 diabetes and obesity. This temporal change could reduce differences between SG and the unexposed group and partly explain the lack of observed benefit for SG. In addition, the shorter follow-up duration and smaller sample size in SG compared with RYGB may limit statistical power for some outcomes. Nevertheless, a mean follow-up of four years remains relatively long, and a sample size of 1105 individuals is substantial for studies evaluating cardiovascular endpoints.[145] Sensitivity analyses in Study III, restricted to four years, showed no difference in mortality or cardiovascular estimates. Furthermore, the limited effects of SG on hard cardiovascular outcomes and mortality observed in the present study should be considered in the context of emerging evidence, including recent RCTs such as Oseberg, SleeveBypass and SM-BOSS, which demonstrated greater reductions in metabolic risk with RYGB than with SG up to ten years after surgery.[76,77,146] Beyond issues related to follow-up and power, heterogeneity in exposure may also have influenced the findings. A small number of individuals in the SG cohort later underwent RYGB and were not excluded from the analyses, which may overestimate SG effects, particularly for certain complications.

At the level of outcome definition, several additional limitations should be considered. Individuals undergoing bariatric surgery may be subject to more specialist referrals and more readily diagnosed with conditions such as malabsorption, even in the absence of objective confirmation, given its well-recognised association with bariatric surgery. Consequently, higher incidence rates of certain diagnoses may partly reflect differential assessment practices.[147] While the NPR has demonstrated high overall accuracy, misclassification and underreporting remain more common for certain conditions.[106] Furthermore, multiple ICD codes related to different diagnoses were aggregated into composite endpoints in the study, which may temper the interpretation of clinical impact.

Finally, when interpreting causal inference, the observational design, the inclusion of multiple outcomes with diverse pathogeneses and relationships to type 2 diabetes, obesity, and metabolic bariatric surgery, and the lack of adjustment for multiple comparisons should be considered. The study was also not designed to directly compare RYGB with SG, so any such comparison should be interpreted with caution. Although the NDR and SOReg are internationally recognised quality registers that support the external validity of the findings, particularly in healthcare systems with similar structures and follow-up practices, race and/or ethnicity are not recorded, which may limit the generalisability to populations with different ethnic constellations.

PAPER IV

RESULTS

This study enrolled the same 8399 individuals who had undergone RYGB and SG in Study III. The primary analysis included 5253 individuals, as they had weight data approximately 5 years after surgery. The event of a favourable composite outcome occurred in 1825 individuals (35%), of whom a greater proportion had undergone RYGB (96 vs 91%) and were female (63% vs 59%) than in the cohort with the unfavourable composite outcome. There was no difference in baseline BMI (median 40.4 kg/m^2) between those with a favourable and unfavourable outcome.

Analyses comparing individuals included in the primary analysis with those excluded due to missing 4-6-year follow-up body weight measurements showed a substantial imbalance in diabetes duration (SMD 0.38), with shorter duration among excluded individuals. HbA1c levels and smoking prevalence were also lower, and a higher proportion of individuals had undergone SG, although RYGB remained more common. Other baseline differences were small.

MODEL PERFORMANCE AND FEATURE IMPORTANCE: MAIN MODEL (PRIMARY COMPOSITE OUTCOME)

The six candidate models, developed using 96 features, achieved similar ROC-AUC scores of approximately 0.65 at the initial phase. The XGB model was chosen for further training and model development. The final XGB model demonstrated a modest ROC-AUC of 0.65 [95% CI 0.61-0.68] and a PR-AUC of 0.46 [95% CI 0.41-0.51]. Brier score was 0.21 [95% CI 0.20-0.22], indicating modest probabilistic accuracy.

In the SHAP analysis, the top 10 predictors for the main model, ranked by importance, included surgery type (SG), depression, anxiety disorders, sedative and hypnotic medications, gastrointestinal reflux and ulceration, employment status (sick leave), functional gastrointestinal disorders, antidepressant drugs, body weight, and low-density lipoprotein (LDL) cholesterol. For the binary features, the SHAP distributions showed no clear separation.

MODEL PERFORMANCE AND FEATURE IMPORTANCE: DOMAIN-SPECIFIC MODELS (SECONDARY OUTCOMES)

The lowest discriminative power was observed in the model for 5-year weight loss, with an ROC-AUC of 0.60 [95% CI 0.57-0.63]. The other three models demonstrated higher discriminative capability, with the highest in the depression and anxiety model (ROC-AUC of 0.93 [0.88–0.97]).

Similar to the main model, there was no clear separation in the SHAP distribution for binary features in the weight-loss model. In contrast, the other three domain-specific models demonstrated clear directional effects for many features. The most important features for all models fell into four clinical domains: psychiatric comorbidities, metabolic markers, somatic burden, and sociodemographic factors.

COMMENTS ON PAPER IV

In recent years, an increasing number of studies have applied ML to optimise outcomes in metabolic bariatric surgery, predominantly focusing on weight loss and short-term surgical complications. However, these outcomes remain difficult to predict. As highlighted in a review by Bektaş et al., this challenge arises from the heterogeneous nature of the underlying risk determinants, which range from socioeconomic factors to biological characteristics.[148] Furthermore, there are no algorithms to identify individuals at both high risk of suboptimal weight loss and postoperative complications.[148] Moreover, few studies have examined how preoperative patterns contribute to the predictions made by these complex models.

Against this background, ML was employed to enable the structured exploration of the high-dimensional registry data and to examine preoperative features associated with the predefined multidimensional net clinical benefit over long-term follow-up. Study IV was not intended to yield a clinically actionable predictive model, and the results should not be interpreted as such. Nevertheless, standard modelling procedures for internal validation and performance assessment were implemented to ensure methodological robustness. Although the dataset was comprehensive, the final modest discriminative performance of the composite model likely reflects the study design, which prioritised the clinical relevance of the outcome over algorithmic performance, as well as the inherent limits of predicting long-term outcomes using preoperative data alone.

To facilitate interpretation of the predictions, SHAP analyses were used to examine feature contributions across the XGB models and to assess whether these contributions were reasonable given the clinical background.[123] It is important to emphasise that SHAP describe what the model is doing within the framework of the data on which it has been trained; it doesn't make causal inference, nor does it necessarily always reveal a direct mechanism.[122,123] While SHAP analyses identified several clinically relevant domains in Study IV, the multidimensional composite did not demonstrate clear separation in SHAP distributions. This likely reflects several factors, including modest overall discriminative ability, heterogeneous mechanisms underlying the domains incorporated into the composite endpoint, and the influence of unmeasured variables on long-term outcomes.[85]

An interesting observation was that several features showed different SHAP associations across the domain-specific models. This heterogeneity can be expected, as individual features likely play distinct roles within the different pathophysiological frameworks underlying the outcomes. In some cases, features could act through a specific harm pathway, such as depression and anxiety, which were among the most influential predictors in the alcohol and substance use model.[149,150] This is consistent with a well-known positive association between depressive symptoms and anxiety with alcohol and other substance use disorders.[149,150] By contrast, in the weight-loss model, depression did not show a clear directional effect, likely reflecting the complex and inconsistent relationships between depression, type 2 diabetes, and weight loss.[151,152] The effect of depression on weight loss may be mediated through unmeasured features, such as disease severity, behavioural patterns, and engagement with long-term follow-up.[153]

In contrast to psychiatric variables, certain metabolic features showed associations in the SHAP analyses that were less intuitive and warrant explanation. Diabetes duration was one such example. Longer diabetes duration was associated with a higher predicted probability of an optimal weight response. These findings contrast with prior studies in more heterogeneous populations with obesity, where longer diabetes duration has generally been associated with suboptimal weight outcomes.[154] In this case, it is important to understand the role of SHAP values, which reflect the contribution of diabetes duration conditional on all other covariates. In the case of diabetes duration, the weight-loss model may have captured a selected subgroup who survived long enough to be eligible for surgery, were more likely to undergo RYGB or had better adherence or metabolic profile postoperatively. By contrast, in the alcohol/substance use model, shorter diabetes duration co-occurred with higher body weight, which may also reflect individuals who were more likely to undergo RYGB, a procedure known to increase the risk of alcohol use disorder through changes in gut-hormonal and pharmacokinetic pathways.[155]

The identified features should not be interpreted as reasons to exclude from surgery. Rather, they highlight preoperative psychosomatic and metabolic complexity that may require more comprehensive preoperative screening and personalised long-term follow-up if surgically treated. Additionally, SHAP outputs can be regarded as generators of clinical hypotheses, indicating where deeper phenotyping or prospective studies may be warranted.

While this study employed a comprehensive dataset, detailed information on genetics, eating behaviours and micronutrient status, as well as standardised questionnaires for psychiatric disorders and HRQoL, was unavailable, which could affect the models' predictive performance. Some of the methodological considerations discussed in Paper III also apply here.

The primary model was furthermore audited for fairness with respect to sex, but not age or ethnic groups, which could affect the results unfavourably against certain age and ethnic minorities. While such analyses are essential for prediction tools, they were deemed beyond the scope of this exploratory study.

DISCUSSION

All four papers comprising this thesis drew on extensive real-world data from well-characterised cohorts, including BASUN, WHO MONICA, NDR and SOReg. These data sources enabled the investigation of both detailed clinical characteristics and long-term outcomes in large populations with obesity with and without type 2 diabetes. Importantly, the analyses were conducted in the context of relevant comparison groups of population-based controls and individuals with obesity not undergoing surgery, thereby providing more reliable estimates of the clinical outcomes and treatment effects addressed.

Type 2 diabetes, being one of the diseases most strongly associated with obesity, has become a central component in guidelines for the surgical management of obesity. Current guidelines state that medical providers should consider surgery as a treatment option if glycemic control is inadequate, even in individuals with a BMI as low as 30 kg/m^2.[156] In Study III, RYGB was clearly associated with reduced long-term risk across multiple clinically relevant outcomes, including mortality and cardiovascular disease, in individuals with obesity and type 2 diabetes. Notably, corresponding benefits were not observed after SG, an important observation given that SG has gained traction over the past decade and is widely used, even among individuals with type 2 diabetes. The mechanisms underlying weight loss and glycaemic improvement following RYGB and SG are still not fully elucidated.[13] However, evidence suggests that multiple factors beyond malabsorption and restriction play a role, including changes in lifestyle behaviour, neuroendocrine signalling, bile acid levels and the gut microbiome, which appear more pronounced after RYGB.[13,157] Furthermore, bypass of the upper gastrointestinal tract has been proposed to induce weight-loss independent improvements in glycaemic control.[15] From an effectiveness perspective, RYGB remains the surgical procedure with the most robust long-term evidence in individuals with type 2 diabetes.[146]

The findings of this thesis are particularly relevant in light of the expanding availability of pharmacotherapies. GLP-1 receptor agonists, dual GIP and GLP-1 agonists, and, more recently, unimolecular GLP-1 and amylin receptor agonists have demonstrated up to 25% weight loss in populations with and without type 2 diabetes.[53,54,158] In addition, a meta-analysis of incretin-based therapies indicates reductions in cardiovascular events and chronic kidney disease over a median follow-up of two years.[55] Although there are a few comparative studies with metabolic bariatric surgery, which preclude firm conclusions regarding efficacy differences, some have shown that surgery is associated with a lower risk of metabolic and cardiovascular outcomes.[159,160]

Nevertheless, the availability of minimally invasive pharmacotherapy alternatives may reshape future treatment algorithms, particularly for individuals with lower BMI or heightened vulnerability to surgical complications. For SG, it could retain a place among selected individuals because of a lower risk of certain long-term complications compared with RYGB, or because of individual or surgeon preference. It may also remain relevant in settings where access to incretin-based therapies is limited.

One such vulnerability is the risk of nutritional complications, which was observed across the studies of this thesis and was not limited to surgical weight-loss treatment. This is consistent with emerging evidence that the more novel pharmacotherapies may also be associated with a higher risk of nutritional deficiency due to reduced nutrient intake and limited dietary diversity.[161] Studies II and IV indicate that individuals with unfavourable somatic and metabolic phenotypes may be particularly susceptible. For vitamin D status, however, improvements were observed following weight loss when supplementation was adhered to, even if S-25(OH)D levels were not optimal, underscoring the importance of both adequate dosing and continued follow-up. In contrast, the risk of anaemia due to micronutrient deficiency remained clearly elevated after RYGB in study III. Data from the BASUN project demonstrated progressive iron deficiency and anaemia over five years of follow-up despite reported supplementation use, indicating that iron homeostasis is particularly sensitive to the anatomical changes of RYGB and may require higher supplementation doses.[29,162] Albeit supplementation guidelines were revised in 2024 with recommendations on higher doses of vitamin D and calcium, iron dosage remained unchanged, a decision that warrants reconsideration in light of emerging evidence. In addition, nutritional monitoring and supplementation should not be confined to individuals undergoing metabolic bariatric surgery, but should be systematically considered across all weight-loss treatments. Evidence from Paper II and a study by Lenér et al. on the BASUN cohort further demonstrates that individuals with obesity have poorer micronutrient status than the general population, suggesting that nutritional assessment should include individuals with obesity more broadly.[29,30]

Mental health outcomes represent another area of vulnerability. After RYGB in particular, the risk of deterioration in depression and anxiety, as well as the development of alcohol and other substance use disorders, remained elevated over time. The co-occurrence of these conditions is well-recognised and associated with more complex clinical presentations and increased morbidity and mortality.[163,164] While depression and anxiety are risk factors for alcohol use disorders, RYGB appears to increase the risk of problematic alcohol use through independent physiological mechanisms, including changes in neural hormonal gut-brain pathways and altered pharmacokinetics, which may reinforce alcohol-dependent behaviours.[150,155] Findings from Study IV further emphasise the importance of psychiatric health, as predictors related to depression and anxiety consistently emerged across models examining long-term outcomes. These observations support a more structured psychiatric assessment before and after surgery as part of a lifelong follow-up to minimise the risk of development and deterioration of psychiatric diseases.

Individuals seeking weight loss treatment differed from the general population already at baseline, with impaired HRQoL, psychiatric morbidity, general illness and vitamin D deficiency. These vulnerabilities may be particularly pronounced among individuals with type 2 diabetes, and if left unaddressed, they may be amplified rather than mitigated by surgical intervention. Several adverse outcomes identified in this thesis, therefore, appear attributable not only to surgical technique but also to discontinuities in long-term care, highlighting system-level shortcomings rather than isolated clinical failures.

These findings are especially relevant in the context of the WHO's classification of obesity as "a chronic, relapsing disease arising from complex interactions".[1] More recently, a commission proposed the concept of "clinical obesity" as a chronic illness, emphasising the "objective clinical manifestation of obesity-related organ dysfunction or alterations of daily activities" directly induced by excess adiposity.[7] Conceptualising obesity in this way has implications not only for individual experience but also for healthcare systems to provide structures for long-term care. In individuals with type 2 diabetes, surgery-induced remission of diabetes may result in loss of follow-up previously linked to diabetes care. Although weight regain or diabetes relapse were not primary outcomes of this thesis, existing evidence indicates that both remain long-term challenges.[165] This reinforces the need for sustained monitoring to identify these individuals early and introduce preventive strategies, including pharmacotherapies, before relapse occurs.

Irrespective of disease classification, obesity continues to be a major risk factor for a wide range of infectious and noncommunicable diseases, including increased mortality. The present thesis confirms that surgical weight-loss treatment, specifically RYGB, is an effective intervention for reducing the risk of obesity-related diseases. At the same time, it highlights the drawbacks, including non-negligible deterioration in nutritional, psychiatric, and gastrointestinal health that persists over time and which can be just as debilitating on health and quality of life as cardiovascular diseases. Taken together, the findings of this thesis support a move toward precision-based obesity management, in which long-term effectiveness and safety are evaluated in the context of individual vulnerability, particularly when considering an invasive and permanent treatment. A core requirement should be a more comprehensive and structured assessment of individuals seeking help with weight loss that includes systematic evaluations of HRQoL, psychiatric and nutritional status, and lifestyle habits, rather than treating these elements as discretionary.

"Care more particularly for the individual patient than for the especial features of the disease."

William Osler, 1899

CONCLUSION

This thesis contributes to a deeper understanding of the broad clinical effects of surgical weight-loss treatment in real-world populations, with particular attention to type 2 diabetes and treatment-related vulnerabilities. Individuals seeking specialist weight-loss care were characterised by higher morbidity, impaired general, mental and physical HRQoL, and poorer vitamin D status compared with the general population. Although surgical treatment can significantly reduce cardiometabolic risks, it does not completely eliminate pre-existing vulnerabilities and, in some domains, is associated with new lifelong risks. Together, these findings support a life-course perspective in which obesity represents an ongoing risk trajectory rather than an isolated condition that a single weight-loss intervention can entirely reverse.

Vitamin D status may improve with weight loss when accompanied by adequate supplementation; however, the risk of micronutrient deficiencies persists over time after metabolic bariatric surgery. Non-surgical weight-loss treatment may also affect nutritional vulnerability, highlighting the need for regular, lifelong monitoring and adherence across all weight-loss strategies. Psychiatric disorders may also deteriorate or develop over the long term following surgery, also emphasising the importance of structured lifelong assessment alongside evaluations of weight, glycaemic, and nutritional status.

Roux-en-Y gastric bypass, rather than SG, remains an effective option for achieving mortality, metabolic and cardiovascular benefits in individuals with type 2 diabetes, but it is associated with sustained nutritional, gastrointestinal, and psychiatric risks. Given the potentially limited long-term benefit of SG, its role in this population should be evaluated alongside other non-surgical therapies with more favourable risk-benefit profiles. Importantly, optimal weight loss and diabetes remission should not signal the end of clinical surveillance, as long-term risks persist. Patient education about the chronic nature of obesity, the long-term consequences of surgery, and the importance of lifelong follow-up is essential.

Finally, individuals with less favourable metabolic, somatic, and psychiatric profiles appear more susceptible to suboptimal clinical responses and adverse long-term outcomes after metabolic bariatric surgery, emphasising the importance of personalised assessment and follow-up. However, overall discrimination in the ML models was modest, underlining the challenge of predicting multidimensional long-term outcomes from preoperative registry-based data alone.

FUTURE PERSPECTIVES

This thesis demonstrates that treatment selection based on average effectiveness does not necessarily yield optimal outcomes for the individual. As the range of available weight-loss interventions continues to expand, future strategies should move beyond a "one-size-fits-all" approach and focus on identifying for whom each treatment is safe and most effective. Furthermore, as the range of weight-management therapies grows, it becomes increasingly important to adopt more structured HRQoL assessments. These can assist individuals and clinicians in distinguishing between treatments that have similar weight-loss outcomes but differ in side-effect profiles.

Although artificial intelligence with ML has shown promise in several areas of medicine, its application to weight-loss treatment remains challenging, given the complex interplay of factors that contribute to obesity and treatment responses. When machine learning models are applied to specific outcome entities, such as diabetes remission, performance is more promising. Further advances will likely require the development of databases that incorporate richer phenotypic characterisation, longitudinal trajectories, and biological and genetic markers, capturing the multifactorial mechanisms underlying the rising obesity epidemic. Such a resource would enable a more comprehensive study of characteristics associated with differential treatment responses and long-term outcomes. Since obesity is a major risk factor for infectious disease severity, non-communicable diseases, cancer, psychiatric disorders, and surgical complications, investment in this area should be a priority. A more nuanced understanding of how metabolic phenotype, comorbidity burden, psychosocial factors, and genetic susceptibility modify treatment response will be central to advancing personalised metabolic care.

The BASUN project is promising, as it includes more granular data on well-being, mental health, gut microbiota, lifestyle and dietary habits, nutritional status, and supplementation and pharmacotherapy. Five-year follow-up data are available, with the ten-year follow-up approaching. Applying and comparing different ML models to these data, alongside careful evaluation of model performance and interpretability, is a logical next step. Linking advanced-phenotyped cohorts, such as BASUN, with national registry data may further facilitate this endeavour.

As the use of modern incretin-based therapies continues to rise and longer-term real-world data become available, national quality registries such as SOReg and the NDR offer valuable opportunities to conduct comparative effectiveness studies to examine treatment outcomes in routine practice. In addition, future studies should evaluate the role of pharmacotherapies as adjuncts to surgical weight-loss interventions, particularly regarding long-term metabolic control, well-being and psychiatric health.

USE OF GENERATIVE AI

Generative AI tools (ChatGPT 5.2 and Grammarly Pro) were used throughout this thesis to support the writing process. The primary purpose was to enhance clarity, coherence, and consistency. ChatGPT was used to help with the outline and to refine language, phrasing, and readability. Grammarly Pro was used for grammar, spelling, and stylistic editing. All scientific content, including analyses, interpretations, and conclusions, was developed and critically reviewed by the author, who assumes full responsibility for its accuracy and integrity.

ACKNOWLEDGEMENT

This thesis would not have been possible without the support and encouragement of many. I would like to express my sincere gratitude to all who contributed along the way, and especially to my supervisors for their guidance and mentorship throughout this journey.

Björn Eliasson, my main supervisor, thank you for giving me the opportunity to pursue a PhD. You created an environment where I felt supported and able to grow as a researcher, generously sharing your knowledge along the way. You were always available when guidance was needed, and the trust you placed in me to work independently made this journey manageable and rewarding.

Kerstin Landin-Wilhelmsen, my co-supervisor, you opened the door to the world of research for me when I was a resident. Your enthusiasm and encouragement have meant a great deal to me, and I always leave our meetings with renewed confidence. Thank you for allowing me to use your unique data from the WHO MONICA project.

Gudrún Höskuldsdóttir, my co-supervisor. Thank you for your wonderful support and for our many great conversations about research and life. You made this journey, especially the statistics, far less intimidating. Who would have thought it could be fun? If it had not been for you, I would never have dared to embark on the journey of learning R and coding.

To all my co-authors, thank you for the invaluable feedback and collaboration. Special thanks to *Hanne Carlsen, Moa Lugner, and Emily Krantz* for your generous help with statistical analyses across the different papers.

Thank you to *Karin Mossberg* and everyone at BASUN for creating an outstanding project that enabled high-quality research. I thank *Penelope Trimpou* for conducting the thorough examinations in the follow-up study of the WHO MONICA project. I would also like to thank *Stella Nakate* and everyone involved in the WHO MONICA project for coordinating and monitoring the follow-ups. I am grateful to *Katarina Eeg-Olofsson* and all the colleagues at NDR for maintaining a remarkable national register and allowing me to work with it. I am also grateful to *Johan Ottosson* and *Erik Stenberg*, the SOReg registry holders in Örebro, for your invaluable surgical perspective along the way, which has greatly strengthened this work. Thank you to everyone at SOReg for maintaining such an exceptional quality registry, which has been invaluable for this work.

To my wonderful colleagues in the Departments of Cardiology and Medicine, Geriatrics and Emergency Medicine at the Sahlgrenska University Hospital/Östra, thank you for creating such a supportive and engaging workplace that I am proud to be part of. I am a better clinician thanks to the knowledge you so generously share and the many valuable discussions we have.

A special thank you to the head of Cardiology, *Erik Thunström*. You provide an excellent environment for both clinical work and research, and gave me the opportunity to pursue Cardiology, for which I am very grateful. Thank you for demonstrating what inspiring leadership looks like and for encouraging me to aim higher by giving me new opportunities along the way.

Sofia Ekdahl, head of the Department of Medicine, Geriatrics and Emergency Medicine, thank you for making this department such a supportive place for both clinical work and research. I would also like to thank my former chief, *Jerzy Kaczynski*, for giving me the time when I first embarked upon my research journey. My sincere thanks to the head of the Department of Medicine at the Sahlgrenska University Hospital, *Lena Bokemark*, for promoting a strong research environment.

To the *coaches* at *Totus Fitness*, thank you for making training one of the best parts of my day.

To my friends, I am incredibly lucky to have you all in my life. *May, Shukri, Shamso, Amina,* and *Balqisa,* thank you for welcoming me into your family, and for the warmth and generosity you have always shown me. *Hanna, Hibo, Zena, Sidra,* and *Aysel,* thank you for your constant support and friendship over the years. Thank you, *Ala Jelil*, for making the cover for this thesis. A special thank you to *Amina* for the invaluable advice throughout this journey, to *Aysel* for always listening and encouraging me to keep going, and to *May* for being there in every sense. The countless hours we spent on Zoom during the final months of writing made this thesis possible and the process far more enjoyable.

To my siblings, *Ali, Assem, Sondes* and *Sara*, you are my dream team and my role models. I find great comfort in knowing I can always turn to you. *Ali,* thank you for always making time to read what I've written from the very beginning and for introducing me to the world of American national parks and forests. *Delia* and *Bushra,* thank you for always being such amazing sisters-in-law. To my cousin *Maha,* thank you for being such a special part of my life. To all my adorable nieces and nephews, you have made my life as your aunt so much richer and brighter.

Finally, to my heroes and biggest supporters, my father, *Younes,* and my mother, *Masouda.* You made me who I am today. This thesis is for you.

إلى والديّ الحبيبين
شكراً لدعمكما ومحبتكما الدائمة
هذه الأطروحة لكما

This thesis and the studies herein were supported by grants from the Department of Medicine, Sahlgrenska University Hospital/Östra Hospital, the Swedish Heart and Lung Foundation, the Novo Nordisk Foundation, the Gothenburg Society of Medicine, and the Swedish state under the agreement between the Swedish government and the county councils, the ALF-agreement.

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