Obesity, Weight Loss and Cardiovascular Risk

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To my *Spiritual Guardian,*

"The most valuable of treasures are hearts filled with love"

Moulana Ali bin Abi Talib[AS]

ABSTRACT

Background: The global prevalence of obesity is on the rise, contributing to an increased incidence and prevalence of cardiovascular morbidity and mortality. Obesity has adverse effects on cardiac structure and function, directly through a hemodynamic overload, and indirectly through cardiovascular risk factors and low-grade inflammation. Nevertheless, epidemiologic studies have found that once cardiovascular disease has developed, people with obesity may experience better prognosis than those with normal weight; a phenomenon termed "the obesity paradox".

Aims: The objectives of the present thesis were: 1) to investigate the effect of surgically induced long-term weight loss on the incidence of atrial fibrillation and heart failure; 2) to study possible mechanisms linking obesity to the development of heart failure; and 3) to examine the prognostic significance of different BMI categories on outcomes in a cohort of patients with ST-elevation myocardial infarction (STEMI) treated with percutaneous coronary intervention (PCI).

Methods: We analyzed data from the Swedish Obese Subjects (SOS) study, a prospective matched intervention study comparing bariatric surgery (n=2,010) and conventional obesity treatment (n=2,040). The SOS data was merged with the Swedish National Patient Register (NPR) and with the Cause of Death Register (COD). Data from the SOS obese control group were used to study the link between obesity and heart failure (n=2,040). Data from the Swedish Registry of Catheter-borne Coronary Vessel Surgery (SCAAR) (n=25,384) were merged with the COD Register to study the prognostic significance of different BMI classes.

Results: Surgically induced weight loss resulted in a significantly lower incidence of atrial fibrillation and heart failure during long-term follow-up. Atrial fibrillation and myocardial infarction, as time-dependent variables, were strongly related to incident heart failure. In patients with STEMI treated with PCI, those with BMI > 30 kg/m^2 had the best outcome in unadjusted analysis, but after adjustment for age and sex individuals with BMI 25-30 kg/m^2 displayed the best prognosis. Underweight patients with BMI < 18.5 kg/m^2 had the highest 30-day and 1-year mortality in both unadjusted and adjusted analysis.

Conclusions: In people with severe obesity, bariatric surgery induced a substantial and a sustained weight loss which resulted in a lower incidence of atrial fibrillation and heart failure. Atrial fibrillation is probably reflected by diastolic dysfunction and myocardial infarction is likely to be related to systolic dysfunction, proposing two different mechanistic pathways for the development of heart failure. Overweight displays the lowest risk for 30-day and 1-year mortality after PCI treatment of STEMI.

Keywords: obesity, bariatric surgery, atrial fibrillation, heart failure, risk factors, myocardial infarction, ST-elevation infarction.

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Sammanfattning på svenska

Introduktion: Den globala förekomsten av fetma ökar kontinuerligt, vilket bidrar till ökad risk för kardiovaskulär sjuklighet och dödlighet. Fetma har ogynnsam effekt på hjärtats struktur och funktion, direkt genom ökad hemodynamisk belastning, och indirekt via ökad förekomst av kardiovaskulära riskfaktorer och låggradig inflammation. Trots detta så visar epidemiologiska studier att vid etablerad kardiovaskulär sjukdom så har patienter med fetma bättre prognos än de som är normalviktiga; ett fenomen som har benämnts ” fetma paradoxen”.

Syfte: Syftet med denna avhandling var 1) att undersöka effekten fetmakirurgi på förekomsten av förmaksflimmer och hjärtsvikt; 2) att studera möjliga patofysiologiska mekanismer bakom sambandet mellan fetma och hjärtsvikt och 3) att utröna effekten av olika BMI-kategorier på prognosen efter behandling av en ST-höjningsinfarkt (STEMI) med ballongvidgning och anläggning av stent (PCI).

Metod: Vi analyserade data från den pågående Swedish Obese Subjects (SOS) studien, en prospektivt matchad interventionsstudie som jämför fetmakirurgi (n=2010) med konventionell fetmabehandling (n=2040). För att undersöka förekomsten av förmaksflimmer och hjärtsvikt slogs data från SOS ihop med det svenska patientregistret och det svenska dödsorsaksregistret. För att studera sambandet mellan fetma och hjärtsvikt länkades data från SOS kontrollgruppen till samma register. Slutligen, för att undersöka den prognostiska betydelsen av olika BMI-kategorier på 30-dagars och 1-årsöverlevnad efter PCI kopplades data från det svenska coronarangiografi- och angioplastikregistret (SCAAR) till det svenska dödsorsaksregistret.

Resultat: Fetmakirurgi resulterade i långvarig viktnedgång samt lägre förekomst av förmaksflimmer och hjärtsvikt. Förmaksflimmer och hjärtinfarkt som tidsberoendevariabler var starkt relaterade till hjärtsvikt. Patienter med BMI >30 kg/m^2 som behandlades med STEMI hade den bästa överlevnaden i ojusterade analyser, men efter justering för ålder och kön hade de med BMI 25–30 kg/m^2 det bästa utfallet. Magerlagda patienter med BMI <18,5 kg/m^2 hade den högsta 30-dagars och 1-årsdödligheten i både ojusterade och justerade analyser.

Slutsats: Patienter med fetma som genomgår viktreducerande kirurgi uppvisar betydande viktminskning som kvarstår över tid, vilket medför minskad risk för utveckling av förmaksflimmer och hjärtsvikt. Förmaksflimmer är sannolikt relaterat till ökad stelhet i hjärtat (diastolisk dysfunktion) och hjärtinfarkt är kopplad till sämre pumpförmåga (systolisk dysfunktion), vilket indikerar två olika mekanismer som kan ge upphov till hjärtsvikt. Övervikt (BMI 25–30 kg/m^2) uppvisar den lägsta risken för 30-dagars och 1-års mortalitet efter PCI behandling av STEMI.

LIST OF PAPERS

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

I. Jamaly, S. Carlsson, L. Peltonen, M. Jacobson, P. Sjöström, L. Karason, K.

Weight loss by bariatric surgery and the risk of new-onset atrial fibrillation among Swedish Obese Subjects

JACC 2016 Dec; **68** (23): 2 4 9 7 – 25 0 4

II. Jamaly, S. Carlsson, L. Peltonen, M. Jacobson, Karason, K.

Surgical obesity treatment and the risk of heart failure

Eur Heart J.2019; **40**(26): 2131–2138.

III. Jamaly, S. Carlsson, L. Peltonen, Andersson Assarsson, J. Karason, K.

Heart failure development in obesity - *Underlying risk factors, mechanistic pathways and phenotypes*.

Submitted for publication.

IV. Jamaly, S. Redfors, B. Omerovic, E. Carlsson, L. Karason, K.

Prognostic significance of obesity after invasive treatment of ST-elevation myocardial infarction ***Analysis from the Swedish Coronary Angiography and Angioplasty Registry.***

Submitted for publication

TABLE OF CONTENTS

ABBREVIATIONS

Abbreviation	Phrase
AF	Atrial fibrillation
Ang	Angiotensin
BMI	Body mass index
CAD	Coronary artery disease
COD	Cause of death
CRF	Cardiorespiratory fitness
CRP	C-reactive protein
CV	Cardiovascular
CVD	Cardiovascular disease
DSE	Diabetes support and education
DVT	Deep vein thrombosis
FFA	Free fatty acids
FFM	Fat free mass
GB	Gastric banding
GBP	Gastric bypass
GLP-1	Glucagon like peptide-1
HCC	Hepatocellular carcinoma
HDL	High density lipoprotein
HF	Heart failure
HOMA-IR	Homeostasis model assessment of insulin resistance
ICD	International Classification of Diseases
IDF	International Diabetes Federation
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IL	Interleukin
ILI	Intensive lifestyle intervention
IR	Insulin resistance
LDL	Low density lipoprotein
LV	Left ventricular
MetS	Metabolic syndrome
MHO	Metabolic healthy obesity
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NPR	National Patient Register
OA	Osteoarthritis
OSA	Obstructive sleep apnea
PCI	Percutaneous coronary intervention
PE	Pulmonary embolism
PIN	Personal identity number

R-RCT	Registry-based randomized prospective clinical trials
RAAS	Renin angiotensin aldosterone system
RMR	Resting metabolic rate
SCAAR	The Swedish Registry of Catheter-borne Coronary Vessel Surgery
SOS	Swedish obese subjects
STEMI	ST-elevation myocardial infarction
T2D	Type-2 diabetes
TG	Triglycerides
TNF-α	Tumor necrosis factor-alpha
UCR	Uppsala Clinical Research Center
VBG	Vertical banded gastroplasty
VO_2	Oxygen consumption
VTE	Venous thromboembolism
WC	Waist circumference
WHR	Waist hip ratio

INTRODUCTION

"THE GLOBAL OBESITY WARNING"

The incidence of obesity has increased worldwide in an exponential manner with a global prevalence estimated to be 13% (1). This has led the World Health Organization to declare obesity a global epidemic and a worldwide public-health problem (2, 3). Accumulation of body fat is the result of a positive energy balance, which is related to a multitude of causes. Obesity has an impact on quality of life and is associated with frequent occurrence of cardiovascular risk factors (4), co-morbidities (5) and increased mortality (6). Globally, obesity-related mortality, has become higher than death related to starvation. Considerable and sustained weight loss has a beneficial effect on the co-morbidities and reduces mortality (7).

HISTORY

"How the good became ugly then bad" - Garabed Eknoya

Early in the history of human evolution food was made available through hunting and gathering. Collecting food, required a high amount of physical activity and a precarious food supply lead to frequent periods of food shortages. These conditions favoured survival in individuals with the ability to conserve energy in the form of adipose tissue. As such, humans developed control systems that favour energy intake and storage, and reduced energy expenditure.

Later, with the development of agriculture, domestication of animals and the technological advances of the eighteenth century, the food supply increased gradually. Consequently, reduced physical activity and readily accessible food, increased the prevalence of overweight and obesity in the society. During this time the cultural perception of corpulence was considered aesthetically desirable (8).

In the early nineteenth century the adverse medical consequences of obesity started to become apparent. Today, with increasing sedentary behaviour and easily available energy rich food, obesity has reached

epidemic proportions and is one of the leading health threats among the world's population (9).

EPIDEMIOLOGY

Since 1975, the worldwide prevalence of obesity has nearly tripled. In 2016, 39% of adults were found to be overweight, and 13% obese (10). Over the past decades, the world has transitioned from a state where the majority of the population was underweight to a situation in which overweight and obesity have become more common (10). The global prevalence of obesity during a forty-year period between 1975 and 2015 is shown in **Figure 1**.

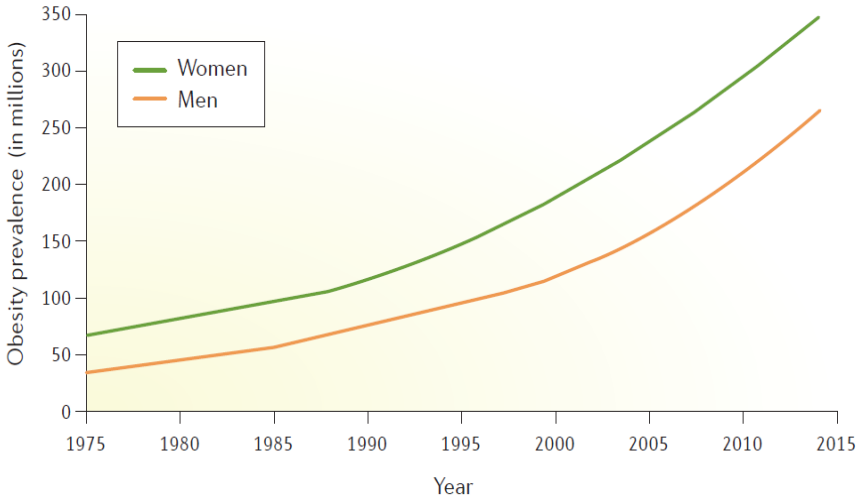

***Figure 1**. Global obesity prevalence between 1975 and 2015(11). Published with permission from Springer Nature.*

OBESITY IN SWEDEN

According to the Public Health Agency of Sweden (*Folkhälsomyndigheten*), the prevalence of overweight and obesity has been slowly rising and now affects approximately 50% of Swedish adults (**Figure 2**). The prevalence of obesity among adults has been estimated to be 15%.

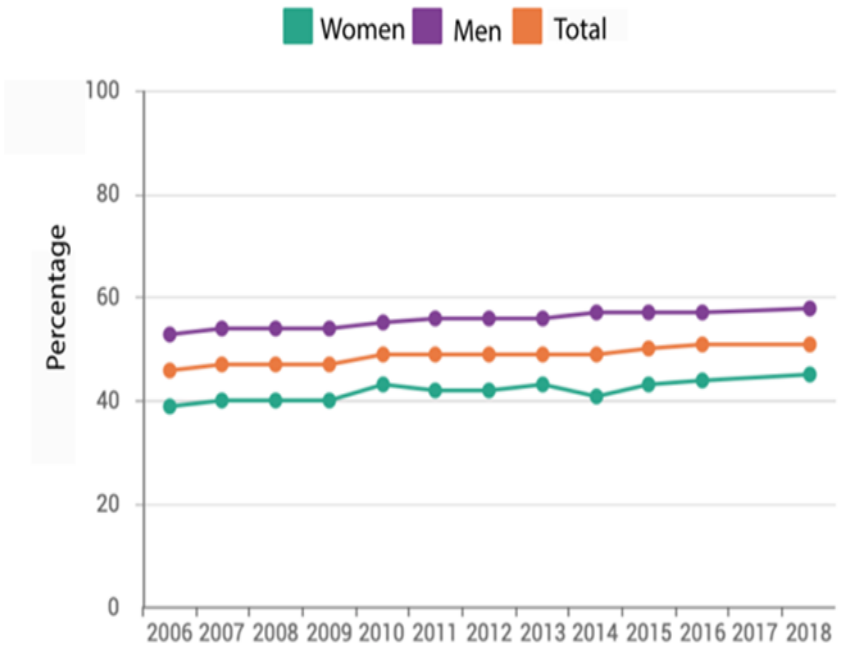

Figure 2. *Prevalence of overweight in adults in Sweden. www.folkhalsomyndigheten.se*

DEFINITION AND ANTHROPOMETRIC MEASUREMENTS

Obesity is defined as excess fat accumulation for a given height, that increases the risk for impaired health (12).

Body mass index (BMI)

BMI is the most widely used measurement to define and classify obesity. It is calculated as weight in kilograms divided by height in meters squared and categorized according to World Health Organization recommendation (13). It is a measure of weight relative to height and not a direct measure of body fat accumulation (**Table 1**).

Table 1. *BMI classification according to WHO.*

Classification	BMI (kg/m^2)
Underweight	<18.5
Normal weight	18.5–24.9
Overweight	25.0–29.9
Obese	
Class I	30–34.9
Class II	35–39.9
Class III	≥40

On the one hand, BMI is a convenient and simple index to monitor obesity in a population and, therefore, widely used as an estimate of body fat accumulation in epidemiological studies. Several reports have found a dose-dependent relationship between BMI and adverse health outcome such as mortality (14).

However, BMI, has its limitations as it doesn't differentiate body fat mass from lean body mass. A muscular person with little fat can have a high BMI and be categorized as being obese despite a low degree of fat mass. For cardiovascular clinical outcomes, a body fat distribution with increased visceral adipose tissue has been shown to be an important risk factor as compared to subcutaneous fat distribution, which is considered to be more neutral with respect to health risks (15, 16).

Waist Circumference (WC) and Waist Hip Ratio (WHR)

Waist–hip ratio (i.e. the waist circumference divided by the hip circumference) is a measure of body fat distribution. The ratio provides an index of both intra- abdominal adipose tissue and subcutaneous fat (17). Waist circumference represents an estimate of abdominal fat.

Waist circumference is measured in a standing posture at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest. Hip circumference is measured around the widest portion of the buttocks. **Table 2** displays the cut off points of waist and waist/hip ratio that have been associated with increased cardiovascular risk in males and females, respectively(18).

Table 2. *WC and WHR cut-off points and risk of metabolic complications.*

Indicator	Cut-off point	Risk for complication
Waist circumference	>94 cm (M) >80 cm (W)	Increased
Waist circumference	>102 cm (M) >88 cm (W)	Substantially increased
Waist-Hip Ratio	≥0.90 cm (M) ≥0.85 cm (W)	Substantially increased

M, men; W, women

Skinfold measurements

Approximately 40% to 60% of total body fat is located in the subcutaneous region. Therefore, measuring the sum of skinfold thickness for assessment of body fat is frequently used (19). Most equations use the sum of at least three skinfolds to estimate body density, from which an estimate body fat amount can be calculated with a reasonable degree of accuracy (20).

BODY COMPOSITION

Body composition is quantified as fat and fat-free mass (FFM). FFM is equal to total body weight minus fat mass and includes the weight of organs, skin, bones, body water and muscles (21).

BODY FAT DISTRIBUTION

Central fat distribution (*android*) within the abdominal region, known as visceral fat, is related to increased risk for metabolic disturbances, leading to cardiovascular disease, and increased all-cause mortality. In contrast, fat accumulation in the gluteo-femoral region (*pear*) is associated with reduced prevalence of cardiometabolic diseases as compared with patients with a high waist circumference (22, 23) (**Figure 3**).

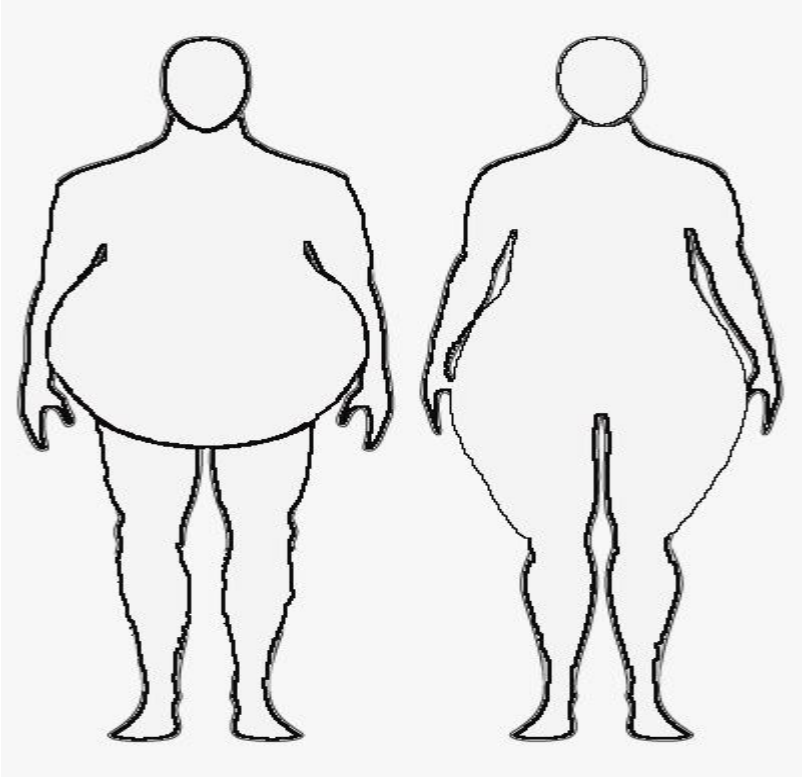

Figure 3. *Android (apple) vs Gynoid (pear) body fat distribution. Illustration by Arwa Haamid.*

Epicardial fat may have local effects on the myocardium, including cardiomyocyte hypertrophy, myocardial fibrosis, and activation of inflammatory pathways relating to macrophage infiltration and cytokine gene expression (24).

In Gothenburg, a research group has shown that a higher ratio of abdominal waist over hip circumferences (WHR), as a crude estimate of abdominal fat, was predictive of a higher risk of coronary artery disease (CAD) whereas no association was shown with BMI as a measure of obesity (25).

MEASUREMENT OF BODY COMPOSITION

Apart from the anthropometric measurements mentioned above, which all have limitations, other methods are available that more accurately

determine fat amount and distribution. These include bioelectrical impedance analyses and densitometry, imaging methods such as dual energy X-ray absorptiometry (DXA), computed tomography scanning and magnetic resonance imaging. These methods are either costly and/or have a low availability, limiting their use in epidemiological studies (11).

ADIPOSOPATHY

The adipose tissue organ is a storage depot for excess energy in the form of triglycerides. The body fat undergoes a continuous turnover and releases free fatty acids (FFA) and glycerol to meet the metabolic needs of the body. However, a positive caloric balance in susceptible individuals leads to excessive accumulation of adipose tissue contributing to metabolic disturbances and in turn to cardiovascular disease.

Deposition of ectopic fat is stored in organs other than adipose tissue such as the liver, pancreas, heart, and skeletal muscle and may have a local effect on these organs. In certain individuals there is also a shift from subcutaneous to visceral fat which is stored in the intraperitoneal and retroperitoneal spaces. Visceral fat is more strongly correlated to adipokine dysregulation, insulin resistance, and inflammation than fat located subcutaneously (16).

PSYCHOLOGICAL ASPECTS

People with obesity frequently face a negative attitude, prejudice and discrimination due to a belief that obesity is evolved from, a lack of willpower, laziness, and/or emotional turmoil (26). In some cases, obese people have been confronted with similar preconceived notions when consulting the medical profession, resulting in patients feeling misinterpreted, humiliated, neglected and rejected(27). This exerts a huge psychosocial burden on obese people, who struggle with issues related to mood, self-esteem, quality of life, and body image. It has been estimated that 20-60% of individuals with obesity suffer from a psychiatric illness such as depression, anxiety, eating disorders and substance abuse (28).

APPETITE REGULATION

The hypothalamus is the center for regulation of food intake and energy metabolism (**Figure 4**). Signals increasing appetite are mainly mediated by neuropeptide Y (NPY) and agouti-related regulatory peptide (AgRP). Signals inducing satiety are mostly facilitated by pro-opiomelanocortin (POMC) (29). The digestive tract communicates with the hypothalamus via the vagus nerve which is stimulated by mechanoreceptors responding to gastric distension, to chemical signals and to a variety of local neurohormones (30). Examples of local gut peptides affecting appetite include, gherelin, which enhances appetite and cholecystokinin (CCK), peptide YY (PYY) and glucagon like peptide-1 (GLP-1), which all suppress appetite. Adipocytes produce leptin which crosses the blood brain barrier and suppresses the appetite by activating POMC neurons and inhibiting NPY and AgRP neurons in the hypothalamus.

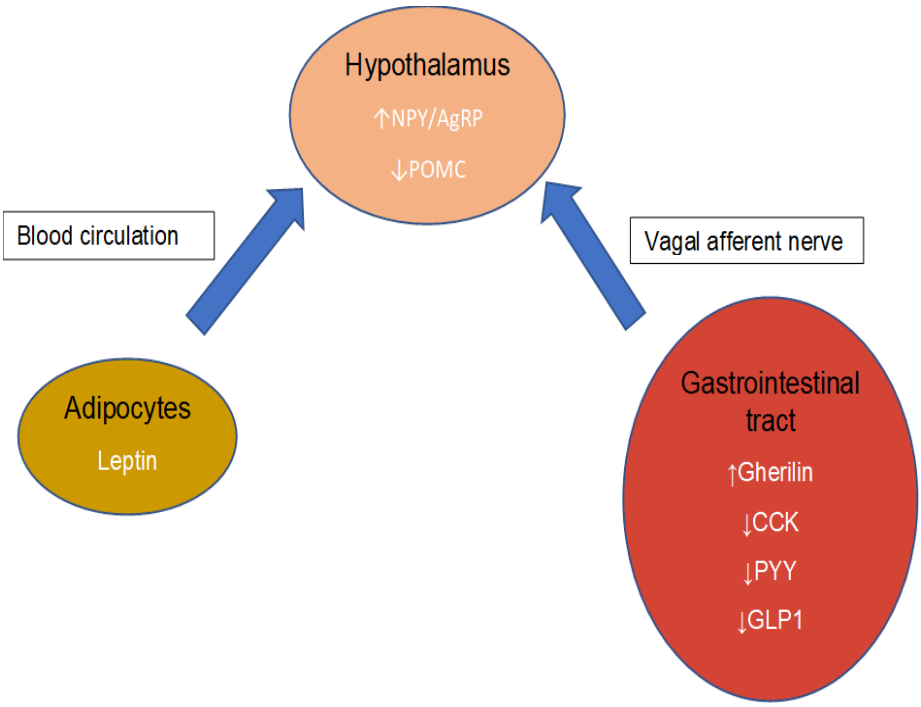

Figure 4. *A simplified schematic illustration of appetite regulating mechanisms. Adapted and simplified from Ueno et al., JDI 2016.*

ASYMMETRICAL REGULATION OF ENERGY BALANCE

The regulation of energy balance has been found to be asymmetrical. (**Figure 5**). The responses that counteract body fat accumulation during times of overfeeding are rather weak regulatory responses aimed at restoring energy balance, whereas the signals that arise during energy deficit and resist weight loss are considerably more potent (31).

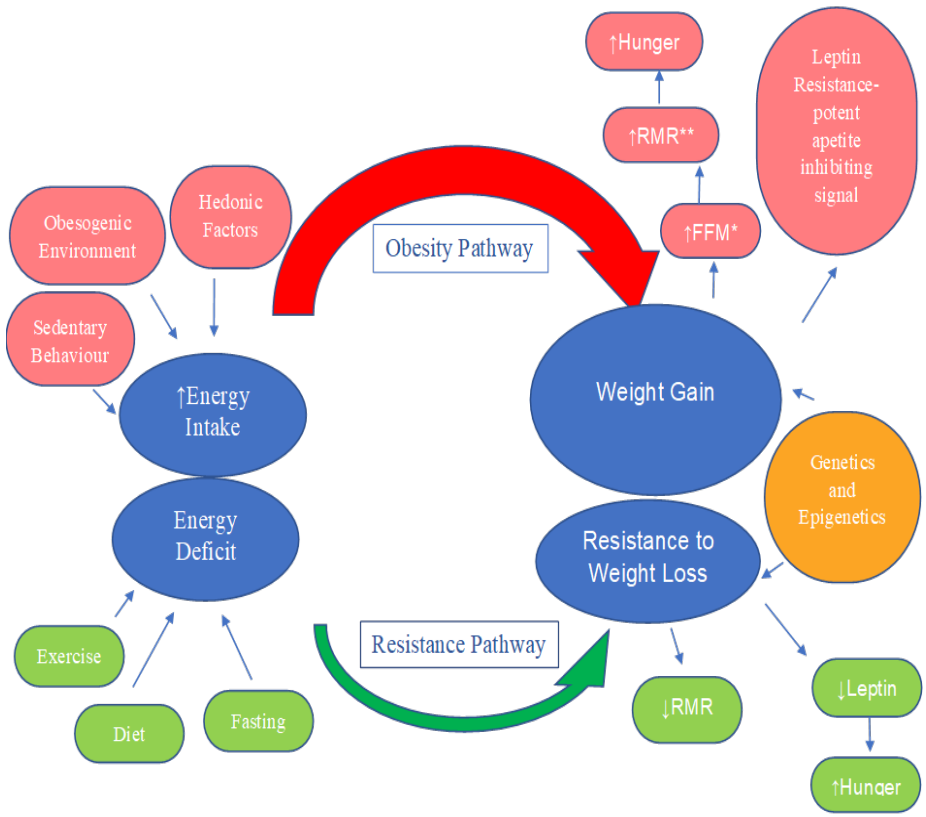

***Figure 5**. A schematic illustration showing regulation of energy balance. Adapted from Hopkins and Bundel 2016. *Free fat Mass **Resting metabolic rate*

OBESITY AND CARDIOVASCULAR RISK FACTORS

Chronic accumulation of excess body fat induces metabolic changes, leading to the development of CV risk factors and activation of low grade inflammation (32). Obesity, and central obesity in particular, is associated with hypertension, dyslipidemia, glucose intolerance, increased levels of inflammation, obstructive sleep apnea, and a prothrombotic state. Obesity is also associated with a progressive decline in physical activity and cardiorespiratory fitness, and has itself been shown to be and independent risk factor for CV diseases (33-35). Obesity is associated with hemodynamic changes that affect left ventricular structure and function (36). Augmented fat mass is linked to increased total blood volume, decreased systemic vascular resistance, and a rise in left ventricular (LV) stroke volume, cardiac output and LV filling pressures. This in turn stimulates LV hypertrophy, left atrial enlargement, and impaired LV systolic and diastolic function. Body fat accumulation is also related to higher pulmonary pressure, greater right ventricular end-diastolic volume and mass (35). The mechanisms by which obesity may cause cardiac dysfunction are displayed in **Figure 6**.

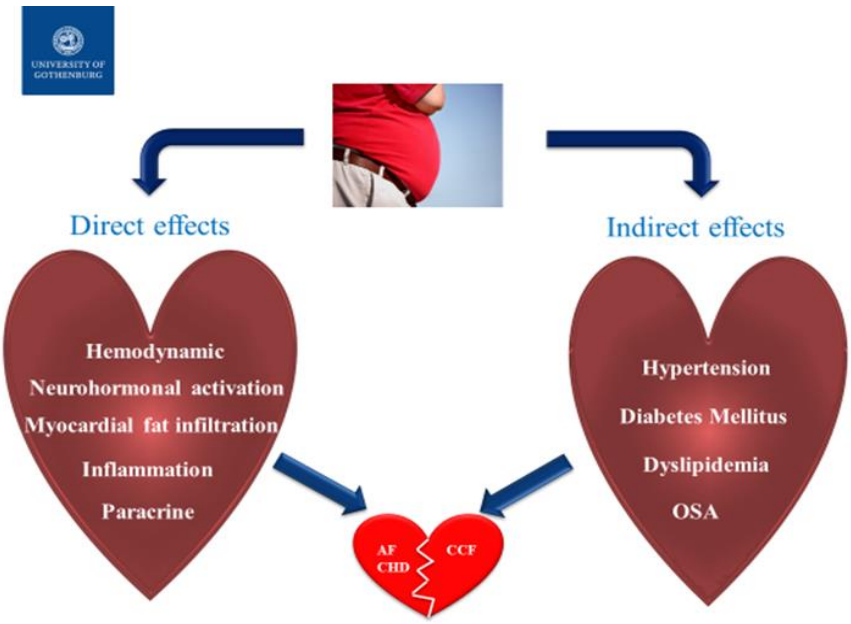

Figure 6. *Visceral obesity and cardiovascular risk, a multifactorial and complex mechanism. Adapted from Majorie Bastien et al, 2014 and Lavie et al. 2013.*

Hypertension

Individuals with central obesity have a 3-fold higher likelihood of having hypertension as compared to those with normal body weight (37). Among individuals with a BMI >30 kg/m^2 the prevalence of hypertension was over 40% (38). Increased renal tubular sodium reabsorption, mediated through activation of the renin-angiotensin-aldosterone system (RAAS) (39) and increased sympathetic nervous system (SNS) activity (40), have been suggested to play an important role in linking obesity with hypertension.

Angiotensinogen (AGN) is produced in the liver and by adipocytes. It is then transformed to angiotensin (Ang) I by renin, secreted by the kidneys. Angiotensin converting enzyme (ACE) transforms Ang I to Angiotensin II which is a powerful vasoconstrictor and promotes cardiac myocyte hypertrophy and cardiac interstitial fibrosis (32). It has also been shown that Ang II, interferes with preadipocyte differentiation to adipocytes, and thereby contributes to the formation of large and dysfunctional adipocytes (41). The expression of AGN is increased in large adipocytes, which leads to activation of RAAS, a mechanism involved in obesity-associated hypertension (32).

Dyslipidemia

Dyslipidemia in obesity consists of increased triglycerides (TG) and fatty free acids (FFA), decreased high density lipoprotein (HDL) with HDL dysfunction and normal or slightly increased low-density lipoproteins (LDL) with increased small dense LDL (VLDL). The concentrations of plasma apolipoprotein (apo) B are also often increased, partly due to the hepatic overproduction of apo B containing lipoproteins (42). HDL-cholesterol has demonstrated protective properties against atherothrombosis. In contrast, low levels of plasma HDL-cholesterol are associated with CAD and are a better predictor of ischemic heart disease than LDL-cholesterol levels (43). From a clinical standpoint, low levels of HDL-cholesterol are rarely an isolated finding, and frequently associated with high triglycerides (TG), high Apo B, and increased insulin resistance (32).

Weight loss by increased exercise and improved dietary habits lead to improvement in the lipid status. Medical therapy can be initiated if lifestyle changes are insufficient. Statins, reduce LDL and remnant

cholesterol levels. Combination of statins and fibrates are used TG levels are high and HDL-cholesterol levels are low (44).

Insulin resistance and T2D

Normal regulation of glucose metabolism is determined by the islet β-cell response and tissue sensitivity to insulin. When insulin resistance is present, the β-cell maintains normal glucose tolerance by increasing insulin output. In the presence of obesity-related insulin resistance, the β-cell becomes incapable of releasing sufficient insulin leading to increased glucose levels, prediabetes and T2D (45). Abdominal obesity is associated with prediabetes, defined as IFG > 6.1 mmol/L and/or impaired glucose tolerance (IGT) [7.8 mmol/L-11.0 mmol/L]. Prediabetes is a risk factor for diabetes and cardiovascular disease (46).

The earliest detectable metabolic defect in patients with obesity is augmented insulin resistance (IR) (47). The adipocytes in central obesity are dysfunctional and increase the rate of lipolysis leading to elevated plasma FFA concentrations (48) which inhibit insulin stimulated peripheral glucose uptake. This causes peripheral and hepatic insulin resistance. The consequences are overproduction of hepatic glucose and underutilization of peripheral sugar giving rise to T2D (49).

It has also been shown that central obesity is associated with an increased prevalence of T2D. For a given BMI value, the WC in patients with diabetes was higher (50). In another study, the risk of developing T2D increased by 20% for each increase in a BMI unit (51). Approximately 50% of patients with T2D have obesity (52).

The higher the BMI, the greater the IR (53). IR develops due to higher FFAs levels and elevated inflammatory markers. CRP and TNF-α mediate the development of T2D in individuals with obesity (54, 55). IR and a deficit in insulin secretion due to decreased pancreatic β-cell function are mechanisms underlying the development of T2D in obese people (56).

Metabolic Syndrome

Metabolic syndrome (MetS) is a constellation of cardiovascular disease risk factors comprising central obesity, systemic hypertension, IR and atherogenic dyslipidemia (specifically hypertriglyceridemia and reduced levels of high-density lipoprotein cholesterol). The syndrome

has been defined by various organizations that have used different criteria. One of the most widely used definitions from the International Diabetes Federation (IDF) 2005 is displayed in **Table 3**. Increased sedentary lifestyle is a major factor for increased prevalence of MetS which can be prevented by physical exercise and dietary treatment.

Table 3. *IDF classification of MetS.*

Waist > 94 cm for men or > 80 cm for women along with the presence of two or more of the following:	
Blood glucose	> 5.6 mmol/L or diagnosed diabetes
HDL cholesterol	< 1.0 mmol/L in men, < 1.3 mmol/L in women or drug treatment for low HDL-C
Blood triglycerides	> 1.7 mmol/L or drug treatment for elevated triglycerides
Blood pressure	> 130/85 mmHg or drug treatment for hypertension

Inflammation

Central obesity is associated with increased circulating levels of interleukin (IL)-6, tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) (57, 58). It has also been shown that the severity of the metabolic syndrome, is positively related to CRP levels (59). Leptin, an adipokine produced by adipose tissue, has been shown to be an independent predictor of CVD (60). Another adipokine with anti-inflammatory activity, adinopectin, was shown to be positively related to the risk of cardiovascular events in patients with established CAD (61).

Prothrombotic state

Obesity is associated with an increased risk for venous thromboembolism (VTE) (62) which encompasses two distinct clinical entities: deep vein thrombosis (DVT) and pulmonary embolism (PE). A meta-analysis has shown that the likelihood of a first spontaneous VTE among people who are obese was more than twice that of individuals with a normal BMI (63). The relative risk of unprovoked PE is raised by 8% per 1 kg/m^2 increase in BMI and approaches a nearly six fold greater

risk among individuals with a BMI ≥ 35 kg/m^2 (64). Intentional weight loss and physical activity reduce the risk for VTE among people with obesity (65).

Hemodynamic overload

Increase in body weight leads to a higher metabolic demand which results in increased blood volume and cardiac output (66-68). A higher BMI is directly related to an increase in renal tubular sodium reabsorption which leads to sodium retention and subsequent plasma volume expansion (69, 70). Thus, obesity contributes to a higher cardiac output, increasing the preload and augmenting the cardiac workload leading to greater LV mass (71). Volume overload leads to eccentric cardiac hypertrophy with enlarged chambers and normal wall thickness (72).

Under these conditions cardiac afterload is also elevated. This is because systemic peripheral resistance does not decline to the same degree as the rise that occurs in cardiac output (73). A higher BMI is associated with increased blood pressure (37) and pressure overload results in a concentric hypertrophy a phenotype characterized by thick ventricular walls and normal LV volume (74-76). As a consequence, obese people may display a combination of eccentric and concentric LV hypertrophy (77).

Abdominal adiposity shows a stronger relationship with concentric LV remodeling, including greater left ventricular mass, but also increased left ventricular end diastolic volume. The degree of abdominal adiposity is positively correlated with the ejection fraction whereas, the duration of overall obesity was inversely associated with a lower ejection fraction (78).

OBESITY AND CARDIOVASCULAR DISEASE (CVD)

Atrial fibrillation (AF)

Obesity is a risk factor for AF. It has been shown that for each increase in one unit of BMI, the risk for AF rises by 4%. Further, obesity independently predicts a transition from paroxysmal to permanent AF and is also associated with a higher recurrence rate and greater burden of AF (79-81). Obesity contributes to the development of AF through

comorbidities like hypertension, coronary artery disease, diabetes mellitus, obstructive sleep apnea, and congestive heart failure (82, 83). It is plausible that significant weight reduction would reduce the risk of new-onset AF, but there is little evidence to support such a belief.

Heart failure (HF)

Obesity is associated with a two-fold higher risk of developing heart failure compared to normal weight (82). The risk of heart failure increases by 5–7% for each increment of BMI (82). Furthermore, one unit increase in BMI, has been shown to be associated with a higher risk for future HF with preserved ejection fraction (HFpEF) compared to HF with a reduced ejection fraction (HFrEF) (84). In men, a higher BMI was independently associated with both HF subtypes where as in women, BMI was associated with incident HFpEF but not HFrEF (84).

In the normal population, HF is represented by about one half HFpEF and one half HFrEF (85). Patients with HFpEF are generally more obese, older and have a higher prevalence of hypertension, diabetes, and atrial fibrillation than those with HFrEF. Coronary artery disease and coronary risk factors are clinical comorbidities in both, HFpEF and HFrEF (86, 87).

Although obesity intervention can improve cardiovascular risk factors and may have beneficial effects in patients with compromised cardiac function there are no large controlled studies investigating the impact of weight loss on the development of heart failure.

Coronary artery disease (CAD)

Obesity is an independent risk factor for CAD (88), and over 80% of patients with CAD are overweight or obese. After diagnosis, obesity is associated with accelerated progression of CAD (89, 90). Weight control is considered to be of fundamental importance in primary prevention aimed at reducing the overall incidence of cardiovascular disease (91) and is also targeted in secondary preventive programs intended to improve outcome in patients with established cardiovascular disease (92, 93). Still, a certain hesitancy has arisen concerning the beneficial effects of weight loss as a secondary prevention practice, since several epidemiologic studies have suggested that obesity may be

protective in patients with coronary artery disease undergoing intervention (94, 95).

OBESITY AND OTHER CO-MORBIDITIES

Increase in total body fat, specifically abdominal fat, is associated with an increase in health risk. The amount of body fat has been associated with an increased risk of comorbidities like joint pains and osteoarthritis, obstructive sleep apnea, non-alcoholic fatty liver disease and some types of cancer.

Joint pains and osteoarthritis (OA)

People with obesity have a high prevalence of joint pain, especially in the lumbar spine and knees, as well as OA in the hips and knees (96, 97). Obesity, apart from causing mechanical overload, causes release of inflammatory cytokines including leptin and resistin which influence the onset and worsening of OA through direct degradation of the joint or stimulation of inflammatory processes (97). Weight loss through bariatric surgery has been shown to improve OA symptoms (98).

Obstructive sleep apnea (OSA)

OSA is a condition characterized by repeated episodes of partial or complete obstruction of the respiratory passages during sleep. People with central obesity have a high prevalence of OSA. Accumulation of fat in the upper body, especially around the neck, in the respiratory area and in the diaphragm, gives rise to OSA (99, 100). A reciprocal relationship exists between the development of OSA and its subsequent sleep fragmentation which appears to accelerate weight gain. Many patients report rapid increases in weight in the year prior to OSA diagnosis (101). There is evidence linking OSA as an independent risk factor for hypertension (102), atrial fibrillation, ischemic heart disease, stroke and mortality (103).

Non-alcoholic fatty liver disease (NAFLD)

The increase in the worldwide prevalence of obesity has led to an increase prevalence of NAFLD which is estimated to affect around 25% of the general population. In the western world, approximately 83% of patients with central obesity have NAFLD which is one of the leading causes of chronic liver disease. NAFLD is divided into a non-progressive form of simple liver steatosis and a progressive form of non-

alcoholic steatohepatitis (NASH) that can lead to cirrhosis, hepatocellular carcinoma (HCC) and liver-related mortality (104, 105).

Cancer

It has been shown that an increase in BMI by 5 kg/m² in men is strongly associated with esophageal adenocarcinoma, thyroid carcinoma, colon cancer, and renal cancers. In women, a similar increase in BMI is associated with endometrial, gallbladder, renal cancer and esophageal adenocarcinoma (106).

METABOLIC HEALTHY OBESE (MHO)

MHO is a phenotype of obesity where individuals lack features of the metabolic syndrome. Several definitions exist for MHO, but in studies the most widely used classification requires the individual to have ≥2 of the following five metabolic syndrome components: high systolic and diastolic blood pressures, high plasma TG concentration, low HDL-C concentration, high fasting blood glucose, and a large waist circumference (107); or having ≥1 abnormal component excluding waist circumference (108). Additional criteria include indices of insulin sensitivity/resistance based on the homeostasis model assessment of insulin resistance (HOMA-IR) score(109). When metabolically healthy, definition is the absence of MetS, about 50% of people with obesity fall into this category. When the definition includes absence of MetS and a normal HOMA-IR, only 5% are considered metabolically healthy (110). Studies have shown MHO is often a temporary state and frequently transforms into a metabolically unhealthy condition with an elevated long-term risk of developing CVD (111, 112). In general, the risks of T2D, CVD, and all-cause mortality are higher in people with obesity who have the metabolic syndrome than in those with MHO (112). However, further research is required to understand the mechanisms responsible for preserved metabolic health in obese people and to enable a consensus concerning the definition of MHO.

WEIGHT LOSS STRATEGIES

There are mainly three different types of weight loss interventions namely, life style intervention, pharmacotherapy and bariatric surgery.

Lifestyle intervention

Lifestyle intervention includes, caloric restrictions using specific diets e.g. very low energy diets where the daily energy intake is restricted to 450-800 kcal (1855-3297 kJ). Increase in physical activity (approximately 1 h per day) is another lifestyle intervention aimed to facilitate weight loss (113). Exercise may not reduce body weight as such, but instead alters body composition by increasing lean body mass and reducing visceral fat; '*waist loss rather than weight loss'*. Such changes in body composition appear to be advantageous with respect to cardiovascular risk (16) Behavioural changes like self-monitoring and goal setting can also be encouraged.

The results of intensive lifestyle intervention (ILI), however, rarely result in weight loss to a degree that is sufficient to reduce cardiovascular events. In the Look-AHEAD trial, patients with obesity and T2D were randomized to either an ILI or diabetes support and education (DSE). The ILI group received treatment consisting of diet modification and increased physical activity to achieve a sustained weight loss (114). The DSE control group were, apart from regularly scheduled clinic visits, offered yearly educational sessions covering diet/nutrition, exercise and social support. After a median follow-up of 9.6 years, the mean weight loss for the ILI group was −6.0 % and for the DSE group −3.5 %. Still, there was no overall significant difference in the primary composite CVD outcome between the groups. Weight loss achieved through lifestyle intervention is difficult to maintain over time and, therefore adjuvant therapies should be considered (115).

Pharmacotherapy

In Sweden, pharmacotherapy is recommended in patients with obesity (BMI ≥ 30 kg/m^2) and in overweight patients (BMI ≥ 27 kg/m^2) who have risk factors for cardiovascular disease.

- ### Orlistat

  Orlistat blocks the enzyme lipase which is found in the intestine and breaks down fats. As a result, about 30% of the total fat intake passes out undigested in the faeces. Orlistat does not inhibit the metabolism of sugars and other non-fat foods. Therefore, calorie intake from these

and other food sources still need to be restricted in patients.

- ### Liraglutide and semaglutide

  Liraglutide and semglutide are glucagon like peptide-1 (GLP-1) receptor agonists that induce weight loss by appetite suppression and delayed gastric emptying (116, 117).

- ### Naltrexone/bupropion

  Naltrexone/bupropion is a combination drug, which induces weight reduction through an effect on the brain's appetite regulation. Naltrexone is an opiate antagonist targeting pathways in the central nervous system that impact eating behavior, presumably influencing the food reward system. Bupropion, is an antidepressant that inhibits reuptake of noradrenaline and dopamine and is also thought to affect the brains appetite regulation through a different mechanism. When combined with lifestyle interventions these agents can induce a clinically significant weight loss for up to one year (118).

- ### SGLT2 inhibitors

  Sodium-glucose cotransporter-2 inhibitors are currently approved for treatment of T2D. These inhibitors reduce renal tubular reabsorption of sodium and glucose, resulting in increased urinary secretion of sodium and glucose. In addition to lowering blood glucose, these agents induce weight loss, lower blood pressure, reduce the incidence of heart failure, and improve CV outcomes (119).

Bariatric Surgery

For people with obesity, bariatric surgery is a therapeutic option that results in substantial weight loss that is maintained over time (7, 120-123). Sustained weight loss leads to improvement in cardiovascular risk factors including hypertension, dyslipidemia and type 2 diabetes

mellitus. Furthermore, obesity surgery reduces cardiovascular events, lowers cancer incidence and contributes to better survival (7, 120, 123-127). According to the Scandinavian Obesity Surgery Registry, about 5,200 bariatric surgical procedures using a laparoscopic technique were performed in Sweden during 2018. Gastric bypass was the most common procedure closely followed by sleeve gastrectomy (128). **Figure 4** shows the two most common surgical methods, gastric bypass and sleeve gastrectomy, that are applied today.

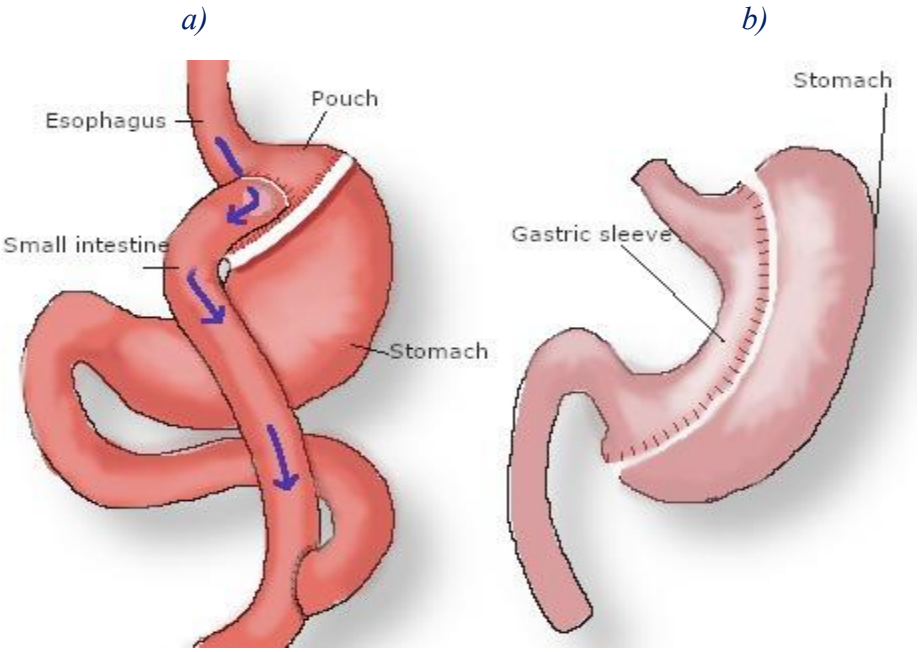

Figure 7. *a) Gastric bypass and b) sleeve gastrectomy. Illustration by Arwa Haamid.*

SIDE EFFECTS OF BARIATRIC SURGERY

Dumping syndrome, is a common complication after bariatric surgery. Typically, symptoms arise after a meal and include abdominal pain, nausea, diarrhea, and also vasomotor symptoms such as fatigue, flushing, palpitations, perspiration, tachycardia and hypotension (129).

Nutritional deficiencies are the most common long-term complications of bariatric surgery resulting from inadequate food intake, malabsorption, or both. Anemia, caused by deficiencies of iron and vitamin B12, is common. Other deficiencies include folate, selenium,

zinc, copper, and vitamins A, B1, B2, B6, C, D, E and K. Therefore, lifelong follow-up is recommended with provision of supplements to ensure an optimal nutritional status (130-132). After bariatric surgery, an increased alcohol consumption has been reported, and other alcohol-related problems, such as alcohol abuse (133) and increased risk for new onset of depression and suicide (134).

THE OBESITY PARADOX

Obesity is associated with an increased prevalence of hypertension, AF, HF and CAD (82, 89, 135, 136). On the other hand, epidemiological studies show that once CVD is present, obese patients have a better prognosis than their leaner counterparts, which is referred to as the obesity paradox (137-139) (**Figure 8**). The obesity paradox may be derived from an interaction between several potential confounders. Such confounders can be related to an elevated BMI due to high lean body mass or subcutaneous fat distribution. A low BMI could be due to chronic illness leading to cachexia. Another confounding source is not being able to account for high levels of CRF despite obesity. Thus, the protective effect of excess body fat is somewhat counter intuitive and a mechanism involving reverse causality has been suggested (140).

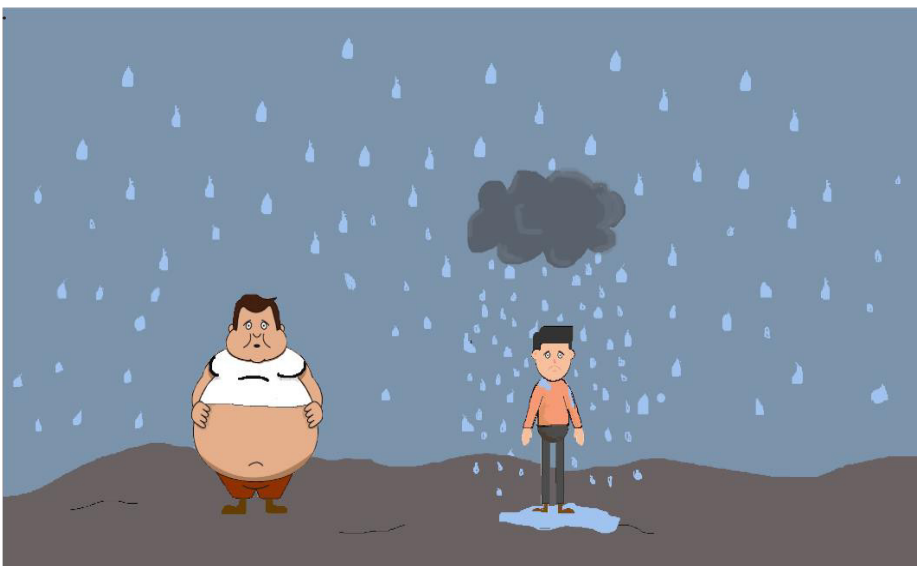

Figure 8 *The obesity paradox. Illustration by Arwa Haamid.*

Fat distribution, fat mass and lean mass

The use of BMI as a measure of adiposity in epidemiological studies has shortcomings since it does not discriminate between body fat and lean mass, nor does it reflect body fat distribution. It has been shown that WC or WHR as estimates of abdominal obesity, correlate more strongly to CVD than BMI, and are better markers of abdominal obesity than BMI (23, 141). In patients with CAD, a higher lean mass was associated with lower mortality rather than body fat (142). BMI values seen in overweight and mildly obese patients can be due to increased lean mass and not to elevations in body fat. Increased lean mass has been shown to be associated with better fitness and exercise capacity, improvement in metabolic profiles and probably better prognosis in patients with cardiovascular diseases (143-145).

Intentional versus unintentional weight loss

Intentional weight loss through diet and physical exercise, results in loss of body fat and an increase in lean body mass. A higher lean mass is associated with better survival (146). Unintentional weight loss where there is loss of both body fat and lean mass is associated with a higher mortality (147). Cachexia is often related to an underlying chronic disease which leads to frailty and adverse outcomes (148). Also, a lower BMI has been related to low lean mass, a condition also known as sarcopenia (149). Patients with sarcopenia have decreased muscle mass, a restricted exercise capacity and reduced mobility, both conditions associated with increased total mortality (150).

Cardiorespiratory fitness (CRF)

Physical activity (PA) and improvements in CRF are associated with lower CVD mortality, independent of weight or BMI (151). Lower mortality was observed in patients with HFrEF that displayed a peak oxygen consumption (VO_2) >14 mL/kg/min, indicating a higher level of CRF. In contrast, in patients with peakVO_2 < 14 mL/kg/min, suggesting poor CRF, had a higher mortality (152, 153).

SWEDISH PERSONAL IDENTITY NUMBER AND NATIONAL HEALTH REGISTERS

In Sweden, every child that is born, and all immigrants who receive Swedish citizenship are assigned a unique personal identity number (PIN) by the National Tax Board. The PIN is updated in the total population register database by Statistics Sweden. In medical research, the PIN is used to link patient data to various national registers like, the Swedish National Patient Register (NPR), the Swedish Cancer Register and the Swedish Cause of Death Register (COD) (154).

A number of national registers are administered by The National Board of Health and Welfare (Socialstyrelsen), including, NPR, COD, as well as the Swedish Cancer Register and the Swedish Medical Birth Register.

The Swedish National Patient Register (NPR)

From 1987 NPR includes diagnoses for all in-patient care, and since 2001 it covers diagnoses for both in- and outpatient doctor visits including day surgery and psychiatric care from both private and public caregivers. Primary care, however, is not covered. Diagnoses at discharge are coded with the International Classification of Diseases (ICD). Reporting to the register is exceptionally high. The register has been validated by quality controls performed on the submitted data (155). Primary diagnoses of atrial fibrillation and heart failure have shown to have a high validity (156, 157).

The Swedish Cause of Death Register (COD)

The Swedish National Board of Health and Welfare has administered the COD since 1994. ICD codes system and the World health organization (WHO) standardized systems for certifying deaths are used. Since 1997 all deaths reported to the tax authority have been included in the register, which covers almost all underlying causes of death in the Swedish population. It has been shown that there is a 77% agreement between the cause of death from death certificates and the cause of death based on medical records (158).

THE SWEDEHEART REGISTRY

The Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SwedeHeart) is a national registry that was established in 2009. The SwedeHeart registry is administered by Uppsala Clinical Research Center (UCR) and is sponsored solely by the Swedish Health Authorities, in particular, the Swedish Association of Local Authorities and Regions (159). Several registry-based randomized prospective clinical trials (R-RCT) have been performed, with TASTE (160), being one of the first R-RCT. Others include, iFR-SWEDEHEART (161), DETO$_2$X-AMI (162) and VALIDATE-SWEDEHEART (163).

Presently, the database includes the following national registries:

- The Registry of Acute Infarction Care (RIKS-HIA).
- The Registry of Secondary Preventive Care after Cardiac Infarction (SEPHIA).
- The Registry of Catheter-borne Coronary Vessel Surgery (SCAAR).
- The Registry of Catheter-borne Valve Replacement (TAVI).
- The Registry of Open-Heart Surgery (Svenska Hjärtkirurgiregistret).

All patients admitted to hospital for acute coronary syndrome investigations, those being followed up in out-patient clinics for secondary prevention, and individuals undergoing coronary- or valvular intervention are included in this registry. The registry database is directly connected to the Swedish National Population Registry and merged, on a yearly basis, with the NPR, COD registry, and the National Registry of Drug Prescriptions.

AIMS

The main underlying hypothesis of the present thesis was that weight loss through bariatric surgery is advantageous for cardiovascular risk. Also, that obesity may exert a protective effect with respect to outcomes after a coronary artery event. In order to address these hypotheses, we formed the following research proposals:

Paper Ⅰ

To investigate whether weight loss through bariatric surgery may reduce the risk of new-onset atrial fibrillation among people with obesity.

Paper Ⅱ

To examine the effect of surgical obesity treatment on the incidence of new-onset heart failure.

Paper Ⅲ

To determine risk factors for the development of heart failure in obesity including both variables registered at baseline as explanatory variables as well as atrial fibrillation and myocardial infarction as time-dependent variables.

Paper Ⅳ

To explore the obesity paradox in a ST-elevation myocardial infarction cohort who had undergone percutaneous coronary intervention.

PATIENTS AND METHODS

Paper Ⅰ, Paper Ⅱ and Paper III

In **Paper I** and **Paper II**, patients were included from the ongoing, nonrandomized, matched, prospective, controlled Swedish Obese Subjects (SOS) intervention study. A total of 4047 eligible obese participants were enrolled between September 1, 1987, and January 31, 2001. The inclusion criteria were age between 37 to 60 years and BMI of at least 34 for men and at least 38 for women.

Subjects were excluded if they had a history of earlier surgery for gastric or duodenal ulcer, earlier bariatric surgery, gastric ulcer during the past 6months, ongoing malignancy, active malignancy during the past 5 years, myocardial infarction during the past 6months, bulimic eating pattern, drug or alcohol abuse, psychiatric or cooperative problems contraindicating bariatric surgery, or other contraindicating conditions (such as chronic glucocorticoid or anti-inflammatory treatment). The study complied with the Declaration of Helsinki and seven regional ethics review boards in Sweden approved the study protocol. All participants gave written or oral consent.

Individuals who expressed a preference for treatment with bariatric surgery constituted the surgery group consisting of 2010 participants. The bariatric surgical procedures in the study at that time included vertical banded gastroplasty (VBG) (68%) gastric banding (GB) (19%), and gastric bypass (GBP)(13%) shown in **Figure 9**.

A matched control group, of 2040 participants, was created using an automatic computerized matching program with 18 matching variables. The matching variables included sex, age, weight, height, waist-hip ratio, blood pressure, serum cholesterol, triglycerides, smoking, diabetes, menopause, 4 psychosocial variables associated with risk for death, and 2 personality traits related to treatment preferences. Among the 2040 patients in the control group, there were three patients who were initially scheduled for surgery, but changed their mind and had declined surgical intervention. The conventional treatment offered to control subjects was according to routine local practice of the health care centers.

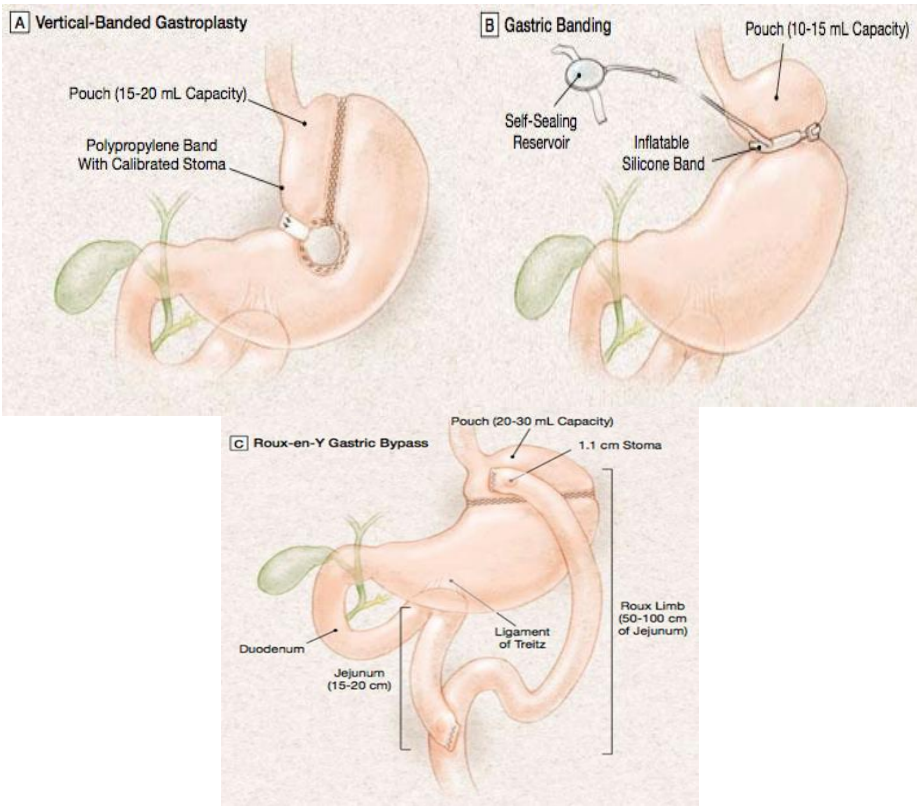

Figure 9. *Surgical techniques used in the SOS study. A) Vertical-Banded Gastroplasty B) Gastric Banding C) Gastric Bypass*

At each visit, measurements of weight, height, waist circumference, and blood pressure were obtained. The SOS database was merged with the NPR to obtain data on new-onset AF. Further, incident HF diagnosis was achieved by merging SOS with the NPR and COD registries. The two study groups underwent identical examinations at the participating surgical departments and primary health care centers both at baseline and during follow-up at 0.5, 1, 2, 3, 4, 6, 8, 10, 15, and 20 years.

After bariatric surgery, the recommended daily nutritional supplementation included oral doses of multivitamin and mineral supplements, vitamin B12, and a combination of calcium and vitamin D3. If laboratory findings indicated deficiencies of iron or folate, replacement therapy was introduced. Matched control patients received standard nonsurgical obesity treatment from their primary health care

centers. No attempt was made to standardize the conventional treatment which ranged from sophisticated lifestyle intervention and behavior modification to, in some practices, no treatment at all.

Body weight was measured with electronic or calibrated scales at baseline and at regular follow-up appointments. Blood samples were analyzed by the Central Laboratory at Sahlgrenska University Hospital (accredited according to the international standard ISO 15189:2012). Self-reported information on cardiovascular disease, medication, smoking, and alcohol intake was obtained through a questionnaire administered. High blood pressure was defined as systolic pressure >140mmHg, or diastolic pressure > 90mmHg, or self-reported use of anti-hypertensive medication. Diabetes was defined as a fasting blood glucose level of at least 6.1mmol/L (110mg/dL) or self-reported use of a prescribed antidiabetic medication.at baseline and during follow-up visits. In **Paper I**, all patients that had reported atrial fibrillation were excluded from analysis and similarly in **Paper II** all patients that reported a history of heart failure at baseline were omitted from statistical analysis.

For **Paper III** we used the control group from the SOS intervention study after excluding all patients with heart failure at baseline.

Paper Ⅳ

For this manuscript, we retrieved data from the SCAAR register and included all consecutive patients who had undergone PCI for ST-elevation myocardial infarction (STEMI) in Sweden between 1st January 2011 and 3rd May 2018. The SCAAR registry data was merged with the COD registry to obtain the primary endpoint, mortality at 30 days and after 1 year.

STATISTICS

Paper I

The data is presented as mean values with standard deviations or as percentages. For continuous variables, t-tests and a logistic-regression model for dichotomous variables was used for comparison between treatment groups. Using Kaplan Meier estimates, survival curves were generated and log rank test performed for comparison between groups. Relative-risk estimates expressed as hazard ratios were obtained by univariable and multivariable Cox proportional hazards regression models intention-to-treat principle was applied for all calculations. Patients who reported atrial fibrillation at baseline were excluded from all analyses (n=26).

Paper II

The differences in changes in BMI between the surgery and control groups were analyzed with multilevel mixed-effects regression models. A competing-risks regression model was used to estimate the cumulative incidence of heart failure. Relative risk estimates expressed as sub-hazard ratios were obtained using univariable and multivariable models. Cox proportional hazard regression models were used to determine the treatment effect in subgroups where continuous variables were dichotomized by a median split, and the homogeneity of between-group differences was evaluated. Patients who reported having a history of heart failure at baseline were excluded from all analyses (n=14).

Paper III

Competing risks regression models were used to estimate the cumulative incidence of heart failure. Differences in sex and various categories of age and BMI were assessed with a log-rank test. Relative risk estimates expressed as sub-hazard ratios for preselected baseline risk factors were obtained using univariate and multivariable models. Analyses were also performed using time-dependent variables (atrial fibrillation and myocardial infarction) as predictors for incident heart failure. Competing risks regression models were used to estimate the cumulative incidence of heart failure. Differences in sex and various categories of age and BMI were assessed with a log-rank test. Relative risk estimates expressed as sub-hazard ratios for preselected baseline risk factors were

obtained using univariate and multivariable models. Analyses were also performed using time-dependent variables (atrial fibrillation and myocardial infarction) as predictors for incident heart failure. Patients who reported having a history of heart failure at baseline were excluded from all analyses (n=10).

Paper Ⅳ

The participants were divided into four BMI categories according to the World Health Origination (WHO) classification (17): Underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5-24.99 kg/m^2), overweight (BMI 25-29.99 kg/m^2) and obese (BMI > 30 kg/m^2). Comparisons between groups at baseline were performed with analysis of variance (ANOVA) for normally distributed numeric data, Kruskal-Wallis rank sum test for non-normally distributed data and Chi-square test for categorical data. Death is presented as a cumulative incidence function and the log rank test was used for comparison between groups. Univariable and multivariable-adjusted hazard ratios (HR) were calculated to evaluate the association between BMI categories and mortality using Cox proportional-hazards regression models. Patients with a BMI of 18.5–24.99 kg/m^2 compatible with normal weight according to the WHO were used as the reference group. Penalized spline regression was applied to study the relationship between BMI as a continuous variable and all-cause mortality. The likelihood ratio test was used to examine the consistency of the association between subgroups.

RESULTS

Baseline data for the SOS study are shown in **Table 4.** Although the 2 study groups were fairly well balanced with respect to baseline characteristics, BMI was higher and several cardiovascular risk factors were less favorable in the surgery group (127). The differences are mainly explained by disparate weight changes occurring in the two groups during a delay between matching and baseline measurements: during the waiting time for bariatric surgery (on average more than 1 year), participants awaiting surgery tended to gain weight and control subjects tended to lose weight. Thus, most differences between the study groups that were observed at matching and at baseline constitute disadvantages for the surgery group with respect to cardiovascular outcomes.

Adverse events in the SOS study have been described in a previous paper (164). Bariatric procedures were performed with open surgery in 89% of cases. There were 5 individuals (0.2%) in the surgery group and 2 (0.1%) in the control group who died within 90 days of surgery/inclusion. In the surgery group, 151 (13.0%) of the participants had 193 postoperative complications. Of these, 46 persons (2.8%) needed additional surgery.

***Table 4**. Baseline variables of the two study groups. **

Variable	Surgery group (N=2010)	Control group (N=2040)	P-Value
Male sex	590 (29)	590 (29)	
Female sex	1420 (71)	1447 (71)	0.79
Age	47.2 ± 5.9	48.7 ± 6.3	<0.001
Weight (kg)	121.0 ± 16.6	114.7 ± 16.5	<0.001
Height (m)	1.69 ± 0.09	1.69 ± 0.09	0.68
Body-mass index†	42.4 ± 4.5	40.1 ± 4.7	<0.001
Anthropometry			
Waist-to-hip ratio†	0.99 ± 0.08	0.98 ± 0.07	<0.001
Waist circumference	125.8 ± 11.0	120.2 ± 11.3	<0.001
Hip circumference	127.1 ± 10.0	123.2 ± 10.0	<0.001
Sagittal diameter	28.9 ± 3.7	27.4 ± 3.7	<0.001
Neck circumference	43.7 ± 4.3	42.9 ± 4.29	<0.001
Upper-arm circumference	39.8 ± 3.8	38.7 ± 3.8	<0.001
Thigh circumference	75.5 ± 7.5	73.4 ± 7.5	<0.001
Blood pressure			
Systolic	145.0 ± 18.8	137.9 ± 18.0	<0.001
Diastolic	89.9 ± 11.1	85.2 ± 10.7	<0.001
Pulse pressure†	55.2 ± 14.5	52.8 ± 13.0	<0.001
Laboratory values			
Glucose (mmol/liter)	5.45 ± 2.11	5.20 ± 1.92	<0.001
Insulin (mU/liter)	21.5 ± 13.7	18.0 ± 11.4	<0.001
Triglycerides (mmol/liter)	2.25 ± 1.54	2.02 ± 1.41	<0.001
Cholesterol (mmol/liter)			
HDL-cholesterol (mmol/liter)	1.20 ± 0.28	1.19 ± 0.29	0.84
Uric acid (µmol/liter)	359.2 ± 79.8	352.3 ± 79.9	0.006
ASAT (µkat/liter)	0.43 ± 0.23	0.39 ± 0.21	<0.001
ALAT (µkat/liter)	3.12 ± 0.84	3.01 ± 0.87	<0.001
ALP (µkat/liter)	3.12±0.84	3.01±0.87	<0.001
Bilirubin (µmol/liter)	9.51 ± 4.28	9.93 ± 5.27	0.005
Co-morbidities			
Daily smoking	518 (25.8)	424 (20.8)	<0.001
Diabetes	215 (10.7)	232 (11.4)	0.520
Sleep apnea	505 (25.1)	452 (22.2)	0.03
Lipid-lowering therapy	36 (1.8)	33 (1.6)	0.67
Previous myocardial infarction	31 (1.5)	29 (1.4)	0.76
Previous cancer	46 (2.3)	49 (2.4)	0.81

Values are given as means ± standard deviation or numbers (percentages) as appropriate. ASAT = Aspartate aminotransferase; ALAT=Alanine aminotransferase; ALP=Alkaline phosphatase.
*In Paper I patients with a history of atrial fibrillation were excluded from analysis (n=26) and for Papers II and III patients with a history of heart failure at baseline were excluded from analysis (n=14 and n=10, respectively).

Figure 10. shows changes in BMI in patients for up to 20 years of follow-up. Bariatric surgery lowered the mean baseline BMI of 42.4 kg/m^2 by 25% at Year 1, by 18% at Year 6, by 16% at Year 15, and by 16% at Year 20. The mean baseline BMI of 40.1 kg/m2 in the control group remained largely unchanged during follow-up. The average of all between-group differences in BMI during a 20-year follow-up was –8.0 kg/m2 (95% CI -7.7 to -8.3); P< 0.001).

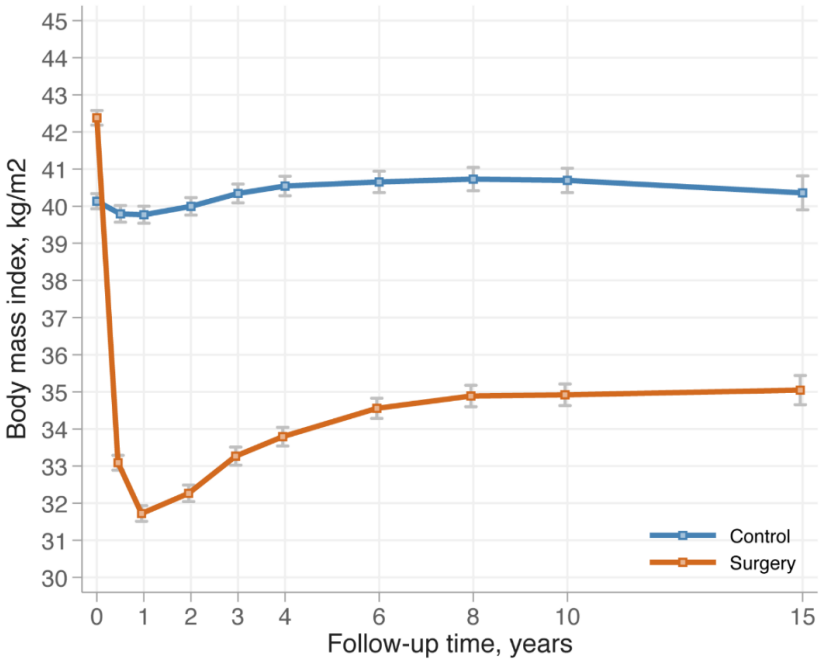

Figure 10. *Change in body mass index during 15 years of follow-up.*

Paper I

The participants had a median follow-up time of 19 years. First-time atrial fibrillation occurred in 247 (12.4%) of those in the surgical group and in 340 (16.8%) in the control group. There was a 31 % lower risk of developing atrial fibrillation in the surgery group as compared to the control group (HR 0.69; 95 % CI 0.59 to 0.82; P<0.001) (**Figure 11**). There was a 5-6-year delay before the incidence curves between the two groups separated. Younger individuals (P-value for interaction 0.002) and those with a high diastolic blood pressure (P-value for interaction 0.024) had a better effect of surgical intervention compared to those who were older or with a low diastolic blood pressure.

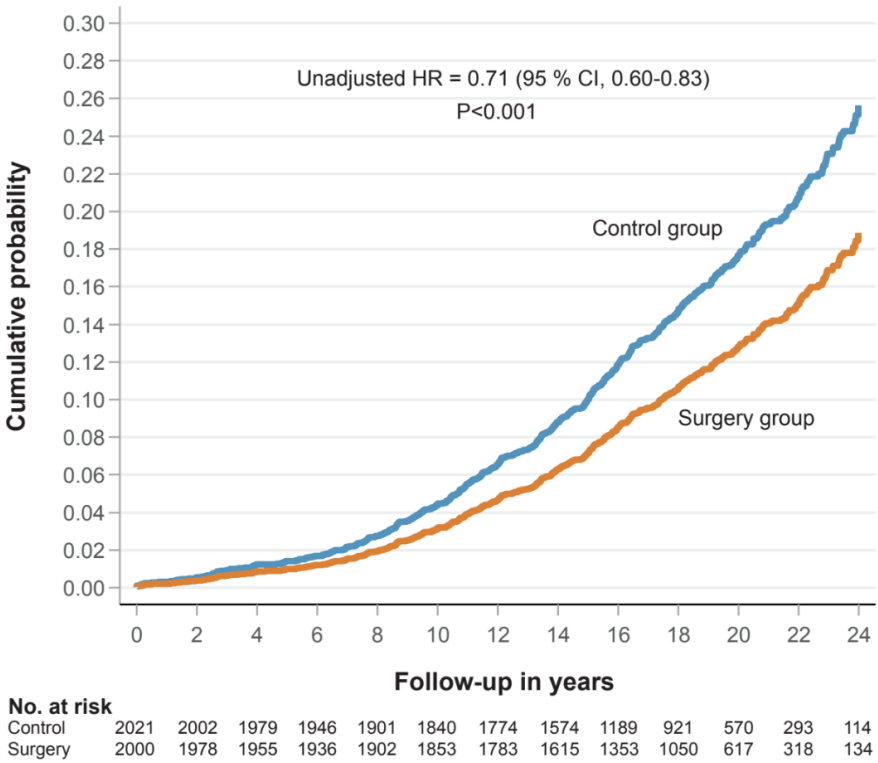

***Figure 11**. Surgical obesity treatment and the risk of atrial fibrillation during long-term follow-up.*

Paper Ⅱ

First-time heart failure occurred in 188 (9.4%) of the participants in the intervention group and in 266 (13.1%) of those receiving usual care. The median follow-up was 22 years. The risk of developing heart failure in the surgery group was 35% lower than in the control group (sHR 0.65; 95% CI 0.54–0.79; P< 0.001) (**Figure 12)**. Data was pooled from the two study groups, the quartile of participants with the largest weight loss after 1 year (mean -41 kg) showed the greatest risk reduction (sHR 0.51; 95% CI 0.30–0.70; P< 0.001). After adjustment for surgical intervention and potential baseline confounders, this association remained statistically significant (sHR 0.60; 95% CI 0.36–0.97; P=0.038).

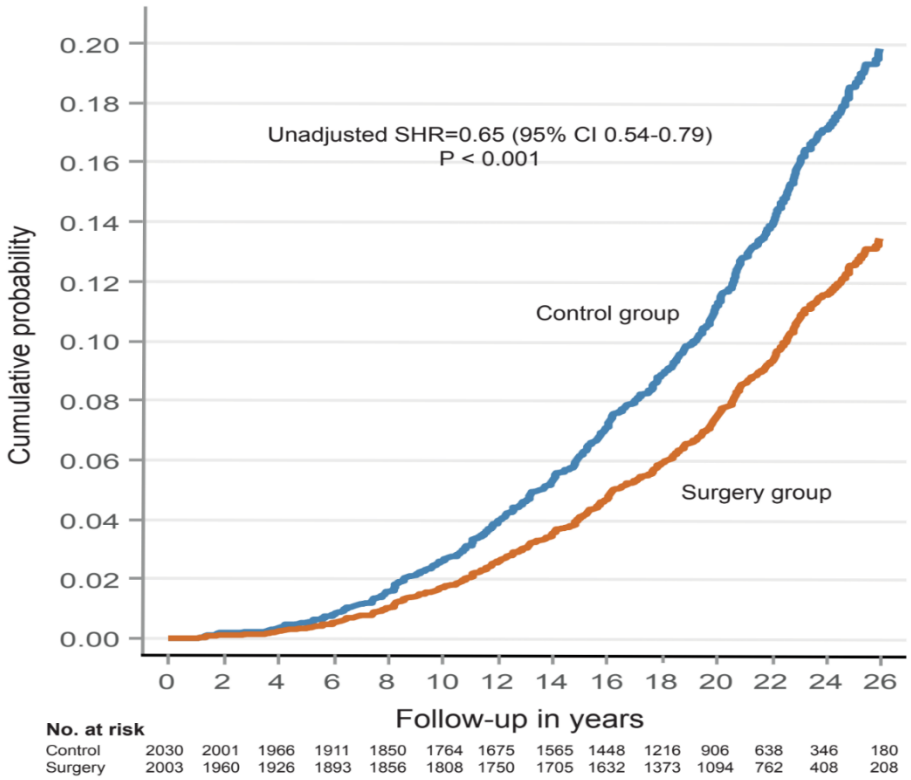

***Figure 12**. Surgical obesity treatment and the risk of heart failure during long-term follow-up.*

Paper III

During a median follow-up of 20.1 years, the BMI of 40.1 kg/m^2 remained unchanged. First-time heart failure occurred in 266 of patients (13%) and was related to male sex, increasing age, hypertension, higher cholesterol, diabetes mellitus and elevated free thyroxine. eGFR was negatively related to heart failure risk. In unadjusted analysis, time-dependent variables, atrial fibrillation (sHR ratio 5.38; 95% CI: 4.06-7.14) and myocardial infarction sHR 5.54; 95% CI: 4.04-7.60) were statistically significant and strongly related to incident heart failure (**Table 5**).

Table 5. *Univariate and multivariate regression models as risk-factors for incident heart failure† including atrial fibrillation and myocardial infarction as time-dependent variables.* [#]

Variable	Model 1 Univariate	Model 2 Univariate	Model 3 AF and MI	Model 4 Multivariate
Atrial Fibrillation (time-dependent)	5.38 (4.06-7.14) ***		4.71 (3.47-6.39) ***	3.66 (2.65-5.04) ***
Myocardial Infarction (time-dependent)		5.54 (4.04-7.60) ***	4.59 (3.23-6.53) ***	3.71 (2.57-5.35) ***
Sex (male vs female)				1.56 (1.12-2.18) **
Age (per 5 years)				1.35 (1.78-1.55) ***
BMI (per 5 kg/m2)				1.05 (0.91-1.22)
Hypertension (yes vs no)				1.16 (0.94-1.19)
Cholesterol (per mmol/L				1.05 (0.70-1.47)
Diabetes (yes vs no)				1.01 (0.67-1.47)
Free thyroxine (per 5 pm/L)				1.28 (1.09-1.51) **
Smoking (yes vs no)				1.19 (0.86-1.65)
Alcohol intake (per 10 g daily)				1.01 (0.87-1.18)
eGFR (per 10ml/min/1,73m^2)				0.93 (0.80-1.08)

†Values are given as sub-hazard ratios along with 95 % confidence intervals.
[#]AF=Atrial fibrillation and MI=Myocardial infarction are applied as time-dependent covariates in all models
** p <0.01; ***p <0.001

The relationships remained stable in adjusted analysis. In a subgroup of patients with available echocardiography (n=47), 53% of patients had heart failure with preserved ejection fraction (EF ≥45%) and 47 % had heart failure with reduced ejection fraction (EF <45%).

Paper Ⅳ

A total of 25,384 subjects underwent coronary artery intervention for STEMI, and 5,529 (21.8%) deaths occurred within one year. Using normal weight as the reference value showed that obese people had the lowest 1-year mortality risk in unadjusted analysis HR 0.59 (95% CI; 0.53–0.67), but when adjusted for age and sex the difference became non-significant, HR 1.06 (95% CI: 0.94-1.20). A low mortality risk was observed in patients with overweight in both unadjusted and age adjusted analysis, HR 0.63 (95% CI 0.57-0.69) and HR 0.86 (95% CI 0.78-0.95), respectively (**Figure 13**). Underweight patients had the highest mortality in both unadjusted HR 2.22 (95% CI 1.69–2.92) and age adjusted analysis 1.72 (95% CI: 1.31-2.26).

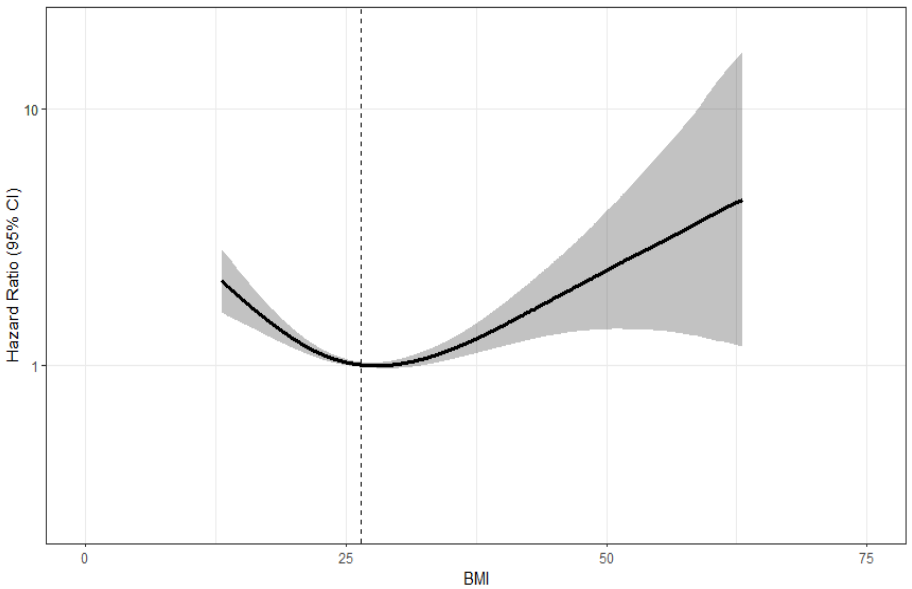

Figure 13. *Age and sex adjusted penalised spline regression (95% CI, shaded area) with continuous risk relationship between BMI and all-cause mortality in patients with STEMI who underwent PCI. HR was referenced to the median value of 26.5. P<0,001 for non-linearity.*

DISCUSSION

Obesity, weight loss and atrial fibrillation

We observed that bariatric surgery induced a sustained weight loss in people with severe obesity, which resulted in a 31 % risk reduction for new-onset AF, as compared to the obese control group. It took several years before this benefit was observed, which was more pronounced in younger patients and in those with higher blood pressure.

Obesity is an independent and modifiable risk factor for AF (165). The underlying mechanisms are probably multifactorial, but one important mediator is left atrial dilatation (79). Obesity directly contributes to the AF substrate through diastolic dysfunction, activation of pro-fibrotic pathways and atrial fibrosis (166). Obesity is associated with increased epicardial adipose tissue (EAT). The epicardial fat cells infiltrate the left atrium and induce fibrosis in the atrium (166). Atrial fibrosis causes conduction abnormalities manifested by intra-atrial conduction delay, reduced atrial voltage, presence of complex atrial electrograms, and electrical silence. These substrate changes contribute to the development and maintenance of AF (167).

Lifestyle changes that target weight loss, physical activity, increased physical fitness and modification of risk factors like high blood pressure, diabetes, smoking and prior cardiac disease have also resulted in significant reductions in the AF burden and its recurrence (168-173).

AF is prevalent in patients with OSA (174). Mechanisms by which OSA may increase the risk of AF include intermittent nocturnal hypoxemia and hypercapnia, and enhanced sympathetic tone with surges in blood pressure during apnoeic episodes leading to left atrial stretch through pressure and volume overload. A further mechanism is increased oxidative stress and inflammatory processes which contribute to left atrial remodelling and fibrosis resulting in aberrations in atrial structure and electrical activity (175-177). Obesity is concomitant risk factor for both, OSA (178) and AF. It has also been shown that OSA is associated with a hypercoagulative state which increases risk of stroke in AF patients (179). Treatment of AF is more effective when combined with CPAP therapy of OSA (180). Weight loss leads to improvement in OSA, thus providing health benefits (181).

Obesity, weight loss and heart failure

In the present study with a median follow-up of 22 years, the surgery group displayed a 35% lower incidence of first-time HF diagnosis compared to the control group (sHR 0.65; 95% CI 0.54–0.79; P< 0.001). Separation of the cumulative incidence curves occurred after 5 years of intervention, showing that a sustainable weight loss over a long period of time is required to observe a primary preventive effect. A greater weight loss was associated with a larger risk reduction.

Obesity leads to an increased cardiac output and hypertension, thus exerting increased preload and afterload on the left ventricle which in turn leads to the development of left ventricular hypertrophy (182). Also, obesity-associated diabetes, obstructive sleep apnea, and systemic inflammation (183), may cause excessive deposition of collagens, abnormal glycosylation of proteins and crosslinking of collagen in the myocardium (184, 185). This process leads to reduced diastolic compliance with increased left ventricular filling pressures and left atrial enlargement (186). The main result is an increased risk for the development of HFpEF and atrial fibrillation. On the other hand, obesity, and abdominal obesity in particular, is associated with atherosclerotic risk factors including hypertension, diabetes, and dyslipidemia which leads to atherosclerotic coronary plaque progression, coronary artery disease, and myocardial infarction (186, 187). Myocardial damage is followed by left ventricular remodeling in the form of left ventricular dilatation and a declining ejection fraction compatible with HFrEF. Heart failure with preserved ejection fraction represents more than half of all new HF diagnoses. More than 80% of patients with HFpEF are either overweight or obese (85, 188).

Data from the Scandinavian Obesity Surgery Registry was compared with a Swedish nationwide registry of subjects treated with a structured intensive lifestyle program (189). This study found that gastric bypass surgery resulted in a greater weight loss than that attained by lifestyle intervention. Further, the surgery group had a significantly lower risk of HF compared to the lifestyle group. However, the incidence rates were low in both treatment groups, for surgery 0.41% and for the lifestyle intervention 0.76%, during a median follow-up of approximately 4 years.

Obesity, HFpEF, AF and thromboembolic risk

AF is a powerful predictor of the development of HFpEF and AF precedes the diagnosis by a few years(190, 191). A critical component of HFpEF is the development of atrial myopathy, which not only contributes to elevated pulmonary venous pressures and exertional dyspnea but also to atrial thrombus formation and thromboembolic stroke, independent of the presence of AF (192, 193). In clinical practice, the association between AF increased risk of stroke is widely accepted based on studies like that of *Wolf et al*, (194). It has been postulated that the mechanism behind the enhanced risk of stroke is directly related to AF causing chaotic atrial contraction which in turn drives thrombus formation. However, it has been shown that the decrease in flow velocity in the left atrium (LA), due to atrial myopathy and inflammation, predisposes to thrombus formation. (195). Obesity promotes systemic inflammation which adversely influences the biology of epicardial adipose tissue (EAT). Proinflammatory secretory adipokines are then produced that promote structural and functional changes in the underlying myocardium (196). When abnormal EAT is associated with the left ventricle (LV), the result is microcirculatory dysfunction and fibrosis. This leads to functional impairment of distensibility, increased cardiac filling pressure which all contribute to exertional dyspnea and development of HFpEF (69, 197). Adverse effects, of proinflammatory EAT on the LA may also result in electroanatomic remodeling leading to atrial myopathy (198). These circumstances predispose the patient to blood stasis, spontaneous thrombus formation and stroke (192). The development of LA myopathy is central to the pathogenesis of both AF and HFpEF. In HFpEF, the greater LA stiffness is due to atrial fibrosis and this has been shown to be a strong determinant of AF which is a biomarker of atrial myopathy (199, 200).

Patients at risk for stroke or with a history of stroke monitored using continuous electrocardiography able to detect AF have not shown a temporal relationship between stroke and AF (201, 202). One-third of patients with stroke, presented AF only after the cerebrovascular event (203). To the contrary, HFpEF increases the risk of a subclinical cerebral infarction in patients without a history

of AF (204). Specifically, the severity of LA disease and the degree of LA fibrosis is associated with stroke and vascular brain injury in patients with or without AF (205, 206). Treatment according to the rhythm control strategy to reduce the burden of AF, using antiarrhythmic agents or catheter ablation where sinus rhythm was achieved, did not reduce the risk of stroke (207-209).

These observations are of importance with respect to our finding concerning atrial fibrillation and HFpEF. They support the importance of atrial myopathy as a component of HFpEF and as the primary source of the systemic thromboembolism in patients with obesity, rather than AF. In obese patients with HFpEF, the association between AF and stroke may be explained by AF being a biomarker of LA myopathy and not a direct mediator of thromboembolic events.

Mechanisms linking obesity to heart failure.

Obesity is an independent risk factor for developing heart failure (82). HF prevalence and incidence have increased due to the therapeutic advances in recent decades which have reduced mortality in HF. However, these advances are mainly limited to HFrEF. In the case of HFpEF, representing around 50% of all HF cases (210), there still remains a lack of specific therapeutic strategies other than treating co-morbidities and obtaining fluid balance (211).

Patients with HFpEF are more often obese than those with HFrEF. One study found that 41% of patients with HFpEF were obese (210). A systematic review from 2017 studying risk prediction models for incident HF showed that most studies were performed in a general population (212). Some investigations were performed in specific populations such as patients with diabetes, atrial fibrillation, coronary heart disease, hypertension, or valve disease. The predictors of HF included age, male sex, systolic blood pressure, diabetes, smoking, left ventricular hypertrophy, coronary heart disease, and myocardial infarction.

To our knowledge no study has been performed to determine predictors of HF in an obese population. A study of this kind is of utmost

importance given the increasing prevalence of obesity and its association with HF. An early intervention by treating risk factors would allow for a preventive strategy in a risk population and, thereby, delaying or preventing HF onset.

In our study of patients with BMI of 40.1 kg/m^2, the risk factors for HF were similar to those observed in the general population and included advanced age male sex, hypertension, higher cholesterol levels, diabetes, and smoking. On the contrary normal renal function had a protective effect.

Furthermore, we observed that free thyroxine levels were independently associated with risk for atrial fibrillation and heart failure, suggesting that subclinical forms of hyperthyroidism maybe of importance with respect to the development of cardiovascular disease in obesity. This relationship which has received little attention previously (213) was apparent in the total study group, especially among females. In a Norwegian study, a positive association between thyroid stimulating hormone (TSH) and BMI was observed (214). Leptin, secreted by adipose cells, plays a role in thyroid hormone regulation by promoting release of thyrotropin releasing hormone which stimulates TSH release (215). Leptin may also increase conversion of thyroxine (T4) to triiodothyronine (T3) (216). In the present series of investigations, the use of thyroid preparations was similar in both patients who developed AF and heart failure and in those who did not develop these conditions. Therefore, this is unlikely to explain our findings. The relationship between elevated thyroid levels within the normal range and incident heart failure in individuals with obesity deserves further research.

Important predictors of cardiac dysfunction may vary over time. In the present study, atrial fibrillation and myocardial infarction as time varying variables displayed a strong correlation with incident heart failure in both unadjusted and adjusted analysis. Based on these findings we speculate that obesity causes heart failure through two separate mechanisms. The first mechanism appears to be related to increased preload and afterload leading to left ventricular hypertrophy atrial enlargement and atrial fibrillation. Further, diabetes (35), obstructive sleep apnea (36), and systemic inflammation (37) are likely to cause excessive deposition of collagens, abnormal glycosylation of proteins and crosslinking of collagen in the myocardium. This would lead to diastolic dysfunction and HFpEF. The second mechanism may

be related to the development of atherosclerotic risk factors including hypertension, diabetes, dyslipidemia and obesity itself leading to atherosclerotic coronary plaque progression, coronary artery disease, and myocardial infarction (43-45). Myocardial damage is followed by left ventricular remodeling in the form of left ventricular dilatation and declining ejection fraction (HFrEF). Diastolic heart failure is the most common heart failure phenotype in people with obesity (85, 217).

Obesity paradox or 'BMI paradox'

In our study on the prognostic implications of BMI after STEMI, no prognostic significance of obesity was observed after adjustment for baseline covariates when compared with subjects of normal weight. After STEMI, patients who were overweight had the lowest mortality, and those who were underweight had the highest mortality. Similar results were seen in a study by *Flegal et al* who found obese patients (BMI > 30 kg/m^2) with CAD had an increased mortality compared to those patients who were overweight (218).

Several studies have shown a phenomenon known as the obesity paradox, where obesity confers a protective effect with regards to adverse outcomes after acute myocardial infarction and percutaneous coronary intervention (219, 220). In acute coronary syndromes, the relationship between BMI and mortality has been found to be U-shaped with the lowest mortality risk in patients with BMI around 35 kg/m^2. Patients who are underweight or normal weight carry the highest risk (219, 220). The question arises whether it is the fat mass that exerts a protective effect. BMI is widely used in epidemiological studies as a surrogate for fat mass. However, BMI reflects the total body weight which includes both fat mass and lean mass. A lean body mass that is proportionally higher than the fat mass is associated with better prognosis (141). Secondly, another factor that confers an improved prognosis is physical fitness. Increased physical activity and higher cardiorespiratory fitness are significant predictors of better CVD outcomes (152). Lavie et al, have shown that HF patients with a high CRF did not conform to the obesity paradox (153). Another factor of importance while studying the obesity paradox is to account for the unintentional weight loss. Cachexia due to cancer and other chronic diseases generate a low BMI that is associated with poor prognosis (142, 221). To study the obesity paradox an optimal design should account for

confounding factors like body composition, the CRF and whether weight loss is unintentional.

The nomenclature obesity paradox has it flaws as it reflects as fat mass having a protective effect whereas it has been shown that there are other confounders that improve the survival once you have established CVD. Designating it as 'BMI paradox' is more applicable.

On a closing note a quote by Carl Lavie is quite appropriated: '*Better Fat and Fit Than Lean and Lazy'*.

Study strengths and limitations

The SOS study was not randomized as Swedish ethical review boards did not approve this design, because of a high postoperative mortality in the 1980s. The surgery group was, therefore, comprised of individuals who expressed a preference for treatment with bariatric surgery. It should also be considered that a significant number of subjects in the obese control group underwent bariatric surgery during follow-up. Thus, many analyses were performed as per protocol and not as intention to treat. Only 13% of participants in the surgery group received GBP, a method that offers the greatest weight loss and is the surgical technique that is most frequently applied in Sweden today. A majority in the surgical group received treatment with surgical techniques including VBG and GB that have largely been abandoned today. The choice of surgical method was based on the techniques that were commonly applied when the study was initiated in 1987. Atrial fibrillation and heart failure were not a pre-specified endpoint of the trial and these diagnoses were obtained by crosslinking the SOS database with the Swedish National Registers.

The main strengths of the SOS study include a large study cohort, a prospective controlled design, and a long period of follow-up and excellent patient compliance with respect to study follow-up.

The main limitation of the SCAAR registry study, is its observational nature, which impedes from making any causal inferences. As only surviving hospitalized patients are included, the possibility of selection bias, residual confounding and survival bias cannot be ruled out. BMI as a surrogate for obesity, has some limitation since it does not

distinguish between body fat and lean body mass nor does it provide information about fat distribution. Waist circumference as a measure of abdominal adiposity was not available. It was not possible to determine whether weight loss was intentional or unintentional. Lastly, cause-specific mortality data was not studied.

The strength of the study based on the SCAAR register includes a large sample size of real-world data and a homogenous group of patients treated with PCI for ST-elevation myocardial infarction.

CONCLUSIONS

In people with severe obesity, bariatric surgery induces a substantial weight loss that is maintained over time. This resulted in significant primary preventive effect on the occurrence of atrial fibrillation and the development of heart failure. A greater weight loss resulted in a larger risk reduction for heart failure. Atrial fibrillation, which is reflected by diastolic dysfunction and myocardial infarction, which is related to systolic dysfunction, include two different mechanistic pathways for the development of heart failure. After adjustment for age and sex overweight displayed the lowest risk for 30-day and 1-year mortality after PCI treatment of STEMI and underweight the highest.

FUTURE PERSPECTIVES

The medical profession should be more pro-active in assessment of fat-mass in patients and to give appropriate advice about life style intervention like PA and CRF and dietary intake. Where appropriate bariatric surgery should be recommended.

More studies are required to map out the obesity paradox using better quantification of obesity, distinguishing between intentional and unintentional weight loss, and assessing the CRF.

Optimal treatment of baseline risk factors, together with treatment of atrial fibrillation and myocardial infarction may promote a further lowering of heart failure incidence and thereby, improving outcomes in patients with obesity.

Obesity is associated with an increase in epicardial fat mass and its close anatomical location the heart makes it interesting candidate in the development heart diseases and, therefore, making it an enthralling area for future research.

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