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DOI (link to publication from Publisher):
10.5278/vbn.phd.med.00076

Publication date:
2016

Document Version
Publisher's PDF, also known as Version of record

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REGISTER-BASED COHORT STUDIES

BY
AZIZA AZIMI

DISSERTATION SUBMITTED 2016

AALBORG UNIVERSITY
DENMARK

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Dissertation submitted 2016

Thesis submitted: Juli 2016

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PhD Series: Faculty of Medicine, Aalborg University
ISSN (online): 2246-1302
ISBN (online): 978-87-7112-753-9

Published by:
Aalborg University Press, Skjernvej 4A, 2nd floor, DK - 9220 Aalborg Ø
Phone: +45 99407140, aauf@forlag.aau.dk, forlag.aau.dk

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ENGLISH SUMMARY

Over the last decades, the prevalence of overweight and obesity have increased and grown to be an important health concern worldwide. Obesity is associated with increased risk of type II diabetes (DM II), cardiovascular diseases (CVD), stroke, myocardial infarction (MI), hypertension, heart failure (HF) and cardiovascular mortality. However, the prognostic influence of obesity on mortality among patients with manifest coronary artery disease (CAD) is still controversial.

Guidelines recommend weight reduction for overweight and obese patients with CAD. While obesity is a risk factor for developing CAD, obese patients with established CAD have reduced mortality risk compared to patients with normal weight. This phenomenon has been called "the obesity paradox" and has fueled many discussions among epidemiologists as to whether this relation is causal.

By linkage of the Danish Coronary Angiography Registries and the National Patient Registry, National Prescription Registry, Danish Register of Causes of Death, and the Danish Civil Registration System, we have been able to examine the association between obesity and mortality in patients with established CAD.

The aims of the present thesis were to examine the following questions in patients with established CAD:

1. Is overweight and obesity associated with increased mortality?

2. Is weight gain associated with reduced mortality?

3. Is low BMI associated with reduced risk of developing HF?

The main finding of the first study was that overweight patients with CAD have improved survival compared to normal weight patients. Underweight and severely obese patients have increased risk of mortality. The study demonstrated the presence of an overweight paradox rather than an obesity paradox. The second study demonstrated that overweight subjects whose weight remained stable had decreased risk of mortality compared to normal weight patients with stable weight. Weight gain or weight loss was not associated with change in mortality risk for overweight and obese patients. The last study illustrated that the risk of developing HF in patients with CAD increases noticeably for underweight and obese patients. On the other hand, overweight subjects had the lowest incidence of HF.

DANSK RESUME

I de sidste årtier er forekomsten af overvægt og fedme øget, og det udgør et stigende sundhedsproblem på verdensplan. Fedme er forbundet med type II-diabetes (DM II), apopleksi, myokardieinfarkt (MI), hypertension, hjertesvigt (HF) og kardiovaskulær mortalitet. Alligevel betydningen af overvægt for dødeligheden hos patienter med koronararteriesygdom (CAD) er stadig omdiskuteret.

Der er evidens for at fedme er en risikofaktor for udvikling af CAD og retningslinjer anbefaler vægttab for overvægtige og svært overvægtige patienter. Dog har man observeret en lavere dødelighed blandt svært overvægtige patienter med CVD sammenlignet med normalvægtige. Dette fænomen er blevet kaldt fedme paradokset og det vakte epidemiologernes opmærksomhed.

I denne afhandling har vi koblet de danske koronarangiografi registre sammen med andre registre; Landspatientregistret, Lægemiddelregistret, danske register over dødsårsager og det danske Centrale Personregister for at undersøge sammenhængen mellem fedme og mortalitet hos patienter med CAD.

Formålene med denne afhandling var at undersøge;

1. Er overvægt og fedme forbundet med øget dødelighed?

2. Er vægtøgning hos patienter med CAD forbundet med reduceret dødelighed?

3. Er lavt BMI forbundet med reduceret risiko for at udvikle HF?

De vigtigste resultater fra den første undersøgelse viste, at overvægtige patienter med CAD har bedre overlevelse sammenlignet med normalvægtige patienter. Undervægtige og svært overvægtige patienter har øget risiko for dødelighed. Vores resultater bekræftede et overvægts paradoks snarere end en fedme paradoks. Den anden undersøgelse viste, at overvægtige patienter som holder deres vægt stabil, har mindre risiko for dødelighed sammenlignet med normalvægtige patienter med stabil vægt. Derimod var vægtøgning og vægttab ikke forbundet med øget risiko for død for overvægtige og svær overvægtige patienter. Den sidste undersøgelse viste, at risikoen for at udvikle HF hos patienter med CAD har steget mærkbart for de undervægtige og svær overvægtige patienter. Derimod havde de overvægtige den laveste risiko for udvikling af HF sammenlignet med de andre BMI grupper.

ACKNOWLEDGEMENTS

I can say that this part is the most difficult. My journey started in 2011while I was looking for a topic and supervisor for my Master's thesis when I met Christian Torp-Pedersen, who suggested a pre-graduate research semester. In the beginning, Christian taught me statistical programming - which seemed very difficult. He was very fast and I thought I would never learn it. Gradually, I learned more about registry-based research, and it caught my attention. Christian was my savior. He always had a solution for any problem that concerned the project and was inspiring. I had spent my pre-graduate research working on the obesity paradox, which was quite interesting. I was also introduced to Mette Gitz Charlot who had just finished her Ph.D. project; and she became my other supervisor. She was helpful with ideas and discussions about the studies. When Christian started working at Aalborg University, it was not easy to knock on his office door when I wanted to discuss or needed help with statistical programming. I worked on the project while I was medical student and later during my clinical work. Christian offered to enroll me at Aalborg University in order to receive six months funding. The financial help gave me time to finish this project. I want to thank Gunnar Gislason for his contribution to this project and for offering me to be part of the Gentofte research team.

I owe a great thanks to all my colleagues at the research department in Gentofte (PA-Forskning), who were always ready to help with statistical programming and a good discussion. Thanks to the support from Aalborg University for funding my project for six months. I also want to thank all the coauthors of this project for their guidance and good comments. Finally, I would like to thank my family and friends for their support, especially my husband, Malek for his encouragement and positive energy

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PAPERS

This Ph.D. thesis is based on three manuscripts carried out during my time as a PhD student at the department of Cardiology, Gentofte Hospital, affiliated with the Graduate School of Health and Medical Sciences, University of Aalborg.

I. **Moderate overweight is beneficial and severe obesity detrimental for patients with documented atherosclerotic heart disease.**
Azimi A, Charlot MG, Torp-Pedersen C, Gislason GH, Kober L, Jensen LO, Thayssen P, Ravkilde J, Tilsted HH, Lassen JF and Thuesen L.
Heart. 2013;99:655-60

II. **Overweight patients with coronary heart disease with stable weight have a better prognosis than normal weight patients**.
Azimi A, Torp-Pedersen C, Gislason GH, Kober L, Jensen LO, Ravkilde J, Tilsted HH, Hansen PR and Charlot MG.
Submitted 2016.

III. **Overweight patients with ischemic heart disease have lower risk of heart failure.**
Azimi A, Torp-Pedersen C, Gislason GH, Kober L, Jensen LO, Ravkilde J, Tilsted HH, Hansen PR and Charlot MG.
Submitted 2016.

ABBREVIATIONS

CAD	Coronary artery disease
CVD	Cardiovascular disease
DM	Diabetes mellitus
HF	Heart failure
BMI	Body mass index
CRF	Cardiorespiratory fitness
CI	Confidence interval
HR	Hazard ratio
ICD	International Classification of Diseases
IRs	Incidence rates
MI	Myocardial infarction
WHO	World Health Organisation

INTRODUCTION

According to the World Health Organization (WHO), overweight and obesity are defined as increased fat accumulation in the body which is higher than is considered a healthy weight for a given height. A person with a body mass index (BMI) over 25 kg/m^2 is defined as overweight, and a BMI over 30 kg/m^2 is defined as obese (103). BMI is an easy and crude measure of body fat, calculated by dividing the weight in kilograms by the square of height in meters however, it does not differentiate between body fat and lean mass (1).

The prevalence of overweight and obesity has increased globally. In 2014, more than 1.9 billion adults were considered overweight and over 600 million were obese (103). Abnormal fat accumulation constitutes a major health problem, as it is associated with increased risk of metabolic and cardiovascular disease. A recent study from the United States showed that obesity was the direct cause of 18% of deaths from 1986-2006(2). There is evidence that overweight and obesity are risk factors of developing cardiovascular disease, type II diabetes, hypertension, colorectal cancer, gallbladder cancer, pancreatic cancer, ovarian cancer, heart failure, and early death. (3-7).

Previous studies investigated the relationship between excess body fat and cardiovascular disease. They found that obesity leads to cardiovascular disease, mediated by an increased risk of acquiring well-known cardiovascular risk factors such as, hypertension, dyslipidemia, glucose intolerance, and low-level inflammation and atherosclerosis by different pathophysiological pathways (8, 9).

Atherosclerosis is the primary cause of coronary artery disease. It is described as an inflammatory disease in the arterial intima, and is seen even in young people. Progression of atherosclerosis initiates with lesions of the artery wall, and includes accumulation of lipids, cholesterol, calcium, macrophages, T-cells, and mast cells. Over time the artery wall will be covered by collagen, forming a plaque. As the plaque hardens and enlarges, the coronary artery gradually narrows, and the blood flow to the heart muscle is impaired (10, 11). Early signs of impaired flow include~~s~~ angina and dyspnea, and in cases of plaque rupture, the blood plates clot~~s~~ on its surface, leading to total occlusion of the coronary artery, and causing a heart attack. By performing a coronary angiography, the stenosis can be verified and further treatment such as percutaneous coronary intervention (PCI) can reduce the stenosis.

However, obesity influences the structure and function of the cardiovascular system by increasing the blood and stroke volume, which leads to higher filling pressure and volume. Furthermore, the cardiac output increases, leading to higher demands on the cardiac system which, over time, causes changes in the left ventricular, resulting in hypertrophy and heart failure (12).

Despite these adverse effects of obesity, numerous epidemiologic studies have demonstrated a phenomenon called the obesity paradox where obese patients with cardiovascular disease have lower risk of mortality compared to patients with normal weight (1, 13-16). The obesity paradox has been found among patients with atrial fibrillation, hypertension, cardiac surgery, and also patients with chronic diseases like diabetes mellitus, chronic kidney disease, and chronic obstructive pulmonary disease (17-22). There are also numerous studies which have not confirmed the favorable effect of obesity among CVD patients (23-28).

Some studies have investigated the association between obesity and mortality by using BMI as a proxy for obesity and have been criticized as a result, because BMI is not a sufficient measure—of body fat, since it does not account for body composition. Nevertheless, other studies using different measurements like body fat and waist circumference have also confirmed the existence of the obesity paradox among patients with CVD (29, 30). Even though the obesity paradox phenomenon has been known for decades possible explanations have been sparse. Apart from possible causality, other explanations are bias, reverse causation, and confounding (31-33). Many guidelines recommend weight loss for overweight and obese individuals (34, 35). Several studies recommend intentional weight loss as it will improve the metabolic syndrome and the prevalence of diabetes mellitus, hypertension, and mortality and CVD (36-39). Other recent studies showed that overweight individuals with no weight change had better prognosis than normal weight patients with no weight change (40-42).

OBJECTIVES

1. To explore the obesity paradox among patients with established CAD, we hypothesized that obese patients have better survival compared with normal weight patients.

2. To explore the effect of weight change on mortality among patients with CAD, we hypothesized that weight loss will improve the survial chance.

3. To explore the risk of incidence HF in patients with CAD, we hypothesized that patients with lower BMI have decreased incidence of HF.

METHODS

DATABASES

The studies of this thesis were based on data from Western Danish Heart Registry, and comprising nationwide angiography data, The Civil Person Registry, The Prescription Registry, The National Patient Registry and The Causes of Death Registry. The Civil Person Registry provides a unique identification number at birth which keeps information on gender and date of birth. This allows individual-level linkage across nationwide registries. The National Patient Registry holds information on hospital admissions and discharge dates, diagnosed according to the International Classification of Diseases (ICD) system, 8th revision (ICD-8) from 1977 until 1994, and the 10th revision (ICD-10) thereafter. The information on prescription drugs, dose and dispensing, obtained from The Danish Prescription Registry, are coded according to the Anatomical Therapeutical Chemical (ATC) classification since 1995 (43).

All data were retrieved and analyzed through Statistics Denmark. Statistics Denmark prepared the linkage of registries and encoded the identification numbers to ensure anonymity.

DEFINITION OF COMORBIDITY AND MEDICATION

Details on medication, comorbidity are listed in Table 1.

Pharmacotherapy	**ATC codes:**
Loop diuretics	C03C
Beta blockers	C07
ACE inhibitors/ARBs	C09
Comorbidities	**ICD codes:**
Periphery vascular disease	I70-3, R02, I771,
Heart failure	I110, I130, I132, J819, I517, I42, I43, I50, 427
Cerebral vascular disease	I60-9,411-4
Chronic obstructive pulmonary disease	J42-4, 490-2,
Renal disease	N03-4, N17-9, R34, I12-3, T858-9, Z992,582-8
liver disease	K70-7, K766, K711, K704, B150, B160, B190, 571-2,456
Malignancy	C00, C97,
Hypertention	Defined from combination treatment with a least two classes of anti-hypertensive drugs
Hyperlipidaemia	Defined from treatment with statin
Arrhythmia	I46-49, 4273-9
Ischemic heart disease	I20, I23-5, 411-4

COHORTS AND OUTCOMES

PAPERS I+II: RISK OF ALL-CAUSE MORTALITY

The population in study I were patients with verified coronary artery disease between 1 January 2000 and 31 December 2010, and in paper II between 1 January 2000 and 31 December 2012. Subjects with no vessel disease, and those lacking information on weight or height were excluded. In Paper II all patients with weight change within the first 6 months of follow-up were excluded. We have adjusted for chronic obstructive pulmonary disease, renal disease, liver disease, prior heart disease, stroke, malignancy, and family history of coronary artery disease (including severity), diabetes, hyperlipidemia, hypertension, and smoking status. In paper I, we divided the study population according to WHO classification of BMI and chose normal weight class II (BMI: 23-25 kg/m2) as the reference group. In paper II, all patients have been divided in four BMI classes then being further divided into three weight categories. Our reference group was of stable, normal weight.

PAPER III: RISK OF HEART FAILURE

The population of this study included all patients with coronary heart disease verified by coronary angiography between 1 January 1998 and 31 December 2012. We included all subjects who got their first prescription of loop diuretic medicament three months after their hospital discharge. We adjusted for chronic obstructive pulmonary disease, renal disease, liver disease, peripheral artery disease, cerebral artery disease, malignancy, and family disposition for ischemic heart disease, as well as age and sex. Additional information on comorbidities such as weight, height, diabetes, Statin treatment, Hypertension treatment, smoking status, indication of coronary angiography and severity of coronary artery disease determined by coronary angiography (0, 1, 2, or 3 vessel disease, multi vessel [≥2] disease, and diffuse [≤50% stenosis] disease, respectively were obtained from Danish angiography registries. Patients with HF were identified by using treatment with loop diuretics, including furosemide (ATC code C03CA01) and bumetanide (C03CA02) as a proxy. We also included data on filled prescriptions of common types of drugs used in treatment of HF, including β-blockers (C07) and angiotensin-converting enzyme (ACE) inhibitors (C09AA). The study population has been divided into five BMI groups. The reference group was of normal weight (BMI: 20-25).

STATISTICAL ANALYSES

All statistical analyses were done with the SAS statistical software version 9.2 (SAS Institute Inc., Cary, NC), Stata software version 11 (Statacorp, College St., TX) and R software version 3.2.2.

Data were presented as categorical variables with numbers and percentages, and continuous variables as means with standard deviation. In paper I-II the incidence rates (IRs) of death were presented per 1000 person-years. We used survival analysis to calculate the difference in survival associated with BMI and weight classes. The Kaplan-Meier estimates gave us a graphic presentation of survival in different BMI groups. The outcomes were estimated by Cox proportional hazard regression models. In paper III, the cumulative incidence of HF taking into account a competing risk for non-HF death was calculated by using the Aalen-Johansen method. Hazard ratios (HRs) with mortality as a competing risk for the study outcome were estimated with a modified Cox proportional hazard regression analysis (*cause-specific proportional hazards model)* adjusted for comorbidities. Model assumptions, linearity of continuous variables, fulfillment of the proportional hazard assumption and lack of relevant interactions were tested and found to be valid.

ETHICS

The research protocol was approved by the Faculty of Health Sciences, University of Aalborg. In Denmark, registry based studies do not require ethical approval and the Danish Data Protection Agency permitted the study (reference no. 2007-58-0015, international reference: GEH-2014-015).

TABLE 2. SUMMARY OF METHODS USED IN THE INDIVIDUAL STUDIES. FOR ABBREVIATIONS, SEE TEXT.

	Paper I	Paper II	Paper III
Study objective	To investigate the influence of obesity on survival in patients with CAD.	To explore the effect of weight change over time on survival in patients with CAD.	To investigate the effect of obesity on incidence of heart failure in patients with CAD.
Design	Register-based cohort study of patients with coronary artery disease from The Western Denmark Heart Registry	Register-based cohort study of patients with coronary artery disease from entire Danish Heart Center.	Register-based cohort study of patients with coronary artery disease from entire Danish heart centers.
Study period	2000-2010	2000-2012	1998-2012
N	37 573	7 683	32 545
Exclusion criteria	Subjects with missing information about height, weight, degree of the vessel disease, prior cardiac surgery or percutaneous coronary intervention and no vessel were excluded.	Patients with missing information about weight or height, weight change within 6 months, no vessel disease were excluded.	Subjects with missing information on weight, height, degree of vessel disease, prior HF or received loop diuretics before the date of coronary angiography and no vessel were excluded.

	Paper I	Paper II	Paper III
Outcomes	All-cause mortality	All-cause mortality	The incidence of HF and all-cause mortality
Covariates	Age, sex, smoking, diabetes, degree of vessel disease, hypertension, hyperlipidemia, serum creatinine, arrhythmia, periphery vascular disease, cerebral vascular disease, heart failure, chronic obstructive lung disease, cancer, prior MI.	Age, sex, smoking, diabetes, degree of vessel disease, hypertension, hyperlipidemia, family history of ischemic heart disease, heart failure, malignancy, chronic obstructive lung disease, cerebral vascular disease, periphery vascular disease, arrhythmia, renal disease and liver disease.	Chronic obstructive pulmonary disease, renal disease, liver disease, Arrhythmia, degree of vessel disease, diabetes, hyperlipidemia, hypertension, smoking status, Indication for coronary angiography, sex and age, cerebral vascular disease, malignancy, and family disposition for ischemic heart disease.
Statistical analyses	Cox proportional hazard regression models to estimate HR, Kaplan-Meier estimates.	Cox proportional hazard regression models to estimate HR, and IR.	Modified Cox proportional hazard regression analysis (cause-specific proportional hazards model). Cumulative incidence calculations.
Main results	Overweight patients with CAD had an improved survival compared with normal weight patients. Underweight and severely obese patients had increased risk of mortality. We confirmed the overweight paradox among this group of patients.	Overweight subjects with stable weight had decreased risk of mortality compared with normal weight patients with stable weight. On the other hand, weight loss in underweight and normal weight subjects was associated with increased risk of mortality.	The risk of developing HF in patients with CAD increased with obesity and underweight. Contrariwise, overweight patients had the lowest risk of HF after normal weight patients.

RESULTS

This section provides the main findings of each paper.

PAPER I: MODERATE OVERWEIGHT IS BENEFICIAL AND SEVERE OBESITY DETRIMENTAL FOR PATIENTS WITH DOCUMENTED ATHEROSCLEROTIC HEART DISEASE.

The objective of this study was to examine the obesity paradox among patients with coronary artery disease.

From 2000-2010 100128 patients who underwent coronary angiography were identified and 37573 patients were the final population of the study (Figure 1).

The mean age was 66.3 (±11) years and 26540 (70.7%) were men. The median follow-up time was 3.2 years and 5866 (15.6%) patients died. The study showed that there was a significant higher mortality risk of (HR 2.04, 95% CI, 1.63 - 2.57; $p<0.001$) for the underweight group (BMI < 18.5 kg/m^2) compared to the reference group of normal weight class II (23 ≤ BMI < 25 kg/m^2). The pre-obese (27.50 ≤ BMI < 30 kg/m^2) had a decreased risk, with a HR: of 0.82 (95% CI 0.71 - 0.95; P= 0.008).The normal weight class I (18.5 ≤ BMI < 23 kg/m^2) had noteworthy risk of mortality HR 1.28 (95% CI, 1.13 - 1.45; $p< 0.001$). The obese class III (BMI ≥ 40 kg/m^2) patients had an increased HR of 1.35 (95% CI, 1.05 - 1.72; p= 0.016) Figure 2.

The conclusions from these findings were that overweight patients class II (27.5 ≤ BMI < 30 kg/m^2) had better survival compared to normal weight class II (23 ≤ BMI < 25 kg/ m^2), on the other hand patients in normal weight class I (18.5-23 kg/m^2) and obese class II (BMI > 40 kg/m^2) had increased risk of mortality compared to normal weigh. Our results pointed towards an overweight paradox rather than an obesity paradox.

Figure 1 *Flowchart of the study population in paper I*

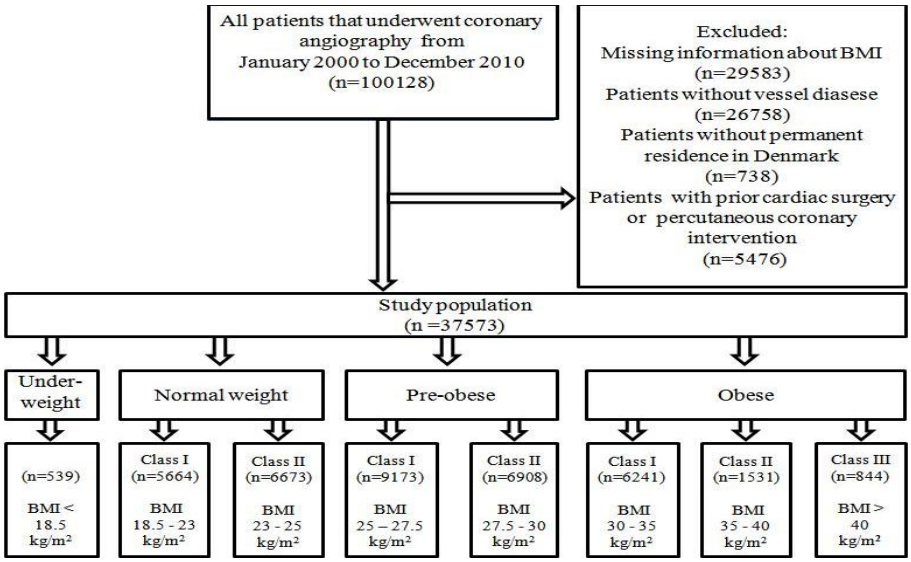
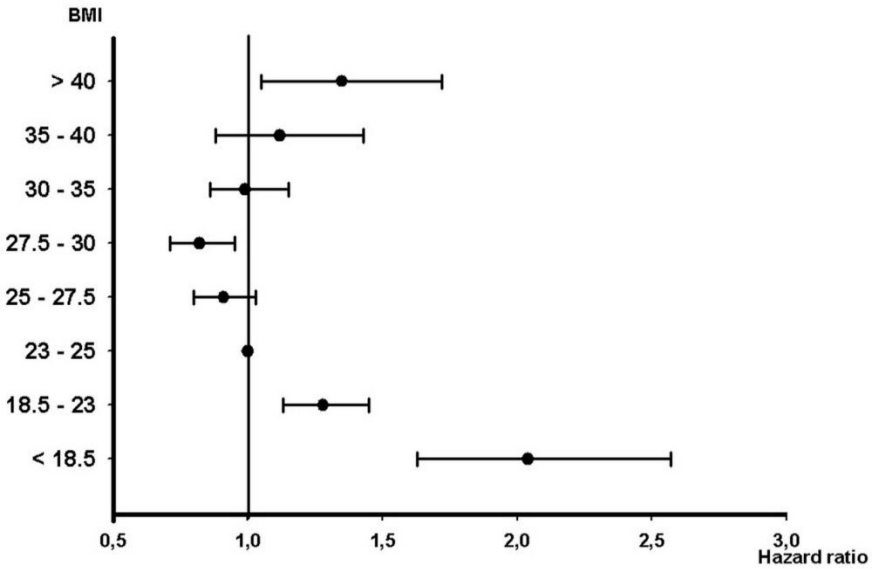


Figure 2*. Adjusted hazard ratio of all-cause mortality in different BMI groups and the normal weight (BMI: 23-25 kg/m^2) as the reference group.*



PAPER II: IMPACT OF WEIGHT LOSS AND WEIGHT GAIN ON MORTALITY RISK IN PATIENTS WITH CORONARY HEART DISEASE.

The aim of this study was to explore the impact of weight change on risk of mortality over time among patients with coronary artery disease.

In this study we enrolled all patients (n= 42372) with two coronary angiographies at two different times. We divided each BMI group into three weight change groups: weight gain, weight loss and stable weight (Figure 3).

The results showed that overweight patients with stable weight had an 18% lower risk of mortality (HR 0.82; 95% CI 0.6–0.9, P=0.04) compared to those with stable weight and normal BMI. We concluded that, overweight patients with stable weight had significantly decreased risk of mortality compared to normal weight patients with stable weight. The weight loss group had more tendencies towards high risk of mortality than stable weight (Figure 4).

Figure 3 *Flowchart of the study population in paper II*

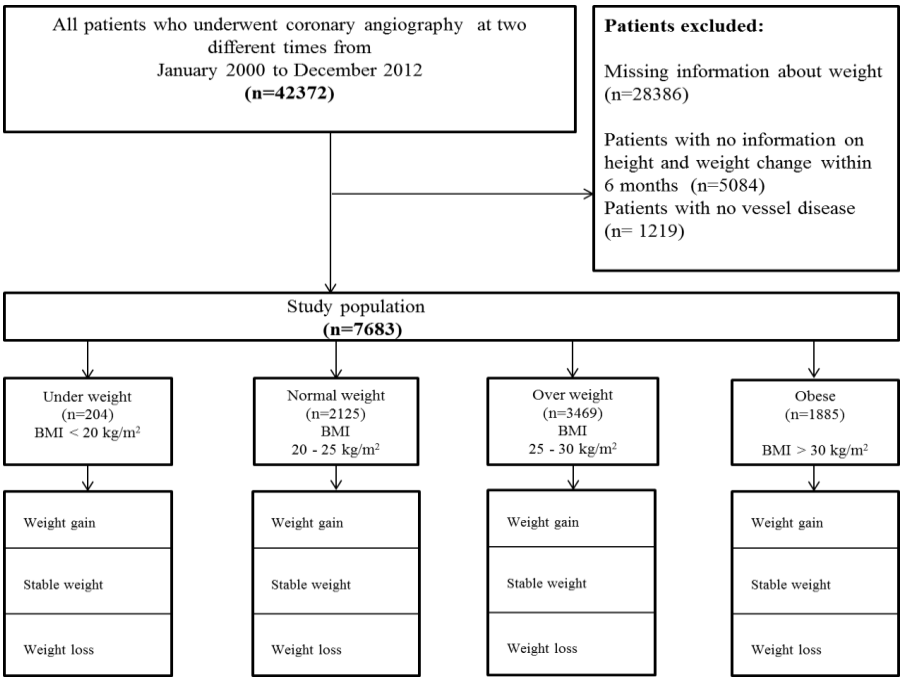
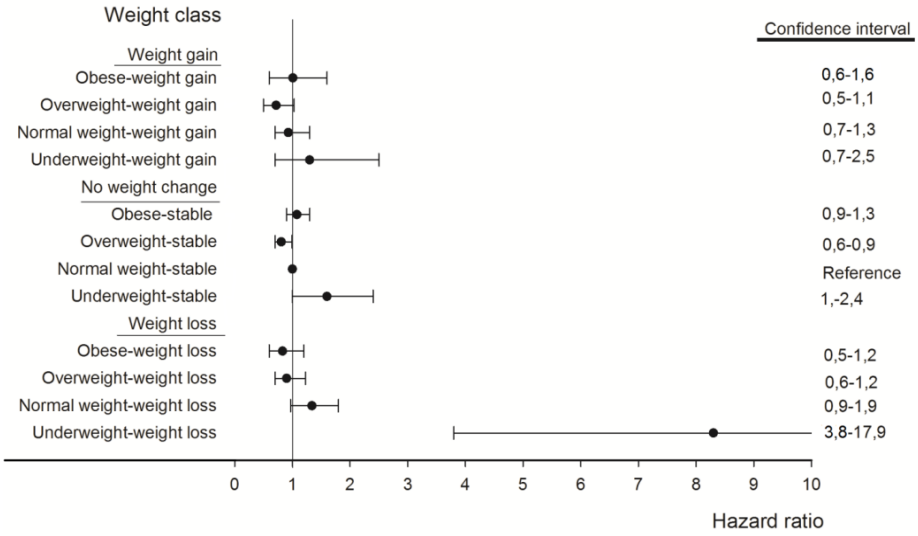


Figure 4 *Association between weight classes and risk of all-cause mortality.*

Adjusted for; age, sex, smoking, diabetes, degree of vessel disease, hypertension, hyperlipidemia, family history of coronary artery disease, heart failure, malignancy, chronic obstructive lung disease, cerebral vascular disease, periphery vascular disease, arrhythmia, renal disease, liver disease



PAPER III: RISK OF HEART FAILURE IN PATIENTS WITH CORONARY HEART DISEASE.

In this study we investigated the risk of heart failure in patients with coronary artery disease. We included a total of 31881 subjects, where 5980 developed HF during the 15 year-follow up period. When patients were divided into five groups according to their BMI (Figure 5), we found that the risk of developing HF was increased in patients with higher BMI rates than those with normal BMI. The overweight group had the lowest risk of HF after the normal weight group (Figure 6). On the other hand the unadjusted cumulative risk of mortality increased as BMI decreased.

Figure 5 *Flowchart of the study population in paper III*

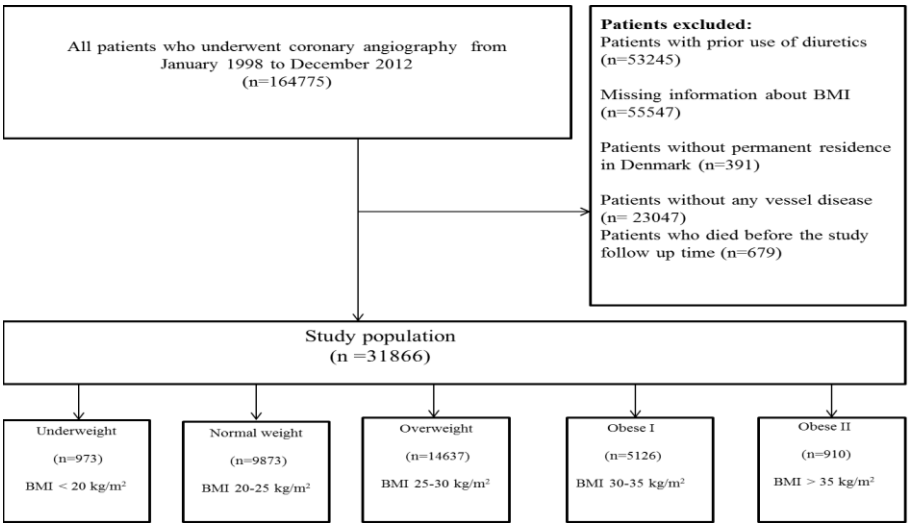
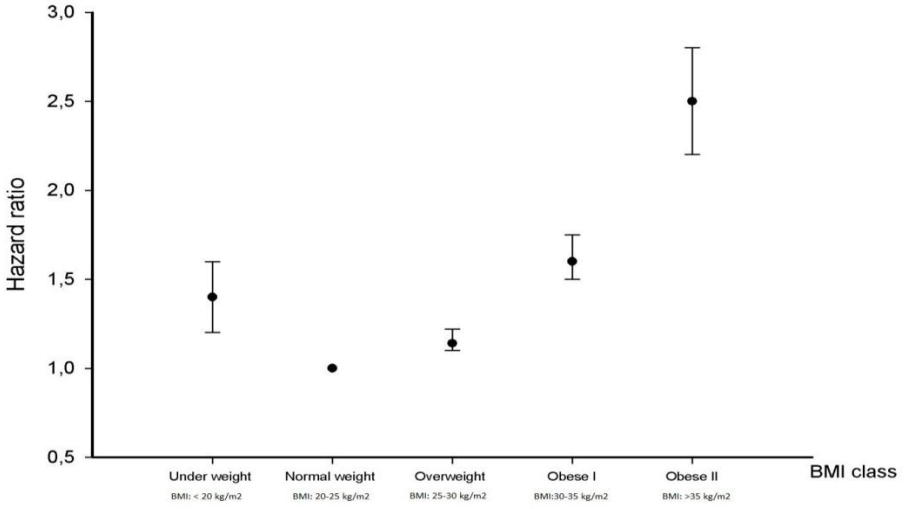


Figure 6 *Association between body mass index (BMI) and risk of heart failure determined by use of loop diuretics.* ***Results*** *adjusted for age, sex, chronic obstructive pulmonary disease, renal disease, liver disease, prior heart disease, degree of vessel disease, diabetes, hyperlipidemia, hypertension, smoking status, stroke, malignancy, and family history of ischemic heart disease.*



DISCUSSION

In this thesis, we examined the association between weight/BMI, and mortality and incidence of heart failure. Our main findings were that moderate overweight in patients with established coronary heart disease was associated with lower risk of mortality compared to normal weight patients. On the other hand, underweight and obese patients had a higher risk of mortality. We further looked at weight change and risk of mortality among this group of patients and found that overweight patients who had stable weight had decreased risk of mortality compared to patients with normal weight and stable weight. We looked at the incidence of onset HF among coronary artery population and the results showed that overweight subjects had the lowest risk of HF. However, the risk increased significantly for subjects with BMI over 30kg/m^2. Overweight and obese patients who developed HF were at lower risk for mortality compared to those of normal weight.

OBESITY AND CARDIOVASCULAR DISEASE

Obesity is a worldwide public health problem and the prevalence is growing. There is increasing evidence that obesity is an independent risk factor for developing cardiovascular disease, type 2 diabetes, metabolic syndrome, dyslipidemia, and hypertension (44, 45). Furthermore, obesity is also related to all-cause mortality (9, 46). According to the WHO, half of all deaths in Europe are caused by CVD (104), while in the USA, CVD is a leading cause of death (47).

OBESITY PARADOX

In spite of obesity being a well-known cardiovascular risk factor~~,~~ over the last three decades, there have been numerous studies that confirmed the existence of the obesity paradox – the fact that obese patients have better survival than their normal weight counterparts (1, 48-61).

We aimed to evaluate the impact of overweight and obesity on mortality and incidence of heart failure in a large cohort of patients with established coronary heart disease.

In paper 1, our main finding was that only overweight patients ($27.5 \leq BMI < 30$ kg/m2) had decreased risk of mortality compared to normal weight ($23 \leq BMI < 25$

kg/ m2). In contrast, severely obese patients (BMI > 40 kg/m2) had increased risk of mortality (15). Our finding confirmed the previous finding, that overweight patients had decreased risk of mortality (1, 62).

This study was done by using BMI as a proxy for obesity and found a J-shape relationship between BMI and all-cause mortality. Furthermore, we found increased risk of mortality for obese patients, even though previous studies have reported good prognosis for this group of patients. In this study, our reference group was patients with a BMI between 23.5-25 kg/m^2, which is a normal weight, intended to reflect the healthiest patients in the study population with respect to BMI. BMI is widely used as a measurement for weight scale, and the weight management recommendations are that people should maintain their BMI between 20-25 kg/m^2. This recommendation is for all age groups with no distinction between young, old, healthy, or people with established diseases.

Despite the obesity paradox evidence, several studies have questioned its existence and presented possible explanations of their own. Explanations include confounding, reverse causality, stating that a real association between weight/ BMI and mortality was nonexistent. A recent study found that in a CVD population, normal weight patients that were formerly overweight or obese had a higher rate of mortality compared to overweight patients with CVD. Conversely, normal weight patients with stable weight had lower mortality rates compared to patients who were always overweight (63). The same finding appeared in a population of smokers with CVD suggesting that weight loss could be due to an undiagnosed disease, which resulted in the weight loss and an increased risk of mortality. Therefore, the overweight patients appeared to have better survival. The author explained the obesity paradox as a product of reverse causality and confounding by smoking (63). Reverse causation means that the BMI and mortality relation can be biased by pre-existing obesity-related disease resulting in weight loss. Reverse causation has been used as explanation for obesity paradox in several studies and it has been pointed out that the reverse causation should be taken into account in interpretation of the results of the obesity and mortality studies (64-66).

Another study investigated the association between dysglycemia and mortality, and found that among normal-weight subjects with dysglycemia, there were more smokers than in the overweight group. The other finding was that normal weight subjects who smoked had a higher rate of mortality than overweight smokers. On the over hand, the normal weight group who never smoked, had a lower mortality rate than the overweight group who never smoked (67). In our studies, the current smokers in population paper I and III were more often normal weight than overweight and obese. In paper II, the proportion of current smokers in the overweight and obese groups was higher than in the normal weight. The number of former smokers appeared to be higher in the overweight and obese groups in all three populations. One explanation could be the fact that being diagnosed with a

severe disease make patients reflect more on their health, motivating them to change their lifestyle and comply with treatment recommendations. There are studies which reported that obese patients, due to better medication and better compliance with guideline recommendations, decreased their risk of morbidities and mortality, providing an explanation for the obesity paradox (68-72).

Another explanation might be age; many studies included younger obese and older, normal, or underweight patients. The older population has experienced more illness and disease than the younger population (73-76). In our population, the obese subjects were at least 8 years younger than the underweight, but the obese suffered more often from hypertension, hyperlipidaemia and diabetes.

Another potential explanation could be selection bias, which suggests that the population of obese patients had been treated earlier and therefore has less severe diseases. This leads us to think that the healthiest obese will be included in the study. Alternatively, the possibility of selection bias occurs when exposure and outcome both influence what is to be included in the study (77-79). In our case, obesity is a major risk factor of CAD as well as death. There are also other risk factors which increase the risk of mortality. If these risk factors are undiagnosed and have higher impact on mortality than obesity, then obese subjects might have better survival than their normal counterparts. Another explanation could be survival bias in middle-aged overweight or obese subjects, suggesting that obesity intolerance leads to low survival rates and greater incidence of CAD. It is also notable to mention lead time bias in overweight and obese patients who get CAD diagnosis at a younger age, enabling them to begin treatment earlier than normal weight patients. This time between diagnose and mortality is longer for overweight or obese than in normal weight subjects.

Weight change

In paper II, we discussed the association between weight change and mortality risk in patients with coronary artery disease. Our main findings were that overweight patients with stable weight had a significantly reduced risk of mortality compared to patients with normal and stable weight. Many researchers recommend intentional weight loss to decrease risk of mortality, CVD and other comorbidity in overweight individuals (80-83). In a recent randomized controlled trial that examined the impact of weight loss through caloric restriction on cardiovascular disease morbidity and mortality in type 2 diabetes patients, improved outcomes were reported on some conditions such as medication usage, depression, sleep apnea and CVD (84). However, other recent studies did not find benefit of weight loss (85, 86).

Additionally, a recent Danish study which investigated the impact of intentional weight loss on mortality and risk of CVD in type 2 diabetes patients found that weight loss did not lower their risk of CVD and mortality (87).

Furthermore, some studies have focused on the importance of fat distribution and visceral fat rather than weight and BMI as risk indicators (88, 89). Concerning the cardiovascular risk, it has been suggested that individuals with abdominal fat have higher risk of cardiovascular disease and mortality. The excess abdominal fat is an indication of visceral adiposity (90, 91). Another theory suggests that, even though a person is overweight, as long he has a good metabolic health and high cardiorespiratory fitness (CRF) (better oxygen supply to the skeletal muscles), the risk of CVD is lower. Additional research reported that high CRF in patients with CVD, despite high BMI and abdominal fat, was beneficial. According to these research results, high BMI and abdominal fat stores do not play an important role when the CFR is high. The benefits of CRF include better blood lipids and blood glucose, lower abdominal fat, decrease high blood pressure and a great influence on reducing CVD risk (92-94).

BMI

Our exposure in the studies has been BMI which is a calculation of bodyweight in kilograms divided by the square of body height in meters. In 1972 Ancel Keys mentioned for the first time BMI as an index for obesity or fatness (95) however, the BMI measurement does not distinguish between muscle, fat or bones. Indeed, young people have more muscle mass than middle-aged or old people and when aging the muscle mass declines and the ratio of fat and lean mass will not be the same (96, 97). Aging also affects the BMI by age-related height decline resulting in an increase of the BMI not necessarily caused by an increase in adiposity (98). The question is whether it is relevant to use the same BMI scale for all age groups. Furthermore, it might even be good for elderly people to be a little overweight since the excess fat might be protective in the event that they develop chronic diseases. We suggest an age-specific BMI to take into account the age related body changes. The studies of the thesis showed that moderate overweight with a BMI between 27.5-30 kg/m^2 is favorable for patients with CVD.

The classification of BMI provided by WHO is widely used and is based on data from 1995, 2000 and 2004 (105). On the other hand, there are debates about the recommended BMI cut-off point of the WHO classification for overweight, and whether age and ethnicity should be take into account. In 2004 a WHO expert consultation reported that current WHO cut-off points for overweight and obese are not sufficient for all Asians, as the observed risk for obesity related disease are from 22- 25 kg/m^2 and for higher risk from 26-31 kg/m^2 (99). Recently a Danish study

showed that over a period of three decades, the BMI association with mortality increased by 3.3(100). The optimal BMI for low mortality among disease free populations is 27.3 kg/m^2 for people older than 60 years and 26.1 kg/m^2 for people who have never smoked (100). Their findings are consistent with our findings from study I. We found that individuals with a BMI between 27.5-30 kg/m^2 have the lowest mortality rate. The difference is that, while our study population consisted of individuals with CAD, and the Danish study population comprised healthy individuals, the results are surprisingly, almost similar. Is it time to change cut off points for BMI categories? Should we have a new BMI scale taking age, sex and ethnicity into account?

STRENGTHS AND LIMITATIONS

The studies of this thesis were based on the retrospectively recorded data on coronary angiography from all cardiovascular intervention centers in Denmark, with adjustment for important confounding factors. There are also important limitations that should be acknowledged since the studies were not randomized. We had to exclude 50% of patients due to lack of information on weight or height, which can cause selection bias. In this case it might have been caused by the fact that we have included patients who had more frequent contact with the health system, and thus registered their weight. Another possible problem is that our studies are observational, suggesting the possibility of unmeasured confounders that could influence the outcome. In the used registries we lacked information on a variety of clinical data, for instance, physical activity, more and exact weight measurements (the weight mostly based of self-reported), alcohol intake, nutritional status, and other chronic–diseases. Another bias that could be important to mention is confounding by indication. Underweight patients were older and more likely to die due to illness than normal weight and overweight patients. We used BMI and weight as proxies for obesity. The BMI is recognized as a rough indicator of obesity, and the use of it as proxy for obesity should be taken with caution, especially in older populations. BMI does not provide information about the percentage of fat or its distribution in the body. However, studies have suggested that waist to hip ratio, waist circumference, the percentage of fat in the body, skinfold thickness, waist-to-

hip circumference ratio, ultrasound, computed tomography, and magnetic resonance imaging are better proxy for obesity. Nevertheless, numerous studies have reported that there is a significant relationship between increased BMI and CVD, HF, ischemic stroke, and death (101, 102).

Since we do not have more than one or two weight records during the follow up time, we cannot be sure that our reference group has always been of normal weight, or if they have ever been overweight/obese previously and may have lost weight due to underdiagnosed diseases.

IMPLICATIONS

This thesis pointed towards an overweight paradox among patients with coronary artery disease, indicate that stable weight is more beneficial than weight change and that moderate overweight is protective for CAD patients. As healthcare professionals, we should keep in mind that weight management for some patient groups are very important. We are also agreeing that the recommendations for patients with coronary artery disease should be focused on lifestyle changes rather than just BMI changes. On the other hand, we know that BMI is used by healthcare and individuals as proxy for obesity and a measurement of health. In this thesis, we showed that the ideal BMI for this group of patients is a BMI under 30 kg/m^2. Therefore, we assume that the focus must be pointed towards patients with a BMI over 30 kg/m^2, as they are at greater risk of mortality and HF.

FUTURE RESEARCH

We suggest a prospective study that registers the weight and body fat percentage of subjects with different ethnicities in very early life stage and follow them over a long period of time to investigate the BMI association with obesity related disease and mortality. The focus should not only be on weight, but also on different risk factors including mental health, as well as social and economic status, as these factors are also important indicators for risk of mortality. The BMI measurement does not take the age or other social factors into consideration, which can have an influence on health, and as we know, the body composition changes over time. By following weight and measuring body fat percentage and other body components e.g. muscle and bone, we can investigate if BMI is a reliable tool as a proxy for obesity in middle-aged or elderly individuals. This information will provide a good base for a new BMI scale or new cut-off points.

CONCLUSIONS

The conclusions of this project are that it confirms the existence of an overweight paradox in patients with CAD by finding a significant beneficial association between overweight and all-cause mortality. The optimal BMI for this group of patients is 27.5-30 kg/m^2. Furthermore, weight management is important for the development of HF for patients with CAD. We have to encourage patients with coronary artery disease that also have a BMI (>30kg/m^2) to change their life style as they are at higher risk of HF.

In the end, we concluded that individuals over 60, who are moderately overweight, but maintain a stable weight, seem to be the healthiest and have a lower risk of mortality and HF, even if they are suffering from chronic disease. We suggest that the optimal BMI for middle-age and elderly individual is between 25-30 kg/m^2.

REFERENCE

1. Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. Lancet. 2006;368(9536):666-78.
2. Masters RK, Reither EN, Powers DA, Yang YC, Burger AE, Link BG. The impact of obesity on US mortality levels: the importance of age and cohort factors in population estimates. Am J Public Health. 2013;103(10):1895-901.
3. Gelber RP, Gaziano JM, Orav EJ, Manson JE, Buring JE, Kurth T. Measures of obesity and cardiovascular risk among men and women. J Am Coll Cardiol. 2008;52(8):605-15.
4. Chrostowska M, Szyndler A, Hoffmann M, Narkiewicz K. Impact of obesity on cardiovascular health. Best Pract Res Clin Endocrinol Metab. 2013;27(2):147-56.
5. Lloyd-Jones DM, Leip EP, Larson MG, D'Agostino RB, Beiser A, Wilson PW, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. Circulation. 2006;113(6):791-8.
6. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health. 2009;9:88.
7. Engeland A, Bjorge T, Sogaard AJ, Tverdal A. Body mass index in adolescence in relation to total mortality: 32-year follow-up of 227,000 Norwegian boys and girls. Am J Epidemiol. 2003;157(6):517-23.
8. Mathieu P, Poirier P, Pibarot P, Lemieux I, Despres JP. Visceral obesity: the link among inflammation, hypertension, and cardiovascular disease. Hypertension. 2009;53(4):577-84.
9. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA. 2013;309(1):71-82.
10. Galkina E, Ley K. Immune and inflammatory mechanisms of atherosclerosis (*). Annu Rev Immunol. 2009;27:165-97.
11. Hansson GK, Hermansson A. The immune system in atherosclerosis. Nat Immunol. 2011;12(3):204-12.
12. Lavie CJ, Alpert MA, Arena R, Mehra MR, Milani RV, Ventura HO. Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. JACC Heart Fail. 2013;1(2):93-102.
13. Clark AL, Fonarow GC, Horwich TB. Obesity and the obesity paradox in heart failure. Prog Cardiovasc Dis. 2014;56(4):409-14.
14. Lavie CJ, Milani RV, Ventura HO, Romero-Corral A. Body composition and heart failure prevalence and prognosis: getting to the fat of the matter in the "obesity paradox". Mayo Clin Proc. 2010;85(7):605-8.
15. Azimi A, Charlot MG, Torp-Pedersen C, Gislason GH, Kober L, Jensen LO, et al. Moderate overweight is beneficial and severe obesity detrimental

for patients with documented atherosclerotic heart disease. Heart. 2013;99(9):655-60.
16. Wannamethee SG, Shaper AG, Whincup PH, Lennon L, Papacosta O, Sattar N. The obesity paradox in men with coronary heart disease and heart failure: the role of muscle mass and leptin. Int J Cardiol. 2014;171(1):49-55.
17. Angeras O, Albertsson P, Karason K, Ramunddal T, Matejka G, James S, et al. Evidence for obesity paradox in patients with acute coronary syndromes: a report from the Swedish Coronary Angiography and Angioplasty Registry. Eur Heart J. 2013;34(5):345-53.
18. Badheka AO, Rathod A, Kizilbash MA, Garg N, Mohamad T, Afonso L, et al. Influence of obesity on outcomes in atrial fibrillation: yet another obesity paradox. Am J Med. 2010;123(7):646-51.
19. Bucholz EM, Rathore SS, Reid KJ, Jones PG, Chan PS, Rich MW, et al. Body mass index and mortality in acute myocardial infarction patients. Am J Med. 2012;125(8):796-803.
20. Lin GM, Li YH, Lai CP, Lin CL, Wang JH. The obesity-mortality paradox in elderly patients with angiographic coronary artery disease: a report from the ET-CHD registry. Acta Cardiol. 2015;70(4):479-86.
21. Costanzo P, Cleland JG, Pellicori P, Clark AL, Hepburn D, Kilpatrick ES, et al. The obesity paradox in type 2 diabetes mellitus: relationship of body mass index to prognosis: a cohort study. Ann Intern Med. 2015;162(9):610-8.
22. Mohebi R, Simforoosh A, Tohidi M, Azizi F, Hadaegh F. Obesity Paradox and Risk of Mortality Events in Chronic Kidney Disease Patients: A Decade of Follow-up in Tehran Lipid and Glucose Study. J Ren Nutr. 2015;25(4):345-50.
23. Dagenais GR, Yi Q, Mann JF, Bosch J, Pogue J, Yusuf S. Prognostic impact of body weight and abdominal obesity in women and men with cardiovascular disease. Am Heart J. 2005;149(1):54-60.
24. Rana JS, Mukamal KJ, Morgan JP, Muller JE, Mittleman MA. Obesity and the risk of death after acute myocardial infarction. Am Heart J. 2004;147(5):841-6.
25. Kaplan RC, Heckbert SR, Furberg CD, Psaty BM. Predictors of subsequent coronary events, stroke, and death among survivors of first hospitalized myocardial infarction. J Clin Epidemiol. 2002;55(7):654-64.
26. Wessel TR, Arant CB, Olson MB, Johnson BD, Reis SE, Sharaf BL, et al. Relationship of physical fitness vs body mass index with coronary artery disease and cardiovascular events in women. JAMA. 2004;292(10):1179-87.
27. Domanski MJ, Jablonski KA, Rice MM, Fowler SE, Braunwald E, Investigators P. Obesity and cardiovascular events in patients with established coronary disease. Eur Heart J. 2006;27(12):1416-22.
28. Benderly M, Boyko V, Goldbourt U. Relation of body mass index to mortality among men with coronary heart disease. Am J Cardiol. 2010;106(3):297-304.
29. Clark AL, Fonarow GC, Horwich TB. Waist circumference, body mass index, and survival in systolic heart failure: the obesity paradox revisited. J Card Fail. 2011;17(5):374-80.

30. De Schutter A, Lavie CJ, Patel DA, Artham SM, Milani RV. Relation of body fat categories by Gallagher classification and by continuous variables to mortality in patients with coronary heart disease. Am J Cardiol. 2013;111(5):657-60.
31. Banack HR, Kaufman JS. Does selection bias explain the obesity paradox among individuals with cardiovascular disease? Ann Epidemiol. 2015;25(5):342-9.
32. Lajous M, Bijon A, Fagherazzi G, Boutron-Ruault MC, Balkau B, Clavel-Chapelon F, et al. Body mass index, diabetes, and mortality in French women: explaining away a "paradox". Epidemiology. 2014;25(1):10-4.
33. Goyal A, Nimmakayala KR, Zonszein J. Is there a paradox in obesity? Cardiol Rev. 2014;22(4):163-70.
34. Ebbert JO, Elrashidi MY, Jensen MD. Managing overweight and obesity in adults to reduce cardiovascular disease risk. Curr Atheroscler Rep. 2014;16(10):445.
35. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren WM, et al. European guidelines on cardiovascular disease prevention in clinical practice (version 2012) : the fifth joint task force of the European society of cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). Int J Behav Med. 2012;19(4):403-88.
36. Sierra-Johnson J, Romero-Corral A, Somers VK, Lopez-Jimenez F, Thomas RJ, Squires RW, et al. Prognostic importance of weight loss in patients with coronary heart disease regardless of initial body mass index. Eur J Cardiovasc Prev Rehabil. 2008;15(3):336-40.
37. Kritchevsky SB, Beavers KM, Miller ME, Shea MK, Houston DK, Kitzman DW, et al. Intentional weight loss and all-cause mortality: a meta-analysis of randomized clinical trials. PLoS One. 2015;10(3):e0121993.
38. Beavers KM, Case LD, Blackwell CS, Katula JA, Goff DC, Jr., Vitolins MZ. Effects of weight regain following intentional weight loss on glucoregulatory function in overweight and obese adults with pre-diabetes. Obes Res Clin Pract. 2015;9(3):266-73.
39. Shantha GP, Kumar AA, Kahan S, Cheah SY, Cheskin LJ. Intentional weight loss and dose reductions of antihypertensive medications: a retrospective cohort study. Cardiorenal Med. 2013;3(1):17-25.
40. Lee CG, Boyko EJ, Nielson CM, Stefanick ML, Bauer DC, Hoffman AR, et al. Mortality risk in older men associated with changes in weight, lean mass, and fat mass. J Am Geriatr Soc. 2011;59(2):233-40.
41. Klenk J, Rapp K, Ulmer H, Concin H, Nagel G. Changes of body mass index in relation to mortality: results of a cohort of 42,099 adults. PLoS One. 2014;9(1):e84817.
42. Rosengren A, Wedel H, Wilhelmsen L. Body weight and weight gain during adult life in men in relation to coronary heart disease and mortality. A prospective population study. Eur Heart J. 1999;20(4):269-77.
43. Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health. 2011;39(7 Suppl):38-41.

44. Wilson PW, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. Arch Intern Med. 2002;162(16):1867-72.
45. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. Arterioscler Thromb Vasc Biol. 2006;26(5):968-76.
46. Adams KF, Schatzkin A, Harris TB, Kipnis V, Mouw T, Ballard-Barbash R, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. N Engl J Med. 2006;355(8):763-78.
47. Sidney S, Rosamond WD, Howard VJ, Luepker RV, National Forum for Heart D, Stroke P. The "heart disease and stroke statistics--2013 update" and the need for a national cardiovascular surveillance system. Circulation. 2013;127(1):21-3.
48. Romero-Corral A, Somers VK, Korinek J, Sierra-Johnson J, Thomas RJ, Allison TG, et al. Update in prevention of atherosclerotic heart disease: management of major cardiovascular risk factors. Rev Invest Clin. 2006;58(3):237-44.
49. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Woo MA, Tillisch JH. The relationship between obesity and mortality in patients with heart failure. J Am Coll Cardiol. 2001;38(3):789-95.
50. Gurm HS, Whitlow PL, Kip KE, Investigators B. The impact of body mass index on short- and long-term outcomes inpatients undergoing coronary revascularization. Insights from the bypass angioplasty revascularization investigation (BARI). J Am Coll Cardiol. 2002;39(5):834-40.
51. Kim J, Hammar N, Jakobsson K, Luepker RV, McGovern PG, Ivert T. Obesity and the risk of early and late mortality after coronary artery bypass graft surgery. Am Heart J. 2003;146(3):555-60.
52. Lopez-Jimenez F, Jacobsen SJ, Reeder GS, Weston SA, Meverden RA, Roger VL. Prevalence and secular trends of excess body weight and impact on outcomes after myocardial infarction in the community. Chest. 2004;125(4):1205-12.
53. Sierra-Johnson J, Wright SR, Lopez-Jimenez F, Allison TG. Relation of body mass index to fatal and nonfatal cardiovascular events after cardiac rehabilitation. Am J Cardiol. 2005;96(2):211-4.
54. Uretsky S, Messerli FH, Bangalore S, Champion A, Cooper-Dehoff RM, Zhou Q, et al. Obesity paradox in patients with hypertension and coronary artery disease. Am J Med. 2007;120(10):863-70.
55. Lea JP, Crenshaw DO, Onufrak SJ, Newsome BB, McClellan WM. Obesity, end-stage renal disease, and survival in an elderly cohort with cardiovascular disease. Obesity (Silver Spring). 2009;17(12):2216-22.
56. Hastie CE, Padmanabhan S, Slack R, Pell AC, Oldroyd KG, Flapan AD, et al. Obesity paradox in a cohort of 4880 consecutive patients undergoing percutaneous coronary intervention. Eur Heart J. 2010;31(2):222-6.
57. Lavie CJ, De Schutter A, Patel D, Artham SM, Milani RV. Body composition and coronary heart disease mortality--an obesity or a lean paradox? Mayo Clin Proc. 2011;86(9):857-64.

58. Lavie CJ, De Schutter A, Patel DA, Romero-Corral A, Artham SM, Milani RV. Body composition and survival in stable coronary heart disease: impact of lean mass index and body fat in the "obesity paradox". J Am Coll Cardiol. 2012;60(15):1374-80.
59. Thomas G, Khunti K, Curcin V, Molokhia M, Millett C, Majeed A, et al. Obesity paradox in people newly diagnosed with type 2 diabetes with and without prior cardiovascular disease. Diabetes Obes Metab. 2014;16(4):317-25.
60. Kaneko H, Yajima J, Oikawa Y, Tanaka S, Fukamachi D, Suzuki S, et al. Obesity paradox in Japanese patients after percutaneous coronary intervention: an observation cohort study. J Cardiol. 2013;62(1):18-24.
61. Bundhun PK, Li N, Chen MH. Does an Obesity Paradox Really Exist After Cardiovascular Intervention?: A Systematic Review and Meta-Analysis of Randomized Controlled Trials and Observational Studies. Medicine (Baltimore). 2015;94(44):e1910.
62. Younge JO, Damen NL, van Domburg RT, Pedersen SS. Obesity, health status, and 7-year mortality in percutaneous coronary intervention: in search of an explanation for the obesity paradox. Int J Cardiol. 2013;167(4):1154-8.
63. Stokes A, Preston SH. Smoking and reverse causation create an obesity paradox in cardiovascular disease. Obesity (Silver Spring). 2015.
64. Flanders WD, Augestad LB. Adjusting for reverse causality in the relationship between obesity and mortality. Int J Obes (Lond). 2008;32 Suppl 3:S42-6.
65. Lawlor DA, Hart CL, Hole DJ, Davey Smith G. Reverse causality and confounding and the associations of overweight and obesity with mortality. Obesity (Silver Spring). 2006;14(12):2294-304.
66. Sun Q, Townsend MK, Okereke OI, Franco OH, Hu FB, Grodstein F. Adiposity and weight change in mid-life in relation to healthy survival after age 70 in women: prospective cohort study. BMJ. 2009;339:b3796.
67. Preston SH, Stokes A. Obesity paradox: conditioning on disease enhances biases in estimating the mortality risks of obesity. Epidemiology. 2014;25(3):454-61.
68. Steinberg BA, Cannon CP, Hernandez AF, Pan W, Peterson ED, Fonarow GC. Medical therapies and invasive treatments for coronary artery disease by body mass: the "obesity paradox" in the Get With The Guidelines database. Am J Cardiol. 2007;100(9):1331-5.
69. Lancefield T, Clark DJ, Andrianopoulos N, Brennan AL, Reid CM, Johns J, et al. Is there an obesity paradox after percutaneous coronary intervention in the contemporary era? An analysis from a multicenter Australian registry. JACC Cardiovasc Interv. 2010;3(6):660-8.
70. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med. 2007;356(15):1503-16.
71. Jaber WA, Lennon RJ, Mathew V, Holmes DR, Jr., Lerman A, Rihal CS. Application of evidence-based medical therapy is associated with improved outcomes after percutaneous coronary intervention and is a valid quality indicator. J Am Coll Cardiol. 2005;46(8):1473-8.

72. Yan AT, Yan RT, Tan M, Huynh T, Soghrati K, Brunner LJ, et al. Optimal medical therapy at discharge in patients with acute coronary syndromes: temporal changes, characteristics, and 1-year outcome. Am Heart J. 2007;154(6):1108-15.
73. Mahaffey KW, Tonev ST, Spinler SA, Levine GN, Gallo R, Ducas J, et al. Obesity in patients with non-ST-segment elevation acute coronary syndromes: results from the SYNERGY trial. Int J Cardiol. 2010;139(2):123-33.
74. Das SR, Alexander KP, Chen AY, Powell-Wiley TM, Diercks DB, Peterson ED, et al. Impact of body weight and extreme obesity on the presentation, treatment, and in-hospital outcomes of 50,149 patients with ST-Segment elevation myocardial infarction results from the NCDR (National Cardiovascular Data Registry). J Am Coll Cardiol. 2011;58(25):2642-50.
75. Herrmann J, Gersh BJ, Goldfinger JZ, Witzenbichler B, Guagliumi G, Dudek D, et al. Body mass index and acute and long-term outcomes after acute myocardial infarction (from the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction Trial). Am J Cardiol. 2014;114(1):9-16.
76. Witassek F, Schwenkglenks M, Erne P, Radovanovic D. Impact of Body Mass Index on mortality in Swiss hospital patients with ST-elevation myocardial infarction: does an obesity paradox exist? Swiss Med Wkly. 2014;144:w13986.
77. Hernan MA, Hernandez-Diaz S, Robins JM. A structural approach to selection bias. Epidemiology. 2004;15(5):615-25.
78. Banack HR, Kaufman JS. The obesity paradox: understanding the effect of obesity on mortality among individuals with cardiovascular disease. Prev Med. 2014;62:96-102.
79. Cole SR, Platt RW, Schisterman EF, Chu H, Westreich D, Richardson D, et al. Illustrating bias due to conditioning on a collider. Int J Epidemiol. 2010;39(2):417-20.
80. Brinkworth GD, Noakes M, Buckley JD, Clifton PM. Weight loss improves heart rate recovery in overweight and obese men with features of the metabolic syndrome. Am Heart J. 2006;152(4):693 e1-6.
81. Andrade FC, Vazquez-Vidal I, Flood T, Aradillas-Garcia C, Vargas-Morales JM, Medina-Cerda E, et al. One-year follow-up changes in weight are associated with changes in blood pressure in young Mexican adults. Public Health. 2012;126(6):535-40.
82. Williamson DF, Thompson TJ, Thun M, Flanders D, Pamuk E, Byers T. Intentional weight loss and mortality among overweight individuals with diabetes. Diabetes Care. 2000;23(10):1499-504.
83. Wannamethee SG, Shaper AG, Lennon L. Reasons for intentional weight loss, unintentional weight loss, and mortality in older men. Arch Intern Med. 2005;165(9):1035-40.
84. Johnston CA, Moreno JP, Foreyt JP. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. Curr Atheroscler Rep. 2014;16(12):457.

85. Karahalios A, Simpson JA, Baglietto L, MacInnis RJ, Hodge AM, Giles GG, et al. Change in body size and mortality: results from the Melbourne collaborative cohort study. PLoS One. 2014;9(7):e99672.
86. Murphy RA, Patel KV, Kritchevsky SB, Houston DK, Newman AB, Koster A, et al. Weight change, body composition, and risk of mobility disability and mortality in older adults: a population-based cohort study. J Am Geriatr Soc. 2014;62(8):1476-83.
87. Koster-Rasmussen R, Simonsen MK, Siersma V, Henriksen JE, Heitmann BL, de Fine Olivarius N. Intentional Weight Loss and Longevity in Overweight Patients with Type 2 Diabetes: A Population-Based Cohort Study. PLoS One. 2016;11(1):e0146889.
88. Bruce SA. The association between central fat distribution and recurrent cardiovascular disease events in female survivors of nonfatal myocardial infarction. J Cardiovasc Nurs. 2015;30(2):E15-22.
89. Scheuer SH, Faerch K, Philipsen A, Jorgensen ME, Johansen NB, Carstensen B, et al. Abdominal Fat Distribution and Cardiovascular Risk in Men and Women With Different Levels of Glucose Tolerance. J Clin Endocrinol Metab. 2015;100(9):3340-7.
90. Despres JP. Body fat distribution and risk of cardiovascular disease: an update. Circulation. 2012;126(10):1301-13.
91. Britton KA, Massaro JM, Murabito JM, Kreger BE, Hoffmann U, Fox CS. Body fat distribution, incident cardiovascular disease, cancer, and all-cause mortality. J Am Coll Cardiol. 2013;62(10):921-5.
92. McAuley PA, Kokkinos PF, Oliveira RB, Emerson BT, Myers JN. Obesity paradox and cardiorespiratory fitness in 12,417 male veterans aged 40 to 70 years. Mayo Clin Proc. 2010;85(2):115-21.
93. Goel K, Thomas RJ, Squires RW, Coutinho T, Trejo-Gutierrez JF, Somers VK, et al. Combined effect of cardiorespiratory fitness and adiposity on mortality in patients with coronary artery disease. Am Heart J. 2011;161(3):590-7.
94. Lavie CJ, Cahalin LP, Chase P, Myers J, Bensimhon D, Peberdy MA, et al. Impact of cardiorespiratory fitness on the obesity paradox in patients with heart failure. Mayo Clin Proc. 2013;88(3):251-8.
95. Keys A, Fidanza F, Karvonen MJ, Kimura N, Taylor HL. Indices of relative weight and obesity. J Chronic Dis. 1972;25(6):329-43.
96. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39(4):412-23.
97. Batsis JA, Mackenzie TA, Barre LK, Lopez-Jimenez F, Bartels SJ. Sarcopenia, sarcopenic obesity and mortality in older adults: results from the National Health and Nutrition Examination Survey III. Eur J Clin Nutr. 2014;68(9):1001-7.
98. Ablove T, Binkley N, Leadley S, Shelton J, Ablove R. Body mass index continues to accurately predict percent body fat as women age despite changes in muscle mass and height. Menopause. 2015;22(7):727-30.

99. Consultation WHOE. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363(9403):157-63.
100. Afzal S, Tybjaerg-Hansen A, Jensen GB, Nordestgaard BG. Change in Body Mass Index Associated With Lowest Mortality in Denmark, 1976-2013. JAMA. 2016;315(18):1989-96.
101. He Y, Lam TH, Jiang B, Li LS, Sun DL, Wu L, et al. Changes in BMI before and during economic development and subsequent risk of cardiovascular disease and total mortality: a 35-year follow-up study in China. Diabetes Care. 2014;37(9):2540-7.
102. Hagg S, Fall T, Ploner A, Magi R, Fischer K, Draisma HH, et al. Adiposity as a cause of cardiovascular disease: a Mendelian randomization study. Int J Epidemiol. 2015;44(2):578-86.

103. World Health Organization. Available online: http://www.who.int/mediacentre/factsheets/fs311/en/ (accessed on 23 October 2015).

104. World Health Organization. Available online: http://www.euro.who.int/en/health-topics/noncommunicable-diseases/cardiovascular-diseases/data-and-statistics (accessed on 15 May 2016).

105. World Health Organization. Available online: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html (accessed on 15 May 2016)

APPENDICES

Moderate overweight is beneficial and severe obesity detrimental for patients with documented atherosclerotic heart disease

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▸ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2012-303066).

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Received 18 September 2012
Revised 28 November 2012
Accepted 10 December 2012
Published Online First
18 January 2013

ABSTRACT

Objective Obesity is paradoxically associated with enhanced survival in patients with established cardiovascular disease. We explored this paradox further by examining the influence of obesity on survival in patients with verified atherosclerotic heart disease.

Design and patients This retrospective registry based cohort study included all patients from the Western Denmark Heart Registry with coronary atherosclerosis confirmed by coronary angiography from January 2000 to December 2010. Patients were divided into eight groups according to body mass index (BMI) based on WHO BMI classification.

Setting Department of Cardiology, Copenhagen University Hospital Gentofte, Hellerup, Denmark.

Results The study included 37 573 patients (70.7% men) with a mean age of (66.3±11.1) years. During the 11 years of follow-up, 5866 (15.6%) patients died. Multivariable analysis confirmed that the risk of death was the lowest among the preobese patients ($27.5 \leq BMI < 30$ kg/m^2) with adjusted HR of 0.82 (95% CI 0.71 to 0.95; p=0.008) and increased with both low ($BMI < 18.50$ kg/m^2) and very high ($BMI \geq 40$ kg/m^2) BMI, HR 2.04 (95% CI 1.63 to 2.57; p<0.001) and HR 1.35 (95% CI 1.05 to 1.72; p<0.01), respectively. Also the normal weight class I ($18.5 \leq BMI < 23$ kg/m^2) had a significant risk of mortality HR 1.28 (95% CI 1.13 to 1.45; p<0.001). Obese classes I and II did not differ from the reference group ($23 \leq BMI < 25$ kg/m^2).

Conclusions Overweight atherosclerotic heart disease patients have improved survival compared with normal weight patients. Underweight and severely obese patients have increased mortality. Our results lean more towards an overweight paradox than an obesity paradox.

INTRODUCTION

While obesity is a major risk factor for cardiovascular disease, a range of studies have demonstrated that obesity paradoxically is associated with improved survival in patients with established cardiovascular disease.[1–4] Further exploration of this paradox is relevant as current guidelines recommend weight loss for overweight and obese patients with cardiovascular disease.[5]

Obesity has been linked to better prognosis in dialysis patients in early 1980s but the obesity paradox phenomenon was first demonstrated in studies of patients with coronary artery disease where underweight and normal weight patients had higher death rate than obese patients.[6 7] Subsequently, the obesity paradox has been found in patients with high age, hypertension, atrial fibrillation, kidney disease, rheumatoid arthritis, chronic obstructive lung disease and atherosclerotic cardiovascular disease.[1 8–10]

A meta-analysis of 40 studies with 250 152 patients with coronary heart disease and 3.8 years of follow-up showed that overweight and obese patients had reduced risk of death compared with underweight and normal weight patients.[11] A more recent study could not confirm the existence of the obesity paradox in extremely obese patient with ST-segment elevation myocardial infarction (MI).[3]

The available contradictory data demonstrate a need for further studies including studies with longer follow-up. We therefore conducted a large retrospective study to explore the association between obesity and risk of death in patients with coronary atherosclerosis documented by coronary angiography.

METHODS

All citizens in Denmark have a unique identification number which facilitates individual-level linkage between different registries. We combined data collected in relation to coronary angiography and subsequent hospitalisations and deaths. This retrospective study is based on information from several Danish registries.

The Western Denmark Heart Registry (WDHR) is a clinical database within the Danish healthcare system that includes all adult patients referred for cardiac intervention in western Denmark, a population of 3.3 million people.[12] The Danish Civil Registry keeps complete information on vital status for all inhabitants.

We also used the Danish National Patient Registry which keeps records of all hospital admissions in Denmark since 1978 with one primary diagnosis and, if applicable, one or more secondary diagnoses, according to the *International Classification of Diseases*.[13]

The population

We included all patients in WDHR diagnosed with coronary atherosclerosis by coronary angiography from 1 January 2000 to 31 December 2010. If patients had more than one coronary angiography during the time period, we included the patients on the date of the first registered coronary angiography. All patients with one, several or diffuse

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▸ http://dx.doi.org/10.1136/heartjnl-2012-303487

To cite: Azimi A, Charlot MG, Torp-Pedersen C, *et al*. *Heart* 2013;**99**:655–660.

vessel disease were included. Vessel disease was defined as presence of focal coronary artery lesions with diameter stenosis ≥50% or diffusely diseased vessels by visual assessment.

Data about degree of vessel disease, left ventricular ejection fraction (LVEF), prior MI and patient specific characteristics were registered in the WDHR database at the time of the coronary angiography. Patients with missing information about height, weight, degree of the vessel disease or without permanent residence in Denmark were excluded. We also excluded all patients with a history of prior cardiac surgery or percutaneous coronary intervention. A patient on antihypertensive or statin treatment was considered as hypertensive or hyperlipidaemic.

Body mass index (BMI) was calculated as weight in kilograms divided by square of height in metres (kg/m^2). We used WHO BMI classification of underweight, normal weight, overweight/preobese and obesity including WHO additional cut-off points within each weight group (http://apps.who.int/bmi/index.jsp?introPage=intro_3.html) to allow detailed analysis. Patients were thus divided into eight groups according to BMI. The underweight group had a BMI<18.5 kg/m^2; normal weight was divided into two classes, normal weight class I: 18.5≤BMI<23 kg/m^2 and normal weight class II: 23≤BMI<25 kg/m^2 (this group was selected as the reference group). The overweight/preobese patients were divided into two classes, class I: 25≤BMI<27.5 kg/m^2 and class II: 27.50≤BMI<30 kg/m^2. Finally, the obese patients were classified in three classes: obese class I: 30≤BMI<35 kg/m^2, obese class II: 35≤BMI<40 kg/m^2 and the severely obese patients in obese class III: BMI≥40 kg/m^2.

Statistical analyses

Categorical variables are presented as numbers and percentages and continuous variables as means with SD. Time to event curve was generated by using Kaplan–Meier estimates.

We used survival analysis to estimate the difference in survival in the eight groups of BMI. Outcome was all-cause mortality. Follow-up started on the day of the coronary angiography and ended on 31 December 2010.

Cox proportional hazard models were used to estimate HR with 95% CI in the eight groups based on BMI. The models were adjusted for the following variables: age, sex, smoking, diabetes, degree of vessel disease, hypertension, hyperlipidaemia, serum creatine, LVEF, arrhythmia, periphery vascular disease, cerebral vascular disease, chronic obstructive lung disease, cancer and prior MI. Model assumptions were tested and found valid unless otherwise indicated. Further, we performed an interaction analysis between BMI groups and smoking groups in which we did not find any interaction (p=0.45).

All statistical analyses were performed with the SAS statistical software V9.2 (SAS Institute Inc., Cary, North Carolina, USA) and Stata software V11 (Statacorp, College st., Texas, USA).

The Danish Data Protection Agency approved the study, and data were made available to us in such a way that individuals could not be identified. Retrospective registry based studies do not require ethical approval in Denmark.

RESULTS

A total of 100 128 patients underwent coronary angiography from 1 January 2000 to 31 December 2010 (figure 1). We excluded 29 583 (29.5%) patients due to missing information about BMI (there was no difference between the excluded patients and the included patients at baseline). Furthermore, we excluded 26 758 (26.7%) patients in whom coronary atherosclerotic disease was ruled out by angiography as well as 738 (0.7%) patients without permanent residence in Denmark and 5476 (5.5%) patients with a history of prior cardiac surgery or percutaneous coronary intervention. The final study population comprised 37 573 patients with coronary atherosclerotic disease.

Baseline characteristics are presented in table 1. The mean age was 66.3 (±11) years and 26 540 (70.7%) were men. Patients in the obese groups were younger than patients in the other groups while the underweight group had the highest mean age. There were more male than female subjects in all groups except in the underweight group. Nearly a third of the population was current smokers and more than a third ex-smokers. As BMI increased, an increasing part of patients had prior MI or diabetes and an increasing number of patients were treated for dyslipidaemia or hypertension. Overall, underweight and severely obese patients (obese class III) had more comorbidity than the rest of the weight groups.

During the 11 years, 5866 (15.6%) patients died. Median follow-up time was 3.2 years (IQR 1.4–5.3). The underweight patients (BMI<18.50 kg/m^2) had the highest incidence rate of death: 133 (95% CI 115.3 to 153.1) per 1000 patient-years while the preobese patients (overweight class II, 27.5≤BMI<30 kg/m^2) had the lowest incidence rate: 33 (95% CI 31.0 to 35.5) per 1000 patient-years (table 2).

The Kaplan–Meier estimates (figure 2) show the survival in the eight BMI groups. The underweight group (BMI<18.5 kg/m^2)

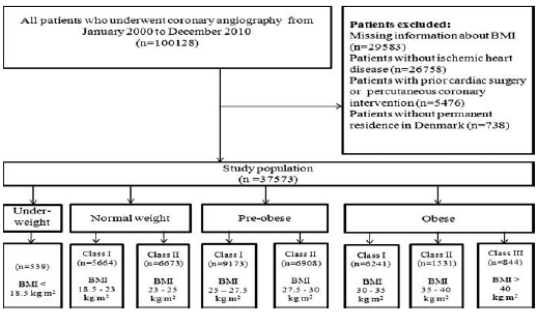

Figure 1 Flow diagram of the population. BMI, body mass index.

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Table 1 Baseline characteristics

Variable	Underweight BMI: <18.5 kg/m² (n=539)	Normal weight Class I BMI: 18.5–23 kg/m² (n=5664)	Normal weight Class II BMI: 23–25 kg/m² (n=6673)	Normal weight Class I BMI: 25–27.5 kg/m² (n=9173)	Preobese Class II BMI: 27.5–30 kg/m² (n=6908)	Preobese Class I BMI: 30–35 kg/m² (n=6241)	Obese Class II BMI: 35–40 kg/m² (n=1531)	Obese Class III BMI: >40 kg/m² (n=844)
Age year (mean)	71.5±(11.5)	68.5±(11.6)	67.5±(11.2)	66.3±(10.9)	65.5±(10.7)	64.3±(10.6)	62.8±(10.6)	64.4±(11.7)
Men (%)	152 (28.2)	3065 (54.1)	4735 (70.9)	7099 (77.4)	5311 (76.9)	4617 (74.0)	1024 (66.9)	537 (63.6)
Smoking								
Never (%)	100 (18.6)	1306 (23.1)	1661 (24.9)	2293 (25.0)	1688 (24.4)	1513 (24.2)	383 (25.0)	208 (24.6)
Current (%)	239 (44.3)	2321 (41.0)	2275 (34.1)	2904 (31.7)	2020 (29.2)	1842 (29.5)	461 (30.1)	263 (31.2)
Ex-smoker (%)	153 (28.4)	1767 (31.2)	2422 (36.3)	3609 (39.3)	2871 (41.6)	2606 (41.8)	610 (39.8)	283 (33.5)
Diabetes								
Non-diabetic	483 (89.6)	5024 (88.7)	5880 (88.1)	7902 (86.1)	5712 (82.7)	4688 (75.2)	1001 (65. 4)	547 (64.8)
Recently diagnosed (%)	6 (1.1)	25 (0.4)	46 (0.7)	57 (0.6)	73 (1.1)	83 (1.3)	25 (1.63)	15 (1.8)
Insulin user (± per oral) (%)	23 (4.3)	228 (4.0)	221 (3.3)	320 (3.5)	311 (4.5)	427 (6.8)	166 (10.8)	95 (11.3)
Per oral (%)	10 (1.9)	210 (3.7)	282 (4.2)	538 (5.9)	521 (7.5)	704 (11.3)	244 (15.9)	124 (14.7)
Non-pharmacological treatment (%)	6 (1.1)	62 (1.1)	110 (1.7)	171 (1.9)	168 (2.4)	186 (3.0)	57 (3.7)	20 (2.4)
One vessel disease (%)	220 (40.8)	2319 (40.9)	2697 (40.4)	3674 (40.1)	2800 (40.5)	2465 (39.5)	623 (40.7)	359 (42.5)
More than one vessel disease (%)	319 (59.1)	3345 (59.1)	3976 (59.6)	5499 (60.0)	4108 (59.5)	3776 (60.50)	908 (59.3)	485 (57.5)
Hypertension treatment (%)	231 (42.9)	2508 (44.3)	3027 (45.4)	4397 (47.9)	3684 (53.3)	3735 (59.9)	1016 (66.4)	502 (59.5)
Statin treatment (%)	182 (33.8)	2577 (45.5)	3284 (49.2)	4662 (50.8)	3736 (54.1)	3489 (55.9)	901 (58.8)	442 (52.4)
Prior myocardial infarction (%)	72 (13.4)	929 (16.4)	1086 (16.3)	1551 (16.9)	1104 (16.0)	1032 (16.5)	239 (15.6)	144 (17.1)
Serum creatine µmol/l (mean)	89.5±(69.2)	99.4±(91.4)	96.8±(68.10)	97.8±(68.0)	95.3±(53.0)	95.5±(53.3)	93.6±(61.8)	102.2±(68.6)
Left ventricular ejection fraction over 45 (%)	225 (41.7)	2315 (40.9)	2803 (42.0)	3873 (42.2)	2990 (43.3)	2694 (43.2)	659 (43.0)	325 (38.5)
Arrhythmia (%)	72 (13.4)	653 (11.5)	696 (10.4)	863 (9.41)	660 (9.5)	625 (10.0)	149 (9.7)	112 (13.3)
Periphery vascular disease (%)	40 (7.4)	239 (4.2)	204 (3.0)	236 (2.6)	160 (2.3)	122 (1.9)	30 (2.0)	23 (2.7)
Cerebral vascular disease (%)	23 (4.3)	217 (3.8)	199 (3.0)	249 (2.7)	156 (2.3)	136 (2.2)	42 (2.7)	27 (3.20)
Chronic obstructive lung disease (%)	74 (13.7)	344 (6.0)	261 (3.9)	277 (3.0)	195 (2.8)	212 (3.4)	62 (4.1)	48 (5.7)
Malignancy (%)	17 (3.2)	118 (2.2)	132 (2.0)	153 (1.7)	96 (1.4)	69 (1.1)	16 (1.1)	17 (2.0)
Cancer (%)	17 (3.2)	118 (2.1)	131 (2.0)	153 (1.7)	95 (1.4)	69 (1.1)	16 (1.1)	17 (2.0)

Data are presented as mean, SD, number of patients (n) and percentages. There was 50% missing data on left ventricle ejection fraction, 20% missing on serum creatine and less than 5% for other variables.
BMI, body mass index.

Table 2 Death rate stratified by BMI class per 1000 patient- years

BMI (kg/m²) groups	Incidence rate	95% CI
<18.5	132.9	115.3 to 153.1
18.5–23	68.5	64.8 to 72.3
23–25	44.5	41.9 to 47.3
25–27.5	37.6	35.6 to 39.7
27.5–30	33.1	31.0 to 35.5
30–35	36.0	33.7 to 38.6
35–40	36.7	31.9 to 42.3
>40	62.6	53.6 to 73.0

BMI, body mass index.

had the highest mortality while the preobese (class II, 27.5≤BMI<30 kg/m²) had the lowest mortality. After 8 years, 70% of the normal weight patients (class II, 23≤BMI<25 kg/m²) and 75% of the preobese (class II: 27.50≤BMI<30 kg/m²) patients were still alive, while only 40% of the underweight patients and less than 70% of the severely obese (obese class III BMI≥40 kg/m²) patients were alive.

Multivariable analysis

Figure 3 shows the results of the Cox proportional hazards regression analysis of all-cause death for each BMI group. There was a 2.04 (95% CI 1.63 to 2.57; p<0.001) times risk of death for the underweight group (BMI<18.5 kg/m²) compared with the reference group of normal weight class II (23≤BMI<25 kg/m²). The preobese (27.50≤BMI<30 kg/m²) had a decreased risk with an HR of 0.82 (95% CI 0.71 to 0.95; p=0.008). The normal weight (class I: 18.5≤BMI<23 kg/m²) had notable risk of death HR 1.28 (95% CI 1.13 to 1.45; p<0.001). The severely obese (obese class III: BMI≥40 kg/m²) patients had an increased HR of 1.35 (95% CI 1.05 to 1.72; p=0.016).

DISCUSSION

In this long term follow-up study on patients with documented coronary arteriosclerotic disease, we demonstrated that preobese patients (overweight) (27.5≤BMI<30 kg/m²) had significantly better survival compared with patients with high-end normal weight (class II: 23≤BMI<25 kg/ m²), whereas low-end normal weight (class I: 18.5≤BMI<23 kg/m²) and severely obese patients (obese class III: BMI>40) had increased risk of death

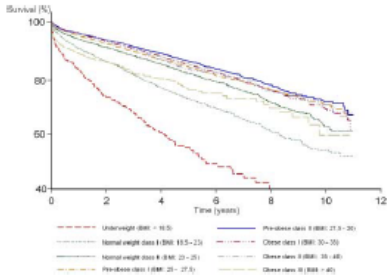

Figure 2 Kaplan–Meier analysis of risk of all-cause death by body mass index (BMI) groups. This figure is only reproduced in colour in the online version.

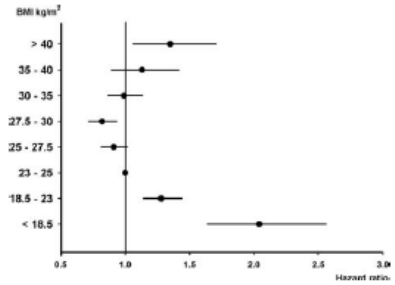

Figure 3 Association between body mass index (BMI) and risk of all-cause death. Adjusted for: age, sex, smoking, diabetes, degree of vessel disease, hypertension, hyperlipidaemia, serum creatine, left ventricle ejection fraction, arrhythmia, periphery vascular disease, cerebral vascular disease, chronic obstructive lung disease, malignancy, cancer and prior myocardial infarction.

compared with the high-end normal weight (class II: 23≤BMI<25 kg/m²) during up to 11 years of follow-up. The results indicated a 'J' shaped risk curve pointing more towards an overweight paradox than obesity paradox, as the extremely obese had increased risk. Similar results have been reported in other studies by Romero-Corral *et al* and recently by Angeras *et al*[14] and Romero-Corral *et al* who found a 'J'-shaped risk curve of cardiovascular mortality, while their results for total mortality in all subgroups including patients with MI, percutaneous coronary intervention and coronary artery bypass grafting were insignificantly 'J'-shaped.[11]

The association between obesity and mortality in patients with cardiovascular disease was first described in the late 1990s. But already in 1980s, the obesity was linked to improved survival in dialysis patients.[6 7] Horwich *et al*[15] investigated the role of obesity in 1203 heart failure patients between 16 and 82 years of age and found that obese patients had improved survival.

Recently, a study of Lancefield and colleagues based on patients undergoing percutaneous coronary intervention (PCI) found improved survival in a group of obese patients after 1 year follow-up.[4] In contrast, Kadakia and colleagues[2] reported significantly lower risk of cardiovascular death after 30 days, but not after 1 year in obese patients with acute coronary syndrome. In our study, with a median follow-up of 3.2 years, the preobese (class II: 27.5≤BMI<30 kg/m²) had better survival compared with high-end normal weight (class II, 23≤BMI<25 kg/m²). Similar to our results, a meta-analysis from 2006 including 250 152 patients with coronary artery disease showed that underweight patients had an increased relative risk of total mortality (1.37 95% CI 1.32 to 1.43) as well as the overweight (BMI 25–29.9 kg/m²) had decreased total mortality (0.87 95% CI 0.81 to 0.94).[11] Unfortunately, several of the included studies did not provide information of whether the obesity paradox was consistent over time.

In our analysis, we divided our participants in eight BMI groups according to the classification provided by WHO, that is, underweight, normal weight, overweight and obesity and including WHO subdivision in groups. This approach gave us the possibility of a more differentiated analysis of the risk in the different BMI classes. Therefore, we could demonstrate that patients with low-end normal weight (class I: 18.5≤BMI<23 kg/ m²) as well as

the underweight patients (BMI< 18.5 kg/m^2) had decreased survival compared with patients with high-end normal weight (class II, 23≤BMI <25 kg/m^2). This might be explained by the fact that these patient groups might have undiagnosed comorbidity not captured by the registries at baseline such as cancer, arrhythmia, peripheral or cerebral vascular disease, chronic obstructive lung disease and heart failure. It is possible that these groups were in a phase of weight loss because of severe disease. Individuals with 18.5≤BMI <25 kg/m^2 are considered to have a normal weight. Here, we demonstrated that patients with 23≤BMI< 25 kg/m^2 had better prognosis than patients with 18.5≤BMI< 23 kg/m^2. This also supports our assumption that this group of patients was the correct reference group in our study.

Also, we found that the severely obese patients (obese class III, BMI≥40 kg/m^2) had an HR 1.35 increase in risk of death whereas obese class II (35≤BMI <40 kg/m^2) had no significantly increased risk of death and obese class I (30≤BMI<35 kg/m^2) had an insignificantly reduced risk of death.

Das and colleagues found similar results among patients with ST-segment elevation MI, where the obese class III patients had higher mortality odds than normal weight and obese class I patients.[16] Different studies explored the obesity paradox by other measurement for fatness like waist circumference (WC), body fatness and lean mass index BMI and demonstrated the existence of an obesity paradox. In contrast, our results rejected the obesity paradox and showed advanced risk of death in obese class III with BMI >40 kg/m^2.[17–19] Thus, our results indicate that we may face an overweight/preobese paradox in patients with ischaemic heart disease rather than the more extreme obesity paradox with ever declining mortality as obesity increases. A recent Swedish paper on the obesity paradox reported better survival for overweight and obese patient, but their choice of reference group differed from ours, as we used our normal weight group with BMI between 23 and 25 as our reference contrasting to theirs with BMI between 21 and 23.5.[14] We assumed that the most 'healthy' patient group might be patients with BMI between 23 and 25, but even with this group as reference the overweight/preobese group had lower risk. This may reflect that patients with cardiovascular disease are healthier, when the BMI is between 25 and 30 kg/m^2. This is highly relevant since European guidelines on cardiovascular disease prevention state that weight reduction is recommend for obese patients and should be considered for those who are overweight (25≤BMI <30 kg/m^2).[5] The assumption that weight reduction in this group of patients would lead to better prognosis is not based on evidence.

Several explanations for the obesity paradox phenomena have been suggested. In a number of studies, obesity has been pointed out as the most important risk factor for hypertension, coronary heart disease, diabetes mellitus, dyslipidaemia, metabolic syndrome and sleep apnoea.[1 3 20] Therefore, obese individuals may have relations to the health system earlier and benefit from preventive treatment. Other suggested explanations for the obesity paradox include whether BMI is an accurate measure of adiposity. We used BMI as measurement for adiposity, while Kadakia and colleagues[2] used both BMI and WC in their analysis and described similar outcomes in BMI and WC groups. A similar study has been performed in a heart failure cohort by Clark *et al*,[17] who examined all-cause mortality in relation to BMI and WC. They reported better survival in both high WC and high BMI groups; furthermore, the combination of high BMI–high WC showed low risk compared with normal BMI–WC.[17] A meta-analysis reported that waist to height ratio is a better measurement than BMI for obesity-related cardiometabolic risk.[21] A recent study on the association of different measures of obesity and mortality reported that high BMI is not directly associated with mortality and suggest that WC and waist to height ratio is a more reliable mortality risk parameter in coronary artery disease.[22]

However, BMI is a widely available, simple and practical obesity measurement and numerous studies have used BMI as proxy for adiposity.[3 11 23 24]

Strengths and limitations

The strengths of this study include that we used a large sample size of a population of unselected patients with atherosclerotic cardiovascular disease confirmed by coronary angiography. Our cohort was from WDHR which includes procedure data for all interventions in western Denmark and thus we minimised the risk of selections bias by not including specific hospitals, age groups or health insurance systems. We furthermore included a wide range of comorbidities in our analysis which gave us more reliable risk estimates. Another strength is the high accuracy of a diagnosis of ischaemic heart disease which in this study was based on a coronary angiography.

There are several limitations of our study, including that our study was conducted in a primarily Caucasian population and generalisation of results to other racial and ethnic groups should be done with caution. We were also missing information about LVEF and serum creatine in respectively 47% and 20% of our population, which limited the analysis including those variables. However, the missing values of LVEF were equally distributed between different BMI groups. We unfortunately did not have information about alcohol intake. Another limitation of our study is lack of information on fitness or physical activity level. This may be an important confounder since a recent study reported that obese patients with coronary artery disease and low cardiorespiratory fitness are associated with increased mortality.[25]

CONCLUSIONS

Patients with documented atherosclerotic heart disease who are overweight/preobese have improved survival compared with patients with normal BMI. Severely obese and underweight patients have increased mortality. If there is a weight paradox for this group of patients, it is an overweight paradox rather than an obesity paradox.

Another analysis

Subgroups of obese class III

We divided our obese class III in two groups (40≤BMI<45 kg/m^2 and BMI>45 kg/m^2) to allow further analyses. Our finding was that the group with BMI between 40 and 45 kg/m^2 had higher risk HR 1.49 (95% CI 1.00 to 2.24; p=0.048) compared with the reference group. For patients with BMI over 45 kg/m^2, we found an HR of 1.28 (95% CI 0.95 to 1.72; p=0.095).

To explore the underweight group of patients further, we performed an analysis where we excluded patients who died during the first 2 years of follow-up, as those patients might suffer from severe pre-existing health problems. The multivariate analyses showed that the underweight group had significant risk of death HR 2.05 (95% CI 1.37 to 3.07; p<0.001), and the preobese group (27.5≤BMI<30 kg/m^2) had a non-significant decreased risk HR 0.86 (95% CI 0.69 to 1.06; p=0.17). Our obese groups had insignificantly increased risk.

Goel *et al*[2.5] found that low fitness was associated with a high risk of death and higher fitness level insignificantly related to better prognosis. McAuley and colleagues also excluded those

patients who died during the first 2 years of follow-up period. Their results did not differ from their main findings. Furthermore, they reported that high fitness level was associated with better survival within each BMI group and that overweight patients with high fitness levels had the lowest risk of death.[26]

Contributors All authors contribution to the study conception, design and interpretation. LT, LOJ, PT, JR, H-HT and JFL contributed to data collection. AA had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. AA made the primary contribution to interpretation of results and writing of the manuscript. All authors contributed to interpretation of results, revising the manuscript critically for important intellectual content and all approved the final manuscript.

Funding This work was supported by the Department of Cardiology, Copenhagen University Hospital Gentofte.

Competing interests None.

Ethics approval In Denmark, registry based studies do not require approval from Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *J Am Coll Cardiol* (Review) 2009;53:1925–32.
2 Kadakia MB, Fox CS, Scirica BM, *et al*. Central obesity and cardiovascular outcomes in patients with acute coronary syndrome: observations from the MERLIN-TIMI 36 trial. *Heart* 2011;97:1782–7.
3 Ovbiagele B, Bath PM, Cotton D, *et al*. Obesity and recurrent vascular risk after a recent ischemic stroke. *Stroke* 2011;42:3397–402.
4 Lancefield T, Clark DJ, Andrianopoulos N, *et al*. Is there an obesity paradox after percutaneous coronary intervention in the contemporary era? An analysis from a multicenter Australian registry. *JACC Cardiovasc Interv* 2010;3:660–8.
5 Perk J, De Backer G, Gohlke H, *et al*. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2012;33:1635–701.
6 McAuley PA, Blair SN. Obesity paradoxes. *J Sports Sci* 2011;29:773–82.
7 Gruberg L, Weissman NJ, Waksman R, *et al*. The impact of obesity on the short-term and long-term outcomes after percutaneous coronary intervention: the obesity paradox? *J Am Coll Cardiol* 2002;39:578–84.
8 Kenchaiah S, Narula J, Vasan RS. Risk factors for heart failure. *Med Clin North Am* 2004;88:1145–72.
9 Wu AH, Eagle KA, Montgomery DG, *et al*. Relation of body mass after development of heart failure due to acute coronary syndrome 2009;103:1736–40.
10 Badheka AO, Rathod A, Kizilbash MA, *et al*. Influence of obesity atrial fibrillation: yet another obesity paradox. *Am J Med* 2010;12
11 Romero-Corral A, Montori VM, Somers VK, *et al*. Association of b total mortality and with cardiovascular events in coronary artery di systematic review of cohort studies. *Lancet* 2006;368:666–78.
12 Jensen LO, Maeng M, Kaltoft A, *et al*. Stent thrombosis, myocardi death after drug-eluting and bare-metal stent coronary interventio *Cardiol* 2007;50:463–70.
13 Andersen TF, Madsen M, Jorgensen J, *et al*. The Danish National H A valuable source of data for modern health sciences. *Dan Med Bu*
14 Angerås O, Albertsson P, Karason K, *et al*. Evidence for obesity pa with acute coronary syndromes: a report from the Swedish Corona and Angioplasty Registry. *Eur Heart J* 2012. 10.1093/eurheartj/eh
15 Horwich TB, Fonarow GC, Hamilton MA, *et al*. The relationship be and mortality in patients with heart failure. *J Am Coll Cardiol* 200
16 Das SR, Alexander KP, Chen AY, *et al*. Impact of body weight and on the presentation, treatment, and in-hospital outcomes of 50,14 ST-Segment elevation myocardial infarction results from the NCDR Cardiovascular Data Registry). *J Am Coll Cardiol* 2011;58:2642–5
17 Clark AL, Fonarow GC, Horwich TB. Waist circumference, body ma survival in systolic heart failure: the obesity paradox revisited. *J Ca* 2011;17:374–80.
18 Lavie CJ, Milani RV, Artham SM, *et al*. The obesity paradox, weigh coronary disease. *Am J Med* 2009;122:1106–4.
19 Lavie CJ, De Schutter A, Patel DA, *et al*. Body composition and su coronary heart disease: impact of lean mass index and body fat in paradox". *J Am Coll Cardiol* 2012;60:1374–80.
20 Valassi E, Biller BM, Klibanski A, *et al*. Adipokines and Cardiovasc Cushing's Syndrome. *Neuroendocrinology* 2012;95:187–206.
21 Ashwell M, Gunn P, Gibson S. Waist-to-height ratio is a better scr waist circumference and BMI for adult cardiometabolic risk factors review and meta-analysis. *Obes Rev* 2012;13:275–86.
22 Coutinho T, Goel K, Correa de Sa D, *et al*. Central obesity and sur with coronary artery disease: a systematic review of the literature analysis with individual subject data. *J Am Coll Cardiol* 2011;57:1
23 Curtis JP, Selter JG, Wang Y, *et al*. The obesity paradox: body mas outcomes in patients with heart failure. *Arch Intern Med* 2005;16
24 Abdulla J, Kober L, Abildstrom SZ, *et al*. Impact of obesity as a m in high-risk patients with myocardial infarction or chronic heart fai analysis of five registries. *Eur Heart J* 2008;29:594–601.
25 Goel K, Thomas RJ, Squires RW, *et al*. Combined effect of cardion and adiposity on mortality in patients with coronary artery disease 2011;161:590–7.
26 McAuley PA, Kokkinos PF, Oliveira RB, *et al*. Obesity paradox and fitness in 12,417 male veterans aged 40 to 70 years. *Mayo Clin P* 2010;85:115–21.

Title page:

Overweight patients with coronary heart disease with stable weight have a better prognosis than normal weight patients.

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Abstract

Objective: Obesity is a major risk factor for cardiovascular disease, and guidelines recommend weight loss for patients with overweight and obesity. We examined the effect of weight change over time on survival in this group of patients.

Methods and Results: We included patients with coronary artery disease with two coronary examinations at different occasions from different Danish Heart Registries and followed up for 13 years. Weight loss was defined as >3% weight loss, stable weight as <±3% weight change, and weight gain as >3% weight gain per year, respectively. We calculated the risk of mortality by Cox proportional-hazard models adjusted for comorbidities, with normal (body mass index 20-25 kg/m^2) stable weight as the reference.

A total of 7683 individuals with a median age of 61 (SD ±11) years were eligible for the study. Multivariable Cox regression analysis demonstrated that patients with overweight and stable weight had a lower risk of mortality (HR 0.82; 95%CI 0.6– 0.9; P=0.04) compared to normal weight patients with stable weight. Weight loss was associated with increased mortality in underweight patients (HR 8.3; 95%CI 3.8–17.9; P=0.000).

Conclusion: In patients with documented coronary artery disease, overweight subjects whose weight remained stable had decreased risk of mortality compared to normal weight patients with stable weight. Weight gain and weight loss was not associated with change in mortality risk for patients with overweight and obesity.

Key words: coronary artery disease, obesity, weight change

Introduction

Obesity and related comorbidities are of increasing concern worldwide and are major risk factors for cardiovascular disease (CVD)[1-3]. Guidelines recommend a rigorous weight control for patients with overweight and obesity with CVD[4]. Interestingly, overweight patients with CVD appear to have better prognosis compared to underweight or normal weight patients, a phenomenon called the obesity or overweight paradox[5 6]. Lifestyle and diet changing are recommended and used as therapy for improving waist circumference, blood pressure and triglycerides and decreasing of weight or body max index (BMI) [7].

Prior studies have investigated the association between weight change and obesity related adverse outcomes including mortality with conflicting results[8-11]. A number of studies have demonstrated an increased risk of mortality and obesity related disease in patients with a weight gain, however, a body of evidence has linked weight loss with increased mortality[12-14].

To our knowledge, only few studies have investigated the relation between changes in weight and all-cause mortality among patients with coronary artery disease. Therefore, we conducted a study to investigate the effect of weight loss or gain on mortality in a Danish nationwide cohort of patients with coronary artery disease documented at coronary angiography.

Methods

The study was retrospective and based on Danish administrative registries. In Denmark, every resident is, at birth or immigration, given a unique and permanent civil registration number, which allows individual-level linkage across nationwide registries. The study contained information from the Danish National Patient Registry which keeps information on all hospital diagnoses since 1978, a coronary angiography registry with data on invasive procedures, the Deaths registry which contains the date and the cause of death. Each hospital admission is recorded by one primary diagnosis, and one or more secondary diagnose(s), according to the International Classification of Diseases, 8th revision (ICD-8) until 1994 and the 10th revision (ICD-10) thereafter.

Study population

The study included a total of 7683 individuals with coronary artery disease verified by angiography. Detailed data about patient characteristics were gathered at baseline from the Danish coronary angiography registries and the Danish National Patient Registry. We used International Classification of Disease (ICD) diagnostic codes to classify chronic obstructive pulmonary disease, renal disease, liver disease, periphery vascular disease, arrhythmia, stroke, malignancy, heart failure and family history of coronary artery disease. Information on comorbidities such as, diabetes, statin treatment, hypertension treatment, smoking status and severity of coronary artery disease (1, 2 or 3 vessel disease, multi vessel [≥2] disease, and diffuse [≤50% stenosis] disease, respectively was obtained from the angiography registers.

Weight change per year was calculated from information about the weight difference in kilograms between the first and second coronary angiography divided by the time between these two procedures. Body mass index (BMI) was calculated as weight in kilograms divided by square of height in meters (kg/m^2). Patients were classified according to BMI at first coronary angiography as underweight (BMI <20kg/m^2; n=204), normal weight (BMI 20-25 kg/m^2; n=2125), overweight (BMI 25-30 kg/m^2; n=3469), and obese (BMI >30kg/m^2; n=1885), respectively. Furthermore, they were categorized according to weight change between the two angiographies into the following three groups: A weight loss group where individuals lost ≥3% of baseline weight per year, a stable weight group where weight change was <±3% of baseline weight per year, and a weight gain group that gained ≥3% weight per year. All patients with weight change within the first 6 months of follow-up were excluded to avoid weight change over relatively short time that could be due to underlying disease including coronary artery disease.

Statistical analyses

Baseline characteristics are presented as categorical variables with numbers and percentages, and continuous variables as means with standard deviation. The study outcome was all-cause mortality. Follow up began on the day of the second coronary angiography and continued until date of death, or December 31st 2012, whichever came first. Incidence rates (IRs) of death are presented per 1000 person-years. Survival analysis was used to calculate the difference in survival associated with BMI and weight classes. To estimate hazard ratios (HRs) with 95% confidence intervals (CIs) we used Cox proportional hazard models adjusted for following variables: age, sex, smoking, diabetes, degree of vessel disease, hypertension, hyperlipidemia, family history of coronary artery disease,

heart failure, malignancy, chronic obstructive lung disease, cerebral vascular disease, periphery vascular disease, arrhythmia, renal disease and liver disease. We estimated HRs for all groups with the normal BMI with stable weight as the reference group.

Model assumptions, linearity of continuous variables, fulfillment of the proportional hazard assumption and lack of relevant interactions, were tested and found to be valid. We investigated the interaction effect of sex, age with BMI and weight. We estimated the effect of weight change by comparing the risk for patients of normal weight with stable weight with other BMI classes included weight change groups by using cox regression models.

All statistical analyses were performed with the SAS statistical software version 9.2 (SAS Institute Inc., Cary, NC) and Stata software version 11 (Statacorp, College St., TX).

The Danish Data Protection Agency approved the study (reference no. 2007-58-0015, international reference: GEH-2014-014), and individual patients could not be identified as the identification numbers were encrypted. Registry based studies do not require ethical approval in Denmark.

Results

We included 42372 patients with at least two coronary angiographies between January 1, 2000 and December 31, 2012. Of these 28386 were excluded due to lack of information about their weight and/or height, 1219 patients had no coronary artery disease and 5084 patients were excluded because of weight change within the first 6 months. Ultimately, a total of 7683 individuals with a median age of 61 (SD ±11) years were eligible for the study.

The flowchart of the selection of the study population is shown in Figure 1. The underweight group included 204, the normal weight group 2125, the overweight group 3469 and the group with obesity

1885 individuals, respectively. Mean follow-up was 4.2 years. The study baseline characteristics are shown in Table 1. The majority (70%) of patients with BMI>25 were men. The weight loss group had fewer smokers, less frequent liver disease and peripheral artery disease compared with the two other weight categories. On the other hand, subjects in the weight loss group were more likely to suffer from cancer, chronic diseases including renal disease, cerebral vascular disease, chronic obstructive lung disease and arrhythmias. Generally the weight loss group had more comorbidities than the other weight groups. In the stable weight group, there were higher rates of liver disease, family history of coronary artery disease, and history of hyperlipidaemia, hypertension and diabetes appeared more frequently in the weight gain group.

Overall 1265 (16%) patients died during the 13 years of follow-up. The crude incidence rates of mortality are shown in Table 2. The highest IR of mortality was found among underweight patients with weight loss, followed by normal weight with weight loss subjects. However, the lowest mortality rate was observed among overweight patients with weight gain, followed by overweight patients with stable weight.

The multivariable adjusted Cox regression analyses confirmed a decreased risk of mortality in individuals with stable weight and an increased risk for individuals with weight loss, Figure 2. Overweight patients who remained stable in weight had an 18% lower risk of mortality (HR 0.82; 95%CI 0.6– 0.9; P=0.04) compared to those with stable weight and normal BMI. Overweight patients who gained weight had a tendency towards decreased risk of mortality, however this was not significant (HR 0.72; 95%CI 0.5–1.1; P=0.07). Patients with obesity, whether they maintained stable weight (HR 1.1; 95%CI 0.9-1.3; P=0.4) or lost weight (HR 0.8; 95%CI 0.5-1.2; P=0.3) had a mortality risk identical to normal weight patients with stable weight. Weight loss was associated with increased mortality in underweight (HR 8.3; 95%CI 3.8-17.9; P=0.000) and normal weight patients (HR 1.3; 95%CI 0.9-1.9; P=0.06). Patients in the underweight group with stable weight had

an increased risk of mortality (HR 1.5; 95%CI 1– 2.4; P=0.04) compared to normal weight subjects with stable weight. On the other hand, mortality risk for individuals with obesity who lost weight was non-significantly decreased (HR 0.83; 95%CI 0.5-1.2; P=0.3).

Discussion

In this study we investigated the association between weight change and mortality risk in patients with angiographically verified coronary artery disease. Our main results were that overweight patients with stable weight had a significantly decreased risk of mortality compared with patients with normal and stable weight. Underweight and normal weight patients who lost weight had increased risk of mortality. Notably, there was no significant association between weight gain and mortality in any of the groups.

There is increasing evidence that obesity is an independent risk factor for developing cardiovascular disease, type 2 diabetes, metabolic syndrome, dyslipidemia and hypertension [15 16]. Furthermore, obesity is also related to all-cause mortality[17 18]. Weight reduction for people with overweight is recommended in a number of clinical guidelines, but the evidence for the benefits of this recommendation is sparse. In contrast to these recommendations, we found that overweight subjects that did not change weight had a lower mortality than normal weight subjects and neither weight loss or weight gain in patients with overweight and obesity reduced mortality risk in these patients with coronary artery disease. The current results are in accordance with data from a prior study from our group that examined the existence of the obesity paradox among patients with coronary artery disease and showed a better prognosis in moderately overweight patients[5].

Numerous previous studies have reported that weight loss is related to higher risk of mortality or and mobility disability[19 20]. A study based on data from the Enhancing Recovery in Coronary Heart Disease Patients Study (ENRICHD) evaluated weight change in patients after myocardial infarction with 29 months of follow up and found worse outcomes for the weight loss group compared to the stable weight group[21]. These results support our finding that weight loss is associated with increased risk of mortality.

Earlier studies have demonstrated that stable weight is associated with a better prognosis and lower risk of mortality compared to subjects that change weight [13 22 23]. It is possible that patients who keep their weight stable over time are healthier. Hence, an essential element in the discussion of weight loss is whether the weight loss is intentional or unintentional. In the present study, patients with weight loss and BMI $\leq$25 kg/m^2 had worse outcomes even after adjustment for important comorbidities. This group of patients might have unknown diseases or a BMI <25 kg/m^2 could be a sign of more severe coronary artery disease[24 25]. Unfortunately, we had no information on whether the weight loss was intentional, but a number of studies have examined the relation between intentional or unintentional weight loss and mortality with conflicting results[26-29].

The results of a case control study conducted with data from six European countries showed that relatively healthy individuals over the age of 60 years with stable weight had lower risk of death compared to the group who lost weight. In contrast, those who gained weight had worse outcomes[12]. This is in accordance with our findings that weight stability decrease risk of mortality. Other recent studies, which have looked at the association between weight change and the risk of CVD and all-cause mortality, reported that weight gain increased risk of CVD and mortality compared with normal weight [8-10 12 22]. In contrast, we found no association between weight gain and all-cause mortality among overweight and obese individuals. Unadjusted analyses showed that weight gain in the overweight group decreased the risk of death but after full adjustment this

association disappeared indicating that the relationship between weight gain and lower mortality was related to these comorbidities. In case we had information on other comorbidities, the results would be different. It is notable that patients recently diagnosed with coronary artery disease face a psychologically stressful situation that makes them reflect more about their personal health. This might motivate for lifestyle changes and compliance with treatment recommendations. Indeed, patients with symptomatic coronary artery disease appear to have more lifestyle changes in the first 12 months after diagnosis and the influence of such behavioral adaptations on our current findings require more study [30].

Strengths and limitations

The strengths of the present study are the retrospectively recorded data on coronary angiography from all cardiovascular intervention centers in Denmark with adjustment for important confounding factors. Also, we excluded subjects with weight change within first 6 months of follow-up to avoid inclusion of patients with other severe diseases. There are also important limitations that should be acknowledged. We had to exclude 60% of patients due to lacked information on weight or height that can cause a selection bias. We did not have information on potential fluctuation of weight between the first and second coronary angiography. Finally, we lacked information on whether the weight loss was intentional or not. We used BMI and weight as proxies for obesity as done previously, even though some researchers suggest that other measurements, e.g., waist circumference, waist-to-height ratio, waist-to-hip ratio or visceral fat mass to be more accurate proxies for obesity[31 32]. In this study $\leq \pm 3\%$ weight change per year was the chosen cut-off point for weight change and the same cut-off point has been used by other investigators[33 34].

Conclusion

Among patients with coronary artery disease, subjects with overweight whose weight remained stable had decreased risk of mortality compared to normal weight patients with stable weight. On the other hand, weight loss in underweight and normal weight subjects was associated with increased risk of mortality compared with normal and stable weight. More evidence on optimal weight-reducing strategies in patients with coronary artery disease is needed for development of future weight management strategies aimed at improved prognosis.

References

1. Gelber RP, Gaziano JM, Orav EJ, et al. Measures of obesity and cardiovascular risk among men and women. *J Am Coll Cardiol* 2008;52:605-15.
2. Chrostowska M, Szyndler A, Hoffmann M, et al. Impact of obesity on cardiovascular health. *Best Pract Res Clin Endocrinol Metab* 2013;27:147-56.
3. Lloyd-Jones DM, Leip EP, Larson MG, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation* 2006;113:791-8.
4. Perk J, De Backer G, Gohlke H, et al. European guidelines on cardiovascular disease prevention in clinical practice (version 2012) : the fifth joint task force of the European society of cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). *Int J Behav Med* 2012;19:403-88.
5. Azimi A, Charlot MG, Torp-Pedersen C, et al. Moderate overweight is beneficial and severe obesity detrimental for patients with documented atherosclerotic heart disease. *Heart* 2013;99:655-60.
6. Dhoot J, Tariq S, Erande A, et al. Effect of morbid obesity on in-hospital mortality and coronary revascularization outcomes after acute myocardial infarction in the United States. *Am J Cardiol* 2013;111:1104-10.
7. Yamaoka K, Tango T. Effects of lifestyle modification on metabolic syndrome: a systematic review and meta-analysis. *BMC Med* 2012;10:138.
8. Cui R, Tanigawa T, Nakano H, et al. Associations between weight change since 20 years of age and sleep-disordered breathing among male truck drivers. *Int J Obes* (Lond) 2009;33:1396-401.
9. de Mutsert R, Sun Q, Willett WC, et al. Overweight in early adulthood, adult weight change, and risk of type 2 diabetes, cardiovascular diseases, and certain cancers in men: a cohort study. *Am J Epidemiol* 2014;179:1353-65.
10. Yun KE, Park HS, Song YM, et al. Increases in body mass index over a 7-year period and risk of cause-specific mortality in Korean men. *Int J Epidemiol* 2010;39:520-8.
11. Bodegard J, Sundstrom J, Svennblad B, et al. Changes in body mass index following newly diagnosed type 2 diabetes and risk of cardiovascular mortality: a cohort study of 8486 primary-care patients. *Diabetes Metab* 2013;39:306-13.
12. Bamia C, Halkjaer J, Lagiou P, et al. Weight change in later life and risk of death amongst the elderly: the European Prospective Investigation into Cancer and Nutrition-Elderly Network on Ageing and Health study. *J Intern Med* 2010;268:133-44.
13. Lee CG, Boyko EJ, Nielson CM, et al. Mortality risk in older men associated with changes in weight, lean mass, and fat mass. *J Am Geriatr Soc* 2011;59:233-40.
14. Wedick NM, Barrett-Connor E, Knoke JD, et al. The relationship between weight loss and all-cause mortality in older men and women with and without diabetes mellitus: the Rancho Bernardo study. *J Am Geriatr Soc* 2002;50:1810-5.
15. Wilson PW, D'Agostino RB, Sullivan L, et al. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. *Arch Intern Med* 2002;162:1867-72.
16. Poirier P, Giles TD, Bray GA, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. *Arterioscler Thromb Vasc Biol* 2006;26:968-76.
17. Adams KF, Schatzkin A, Harris TB, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. *N Engl J Med* 2006;355:763-78.
18. Flegal KM, Kit BK, Orpana H, et al. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA* 2013;309:71-82.
19. Karahalios A, Simpson JA, Baglietto L, et al. Change in body size and mortality: results from the Melbourne collaborative cohort study. *PLoS One* 2014;9:e99672.

20. Murphy RA, Patel KV, Kritchevsky SB, et al. Weight change, body composition, and risk of mobility disability and mortality in older adults: a population-based cohort study. *J Am Geriatr Soc* 2014;62:1476-83.
21. Lopez-Jimenez F, Wu CO, Tian X, et al. Weight change after myocardial infarction--the Enhancing Recovery in Coronary Heart Disease patients (ENRICHD) experience. *Am Heart J* 2008;155:478-84.
22. Klenk J, Rapp K, Ulmer H, et al. Changes of body mass index in relation to mortality: results of a cohort of 42,099 adults. *PLoS One* 2014;9:e84817.
23. Rosengren A, Wedel H, Wilhelmsen L. Body weight and weight gain during adult life in men in relation to coronary heart disease and mortality. A prospective population study. *Eur Heart J* 1999;20:269-77.
24. Newman AB, Yanez D, Harris T, et al. Weight change in old age and its association with mortality. *J Am Geriatr Soc* 2001;49:1309-18.
25. Alley DE, Metter EJ, Griswold ME, et al. Changes in weight at the end of life: characterizing weight loss by time to death in a cohort study of older men. *Am J Epidemiol* 2010;172:558-65.
26. Harrington M, Gibson S, Cottrell RC. A review and meta-analysis of the effect of weight loss on all-cause mortality risk. *Nutr Res Rev* 2009;22:93-108.
27. Gregg EW, Gerzoff RB, Thompson TJ, et al. Intentional weight loss and death in overweight and obese U.S. adults 35 years of age and older. *Ann Intern Med* 2003;138:383-9.
28. Nilsson PM, Nilsson JA, Hedblad B, et al. The enigma of increased non-cancer mortality after weight loss in healthy men who are overweight or obese. *J Intern Med* 2002;252:70-8.
29. Wannamethee SG, Shaper AG, Lennon L. Reasons for intentional weight loss, unintentional weight loss, and mortality in older men. *Arch Intern Med* 2005;165:1035-40.
30. Razavi M, Fournier S, Shepard DS, et al. Effects of Lifestyle Modification Programs on Cardiac Risk Factors. *PLoS One* 2014;9:e114772.
31. Song X, Jousilahti P, Stehouwer CD, et al. Comparison of various surrogate obesity indicators as predictors of cardiovascular mortality in four European populations. *Eur J Clin Nutr* 2013;67:1298-302.
32. Ashwell M, Gunn P, Gibson S. Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. *Obes Rev* 2012;13:275-86.
33. Lee JS, Visser M, Tylavsky FA, et al. Weight loss and regain and effects on body composition: the Health, Aging, and Body Composition Study. *J Gerontol A Biol Sci Med Sci* 2010;65:78-83.
34. Newman AB, Lee JS, Visser M, et al. Weight change and the conservation of lean mass in old age: the Health, Aging and Body Composition Study. *Am J Clin Nutr* 2005;82:872-8; quiz 915-6.

Table1: Baseline characteristics

	Underweight			Normal weight			Overweight			Obese		
	Stable weight (n=132)	Weight loss (n=18)	Weight gain (n=54)	Stable weight (n=1503)	Weight loss (n=226)	Weight gain (n=396)	Stable weight (n=2525)	Weight loss (n=429)	Weight gain (n=515)	Stable weight (n=1322)	weight loss (n=329)	Weight gain (n=234)
Age year (mean)	66 (± 12)	62 (± 14)	64 (± 11)	64 (± 11)	67 (± 11)	63 (± 11)	64 (± 10)	66 (± 11)	61 (± 10)	62 (± 10)	63 (± 10)	60 (± 11)
Men (%)	37 (28.1)	5 (27.7)	25 (46.3)	998 (66.4)	143 (63.2)	249 (62.8)	2010 (79.6)	338 (78.8)	390 (75.7)	317 (76.1)	95 71.1)	62 (73.5)
Never smoker (%)	35 (26.5)	1 (5.6)	4 (7.4)	400 (26.6)	55 (24.3)	70 (17.7)	584 (23.1)	94 (21.9)	70 (13.6)	281 (21.3)	89 (27.1)	39 (16.6)
Current Smoker (%)	39 (29.5)	10 (55.6)	27 (50)	656 (43.6)	92 (40.7)	201 (50.7)	1284 (50.8)	222 (51.75)	288 (55.9)	674 (50.9)	147 (44.7)	144 (61.5)
Ex-smoker (%)	47 (35.6)	6 (33.3)	19 (35.2)	358 (23.8)	53 (23.5)	100 (25.6)	506 (20.1)	83 (19.3)	129 (25.1)	290 (21.9)	70 (21.2)	36 (15.3)
Diabetes (%)	10 (7.6)	1 (5.6)	9 (16.7)	166 (11.1)	34 (15.1)	60 (15.1)	391 (15.4)	75 (17.5)	87 (17.9)	426 (32.2)	107 (32.5)	82 (35.1)
Multi vessel disease (%)	60 (45.5)	7 (38.9)	23 (42.6)	750 (49.9)	124 (54.9)	187 (47.2)	1344 (53.2)	231 (53.85)	265 (51.5)	671 (50.7)	173 (52.6)	114 (48.7)
Diffuse vessel disease (%)	16 (12.1)	2 (11.1)	8 (14.5)	117 (7.8)	12 (5.3)	21 (5.3)	144 (5.7)	12 (2.8)	23 (4.5)	100 (7.6)	20 (6.1)	15 (6.41)
Hypertension treatment (%)	75 (56.8)	9 (50.5)	39 (72.2)	898 (59.8)	120 (53.1)	245 (61.9)	1645 (65.2)	259 (60.4)	311 (60.4)	980 (74.1)	248 (75.4)	181 (77.4)
Statin treatment (%)	97 (73.5)	10 (55.6)	43 (79.6)	1215 (80.8)	189 (83.6)	347 (87.6)	2168 (85.8)	355 (82.7)	454 (88.1)	1147 (86.6)	285 (86.6)	215 (91.8)
Liver disease (%)	0	0	1 (1.9)	2 (0.1)	0	0	3 (0.1)	0	0	3 (0.2)	0	1 (0.4)
Renal disease (%)	4 (3.0)	1 (5.6)	1 (1.8)	11 (0.7)	1 (0.4)	3 (0.8)	8 (0.3)	7 (1.6)	2 (0.4)	5 (0.4)	3 (0.9)	1 (0.4)
Arrhythmia (%)	2 (1.5)	1 (5.6)	1 (1.5)	26 (1.7)	5 (2.2)	7 (1.7)	60 (2.4)	12 (2.7)	10 (2.0)	26 (2.0)	9 (2.7)	3 (1.2)
Periphery vas-cular disease (%)	0	0	4 (7.4)	28 (1.8)	4 (1.7)	9 (2.3)	42 (1.7)	5 (1.1)	7 (1.3)	16 (1.2)	2 (0.6)	6 (0.8)
Cerebral vas-cular disease (%)	1 (0.7)	1 (5.5)	0	17 (1.1)	3 (1.3)	3 (0.7)	37 (1.4)	7 (1.6)	3 (0.6)	17 (1.2)	2 (0.6)	0
Chronic ob-structive lung disease (%)	2 (1.5)	0	2 (3.7)	14 (0.1)	4 (1.7)	4 (1.0)	20 (0.8)	4 (0.9)	3 (0.6)	2 (0.1)	5 (1.5)	2 (0.8)
Cancer (%)	2 (1.5)	0	3 (5.5)	29 (1.93)	9 (4.0)	6 (1.5)	45 (1.7)	7 (1.6)	8 (1.5)	22 (1.6)	7 (2.1)	3 (1.3)
Heart failure (%)	1 (0.7)	0	0	10 (0.7)	1 (0.44)	2 (0.5)	34 (1.3)	7 (1.6)	6 (1.7)	9 (0.68)	4 (1.2)	4 (1.7)
Family history of coronary artery disease (%)	60 (54.5)	9 (50)	24 (44.4)	739 (49.1)	114 (50.4)	197 (49.8)	1313 (51.9)	198 (46.2)	254 (49.3)	664 (50.2)	153 (46.5)	127 (54.0)

Table 2:The incidence rate of death per 1000 person year

BMI- weight change	Number of death	Rate	95% CI
Underweight-stable	37	77.3	56.1 – 106.7
Underweight-loss	12	280.1	159 – 494.7
Underweight-gain	14	69.7	41.2– 117.7
Normal weight-stable	264	43.8	38.8 – 45.5
Normal weight-loss	71	77.4	61.3 – 97.6
Normal weight-gain	66	38.9	30.6 – 49.5
Overweight-stable	364	34.7	31.4 – 38.5
Overweight-loss	84	45.3	36.5 – 56.1
Overweight -gain	61	25.9	20.1 – 33.3
Obese-stable	202	37.7	32.1 – 43.4
Obese-loss	54	36.7	28.1– 47.9
Obese-gain	36	36.4	26.2– 50.5

Figure 1: Follow chart of the study

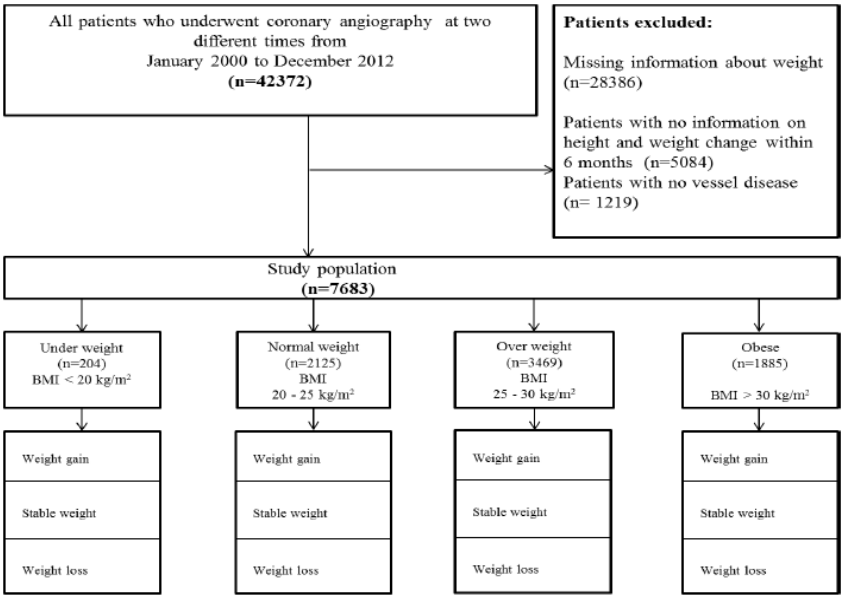
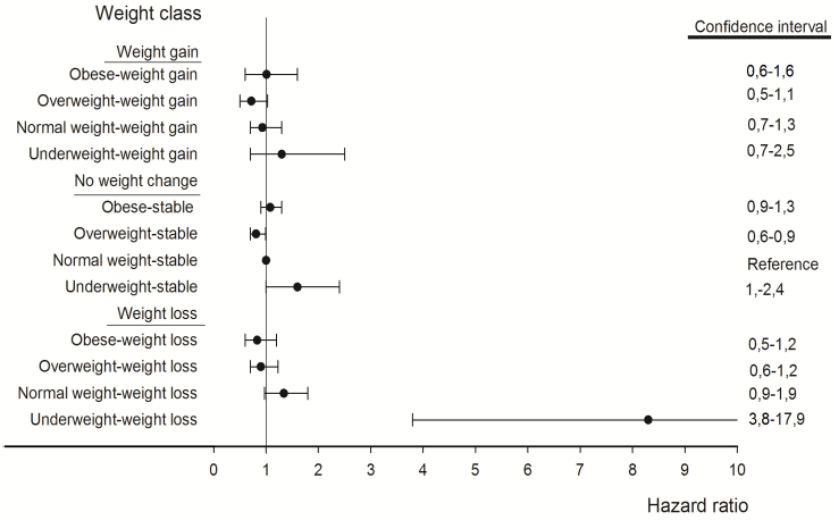


Figure 2: Association between weight classes and risk of all-cause mortality.



Adjusted for; age, sex, smoking, diabetes, degree of vessel disease, hypertension, hyperlipidemia, family history of coronary artery disease, heart failure, malignancy, chronic obstructive lung disease, cerebral vascular disease, periphery vascular disease, arrhythmia, renal disease, liver disease

Title page:

Impact of body mass index on risk of heart failure

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Introduction

Despite an intense focus on the prevention of obesity, its prevalence is increasing. Obesity is associated with increased morbidity, mortality and, especially with the development of ischemic heart disease. There is also increasing evidence that obesity is a risk factor of heart failure (HF) although the exact mechanisms are still unknown [1 2]. It is a well-known fact that the incidence of HF increases with age, and it is one of the primary causes of hospital admission for the elderly. During a lifetime, it affects about 10 % of men and 8 % of women[3-5].

In spite of recent improvements in the treatment of HF, it remains a chronic and detrimental condition with a high risk of mortality. Patients with ischemic heart disease have a high risk of developing HF, and by identifying specific risk factors that contribute to the development of HF, it is possible to introduce preventive treatment. A recent report from the European Society of Cardiology documented that patients with ischemic heart disease do not follow the recommended guidelines for secondary prevention including weight management, and that management of risk factors is insufficient [6]. However, data on the incidence of HF among patients with ischemic heart disease and the relation to body-mass index (BMI) are inadequate, and, paradoxically, many studies have shown that obese HF patients have a lower risk of mortality compared with normal weight HF patients [7-9].

In this study, we examined the association between BMI and the risk of developing HF in patients with ischemic heart disease documented with coronary angiography.

Methods

Danish residents are provided with individual civil registration numbers. This allows linkage of data across registers on an individual level. Our study was based on data from Danish coronary angiography registries, the Danish Civil Registry, the Danish National Patient Registry, the

National Causes of Death Registry (which holds information about date and causes of death) and the National Prescription Registry (provides information about all prescriptions dispensed out from Danish pharmacies since 1995[10]). We used diagnosis codes according to the International Classification of Diseases, 8th revision (ICD-8) until 1994 and subsequently the 10th revision (ICD-10). For administrative reasons ICD-9 was never used in Denmark. We collected information on the following comorbidities relevant for the present study: chronic obstructive pulmonary disease, renal disease, liver disease, peripheral artery disease, cerebral artery disease, malignancy, as well as family disposition for ischemic heart disease. Additional information such as weight, height, diabetes, ag, sex, statin treatment, hypertension treatment, smoking status, indication of coronary angiography and severity of coronary artery disease determined by coronary angiography (0, 1, 2, or 3 vessel disease, multi vessel [≥2] disease, and diffuse [≤50% stenosis] disease, respectively, assessed by experienced invasive cardiologists) was obtained from Danish angiography registries. Patients with HF were identified by using treatment with loop diuretics including furosemide (ATC code C03CA01) and bumetanide (C03CA02) as a proxy. We also included data on filled prescriptions of common types of drugs used in treatment of HF including β-blockers (C07) and angiotensin-converting enzyme (ACE) inhibitors (C09AA) for use in sensitivity analyses.

Study population

We identified 164775 patients that had coronary angiography performed from January 1st 1998 to December 31st 2012. Out of 164775 patients we excluded all cases with missing information on weight, height, or severity of coronary artery disease. We also excluded patients with prior HF as well as patients who received loop diuretics before the date of coronary angiography, and patients

who died before the study follow up time. We included subjects who claimed loop diuretics prescription 90 days after hospital discharge to avoid prescription of loop diuretics due to renal failure or edema. We used loop diuretic as proxy for HF instead of HF hospitalizations because mild condition of HF will be treated by the general practitioner (GP) and do not need a hospital admission. We thought by using loop diuretic, we can catch more new-onset HF.

We end up with 31866 patients divided into five groups according to body mass index (BMI) as defined by the World health Organization (WHO). Patients were classified according to their BMI at the baseline coronary angiography as underweight (BMI <20kg/m^2; n=973), normal weight (BMI 20-25 kg/m^2; n=9873), overweight (BMI 25-30 kg/m^2; n=14637), obese class I (BMI 30-35kg/m^2; n=5126), or obese class II (BMI >35kg/m^2; n=1257) (figure 1). The group of patients with normal BMI was used as the reference group. Furthermore, we performed a sensitivity analysis where an alternative proxy for HF was use of loop-diuretics in combination with angiotensin-converting inhibitor and beta-blockers. Additionally, cumulative risk curves were estimated for incidence of HF and risk of mortality.

Outcome

The primary outcome for the study was the development of new onset HF, defined as the first prescription of loop diuretics after time of baseline coronary angiography. Furthermore, we were interested for an estimate of cumulative risk of mortality.

Statistical analyses

Data are presented as categorical variables with numbers, percentages and as mean with standard deviations for continuous variables. Hazard ratios (HRs) with mortality as a competing risk for the

study outcome were estimated with a modified Cox proportional hazard regression analysis (*cause-specific* proportional *hazards model)* adjusted for comorbidities.

The Cumulative Incidence/Risk was presented as percentages. Follow-up time started 90 days after coronary angiography date, and ended at death or at December 31st 2012, whichever came first.

For Cox models, the proportional hazard assumption and linearity of continuous variables were tested and found valid. There was no interaction between sex, age, degree of coronary artery disease, hyperlipidemia and BMI, respectively.

All statistical analyses were done by using SAS statistical software version 9.4 (SAS Institute inc., Cary, NC) and R software version 3.2.2.

In Denmark, registry based studies do not require ethical approval and the Danish Data Protection Agency permitted the study (reference no. 2007-58-0015, international reference: GEH-2014-015).

Results

The study comprised a total of 31866 participants, where of 5980 developed HF during 15 years of follow up period. The baseline characteristics of the study are presented in Table 1.

The overweight and obese groups comprised of 81% males and 19% women, while the underweight group was 35% males and 65% women. In general, the younger subjects had higher BMI values. At baseline, smoking was most prevalent in the underweight group, followed by the normal weight group. The prevalence of hypertension, diabetes, family disposition for ischemic heart disease and hyperlipidemia increased as the BMI increased. In contrast, malignancy and peripheral artery disease were more likely as BMI decreased.

Risk of HF

The cumulative incidences of HF for the five groups are illustrated in Figure 2. After 10 years, the incidence of HF was 30% in the underweight group, 25% in normal, 27% in overweight, 40% in obese class I and 45% in obese class II.

The results of the adjusted Cause-Specific Hazards Model indicated that the risk of developing HF was increased in the severely obese patients with the highest BMI rates compared to normal BMI. The overweight group had the lowest risk of developing HF (HR 1.14; 95% confidence interval [CI] 1.1-1.2; P <0.001), followed by the underweight (HR 1.39; 95% CI 1.2-1.6; P< 0.001). The obese class I had a 58% higher risk (HR 1.58; 95% CI 1.4-1.7; P <0.001) compared with the normal weight group. However, the risk of HF was more than doubled for obese class II group (HR 2.45; 95% CI 2.2–2.8; P <0.001), Figure 3.

To estimate the risk of mortality, we performed a Cumulative Risk Curve, which showed that at a 10 year cut off point the risk of mortality was 28% in the underweight group, 9% in normal, 7% in overweight, 6% in obese class I and 5% in obese class II, Figure 4.

Sensitivity analyses

In this analysis we used loop diuretics in combination with angiotensin-converting inhibitor and beta-blocker as a proxy for HF (n=5450). We found similar results as in the primary analysis with only loop diuretics. Compared to normal weight subjects, the overweight group had a 16% increased risk of HF (P <0.001) and the underweight group had a 35% increased risk of HF (P< 0.01). The obese class I had a 56% increased risk (P <0.001) compared with the normal weight group, and the obese class II had 2.5 times increased risk of HF (P <0.001), Figure 5.

Discussion:

This study demonstrated that a BMI > 30 kg/m^2 was associated with a notably increased risk of HF defined by use of loop-diuretics even after adjustment for comorbidities. Obese class II subjects with a BMI >35kg/m^2 had a 2.5-fold increased risk of HF compared with normal weight patients. The cumulative incidence curve also showed that the percentage of patients who developed HF increased as BMI increased, and the result was supported by a sensitivity analysis where HF was defined by use of combination drug therapy for HF. On the other hand the cumulative risk curve of mortality indicated that as BMI increased, mortality risk decreased.

Our current findings are similar to a recently published Swedish study in a non-ischemic population which investigated the incidence of some risk factors included heart failure. They found a strong relation between obesity and risk of developing HF, as well as an increased risk of developing HF as BMI increased[11]. Furthermore, it is well-known that obesity is also an independent risk factor for developing ischemic heart disease, type 2 diabetes, metabolic syndrome, dyslipidemia and hypertension, and that obesity is associated with increased risk of death [12-15]. Not surprisingly, patients in obese class I and II in our study more often had obesity-related conditions such as hyperlipidemia, hypertension and diabetes, and it is well known that these are risk factors for developing HF.

While there is substantial evidence that obesity is an important risk factor for HF, the mechanism underlying obesity-related development of HF is unclear. A study conducted in the US that investigated obesity and subclinical myocardial injury and incidence of HF, reported that obesity was independently associated with increased risk of HF and the risk increases within each BMI category [2]. Moreover, individuals with severe obesity were at the greatest risk of HF, which is consistent with our findings. In our study, overweight patients had a 14% higher risk of HF, whereas the risk was a 2.5-fold increase in patients with severe obesity compared with normal

weight subjects. The results of our study emphasize the importance of identifying obese patients at the time of coronary angiography, as these have substantially higher risk of developing HF. The treatment of HF requires enormous economic and healthcare-related resources, and identifying groups of patients who are most likely to develop HF is important in order to initiate the most effective preventive measures for this group of patients[16]. Relatedly, a Framingham heart study from 2002 showed a lifetime risk of heart failure was about 20% higher in obese patients [17]. In our study, the underweight group had a 39 % risk of HF, which was higher than the 14 % increased risk of HF in the overweight group. Underweight patients clearly represent a distinct group of patients at high risk with special clinical needs. This is not surprising, since severe HF in itself is associated with weight loss (cardiac cachexia) [18 19].

The European guidelines for HF do not recommend weight loss as part of management of chronic HF due to lack of studies that prove favorable effects of weight loss in these patients [20]. Numerous studies have shown that obese individuals with HF have better survival rates than underweight or normal weight subjects, i.e., a so-called obesity paradox [21-24]. Our estimate of cumulative risk of mortality showed that the obese and the overweight subjects had a decreased mortality risk compared with normal weight subjects. A recently published study that evaluated the impact of BMI on mortality in HF patients demonstrated that obesity increased the risk of mortality among this group of patients [25]. However, another study investigated the in-hospital mortality among HF patients found that overweight and obese patients had a 26% and 48% lower mortality risk than normal weight patients, respectively, and it was suggested that a higher BMI could be a marker of less severe HF [26]. However, many studies have confirmed the existence of the obesity paradox among HF patients [8 23 27]. One contributing factor may be related to methodological issues, e.g. confounding and biases. [24]. Moreover, it has been suggested that adipose tissues may be protective

in diseased states, and that the neuroendocrine profile of obese patients, e.g., with lower circulating levels of atrial natriuretic peptides, can be protective in HF patients [8 28].

Strength and limitations

The strengths of our study include application of nationwide data from registries, as well as data obtained at coronary angiographies. We had information on important comorbidities which were applied in order to adjust for confounding factors. Furthermore, we included a large study population allowing us to reduce the risk of selection bias. We identified all patients who claimed loop diuretics after 90 days and excluded patients with a history of HF or use of loop diuretics at baseline to ensure an exact allocation of time at risk. Unfortunately, we did not have information on selected clinical parameters, e.g., left ventricular ejection fraction, NYHA class or measures of abdominal visceral fat. The definition of HF based on claimed prescriptions of loop diuretics, which could include patients without HF, e.g., patients prescribed loop diuretics for kidney disease or non-cardiac peripheral edema. There is worthy to mention that the codifications of some comorbidity are not fully registered and we have higher percentage of missing on some comorbidity e.g. chronic obstructive lung disease.

Conclusion

In this study, we found that the risk of developing HF in patients that underwent coronary angiography increased with increasing BMI, especially for those with a BMI >30 kg/m^2, albeit that the risk of HF was also increased in underweight patients. We need a more intensive preventive arrogate for the obese patients. On the other hand, the cumulative risk of mortality showed a decreased risk of mortality for obese and overweight patients.

Conflicts of Interest: none declared.

Funding: this work was supported by Department of Health Science and Technology, Aalborg University, Aalborg, Denmark.

Reference

1. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, Kannel WB, Vasan RS.. Obesity and the risk of heart failure. N Engl J Med 2002;5:305-13.
2. Ndumele CE, Coresh J, Lazo M, Hoogeveen RC, Blumenthal RS, Folsom AR, Selvin E, Ballantyne CM, Nambi V. Obesity, subclinical myocardial injury, and incident heart failure. JACC Heart Fail 2014;6:600-7.
3. Braunwald E. Heart failure. JACC Heart Fail 2013;1:1-20.
4. Braunwald E. The war against heart failure: the Lancet lecture. Lancet 2015;9970:812-24.
5. Bleumink GS, Knetsch AM, Sturkenboom MC, Straus SM, Hofman A, Deckers JW, Witteman JC, Stricker BH. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. Eur Heart J 2004;18:1614-9.
6. Kotseva K, Wood D, De Bacquer D, De Backer G, Rydén L, Jennings C, Gyberg V, Amouyel P, Bruthans J, Castro Conde A, Cífková R, Deckers JW, De Sutter J, Dilic M, Dolzhenko M, Erglis A, Fras Z, Gaita D, Gotcheva N, Goudevenos J, Heuschmann P, Laucevicius A, Lehto S, Lovic D, Miličić D, Moore D, Nicolaides E, Oganov R, Pajak A, Pogosova N, Reiner Z, Stagmo M, Störk S,Tokgözoğlu L,Vulic D. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. Eur J Prev Cardiol 2015.
7. Sharma A, Lavie CJ, Borer JS, Vallakati A, Goel S, Lopez-Jimenez F, Arbab-Zadeh A, Mukherjee D, Lazar JM. Meta-Analysis of the Relation of Body Mass Index to All-Cause and Cardiovascular Mortality and Hospitalization in Patients With Chronic Heart Failure. Am J Cardiol 2015.
8. Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: a meta-analysis. Am Heart J 2008;1:13-22.
9. Littnerova S, Parenica J, Spinar J, Vitovec J, Linhart A, Widimsky P, Jarkovsky J,Miklik R, Spinarova L, Zeman K, Belohlavek J, Malek F, Felsoci M, Kettner J, Ostadal P, Cihalik C, Spac J, Al-Hiti H, Fedorco M, Fojt R, Kruger A, Malek J, Mikusová T, Monhart Z, Bohacova S,Pohludkova L, Rohac F, Vaclavik J, Vondrakova D, Vyskocilova K, Bambuch M, Dusek L.Positive influence of being overweight/obese on long term survival in patients hospitalised due to acute heart failure. PLoS One 2015;2:e0117142.
10. Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health 2011;7 Suppl:38-41.
11. Bjorck L, Novak M, Schaufelberger M, Giang KW, Rosengren A. Body weight in midlife and long-term risk of developing heart failure-a 35-year follow-up of the primary prevention study in Gothenburg, Sweden. BMC Cardiovasc Disord 2015;1:19.
12. Wilson PW, D'Agostino RB, Sullivan L, et al. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. Arch Intern Med 2002;**162**(16):1867-72.
13. Poirier P, Giles TD, Bray GA, Parise H, Kannel WB. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. Arterioscler Thromb Vasc Biol 2006;5:968-76.
14. Adams KF, Schatzkin A, Harris TB, Kipnis V, Mouw T, Ballard-Barbash R, Hollenbeck A, Leitzmann MF. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. N Engl J Med 2006;8:763-78.
15. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA 2013;1:71-82.
16. Braunschweig F, Cowie MR, Auricchio A. What are the costs of heart failure? Europace 2011;**13 Suppl 2**:ii13-7.

17. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ, Levy D. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. Circulation 2002;24:3068-72.
18. Anker SD, Negassa A, Coats AJ, Afzal R, Poole-Wilson PA, Cohn JN, Yusuf S. Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. Lancet 2003;9363:1077-83.
19. Kalantar-Zadeh K, Block G, Horwich T, Fonarow GC. Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. J Am Coll Cardiol 2004;8:1439-44.
20. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC,Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;16:e147-239.
21. Lavie CJ, Osman AF, Milani RV, Mehra MR. et al. Body composition and prognosis in chronic systolic heart failure: the obesity paradox. Am J Cardiol 2003;7:891-4.
22. Clark AL, Chyu J, Horwich TB. The obesity paradox in men versus women with systolic heart failure. Am J Cardiol 2012;1:77-82.
23. Shah R, Gayat E, Januzzi JL, Jr., Sato N, Cohen-Solal A, diSomma S, Fairman E, Harjola VP, Ishihara S, Lassus J, Maggioni A, Metra M,Mueller C, Mueller T, Parenica J, Pascual-Figal D, Peacock WF, Spinar J, van Kimmenade R, Mebazaa A. Body mass index and mortality in acutely decompensated heart failure across the world: a global obesity paradox. J Am Coll Cardiol 2014;8:778-85.
24. Khalid U, Ather S, Bavishi C, Chan W, Loehr LR, Wruck LM, Rosamond WD, Chang PP, Coresh J, Virani SS, Nambi V, Bozkurt B, Ballantyne CM, Deswal A. Pre-Morbid Body Mass Index and Mortality After Incident Heart Failure: The ARIC Study. J Am Coll Cardiol 2014;25:2743-9.
25. Takiguchi M, Yoshihisa A, Miura S, Shimizu T, Nakamura Y, Yamauchi H, Iwaya S, Owada T, Miyata M, Abe S, Sato T, Suzuki S, Suzuki H, Saitoh S, Takeishi Y. Impact of body mass index on mortality in heart failure patients. Eur J Clin Invest 2014;12:1197-205.
26. Fonarow GC, Srikanthan P, Costanzo MR, Cintron GB, Lopatin M. An obesity paradox in acute heart failure: analysis of body mass index and inhospital mortality for 108,927 patients in the Acute Decompensated Heart Failure National Registry. Am Heart J 2007;1:74-81.
27. Clark AL, Fonarow GC, Horwich TB. Impact of cardiorespiratory fitness on the obesity paradox in patients with systolic heart failure. Am J Cardiol 2015;2:209-13.
28. Lavie CJ, Alpert MA, Arena R, Mehra MR, Milani RV, Ventura HO. Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. JACC Heart Fail 2013;2:93-102.

Table1. Characteristics of Study Population

	Underweight (n= 973)	Normal weight (n=9,873)	Over weight (n=14,637)	Obese class I (n=5,126)	Obese class II (n=1,257)
Age, years (mean±SD)	68 (± 12)	65 (± 11)	64 (± 10)	62 (± 10)	58 (± 11)
Men (n, [%])	345 (35.4)	6745 (68.3)	11895 (81.2)	4110 (80.2)	910 (72.3)
Never smoker (n, [%])	203 (20.8)	2406 (24.3)	3653 (24.9)	1249 (24.3)	323 (25.7)
Current smoker (n, [%]) (%)	492(50.5)	3937 (39.8)	4761 (32.5)	1679 (32.7)	434 (34.5)
Ex-smoker (n, [%])	234 (24.1)	3159 (32)	5702 (38.9)	2032 (39.6)	434 (34.5)
Diabetes (n, [%])	63 (6.5)	585 (5.9)	1263 (8.6)	796 (15.5)	301 (23.9)
Multi vessel coronary artery disease(n, [%])	396 (40.6)	4508 (45,6)	6950 (47.2)	2372 (46.2)	515 (41.1)
Diffuse (<50% stenosis) coronary artery disease(n, [%])	110 (11.3)	913 (9.2)	1241 (8.4)	508 (9.7)	136 (10.8)
Hypertension treatment(n, [%])	406 (41.7)	4182 (42.3)	6972 (47.6)	2857 (55.8)	792 (63)
Statin treatment (n, [%])	416 (41.7)	4752 (48.1)	7699 (52.6)	2845 (55.5)	725 (57.6)
Liver disease (n, [%])	1 (0.1)	7 (0.07)	23(0.2)	8 (0.2)	2 (0.1)
Renal disease(n, [%])	1(0.1)	16 (0.2)	17 (0.1)	1 (0.02)	0
Arrhythmia(n, [%])	12 (1.2)	154 (1.6)	208 (1.4)	58 (1.1)	16 (1.3)
Periphery vascular disease (n, [%])	28 (2.8)	126 (1.3)	154 (1.1)	49 (1)	6 (0.5)
Cerebral vascular disease (n, [%])	10 (1.0)	77 (0.8)	122 (0.8)	49 (1)	8 (0.6)
Chronic obstructive lung disease (n, [%])	15 (1.5)	59 (0.6)	78 (0.5)	10 (0.2)	4 (0.3)
Malignancy (n, [%])	23 (2.3)	250 (2.5)	265 (1.8)	90(1.8)	16 (1.2)
Ischemic heart disease (n, [%])	127 (13)	1647 (16.6)	2526(17.2)	835 (16.3)	193 (15.3)
Family history of ischemic heart disease (n, [%])	403 (41.2)	4390 (44.4)	6763 (46.2)	2448 (47.7)	621 (49.4)
Acute CAG (n, [%])	256 (24.6)	2362 (23.3)	3007 (20.2)	970 (18.7)	231 (18.1)
Sub-acute CAG (n, [%])	315 (30.3)	2742 (27.1)	4134 (27.7)	1370 (26.3)	380 (46.5)
Elective CAG (%)	416 (40.1)	4424 (43.7)	6879 (46.16)	2530 (48.6)	594 (46.5)

Figure1: Follow chart of the study population

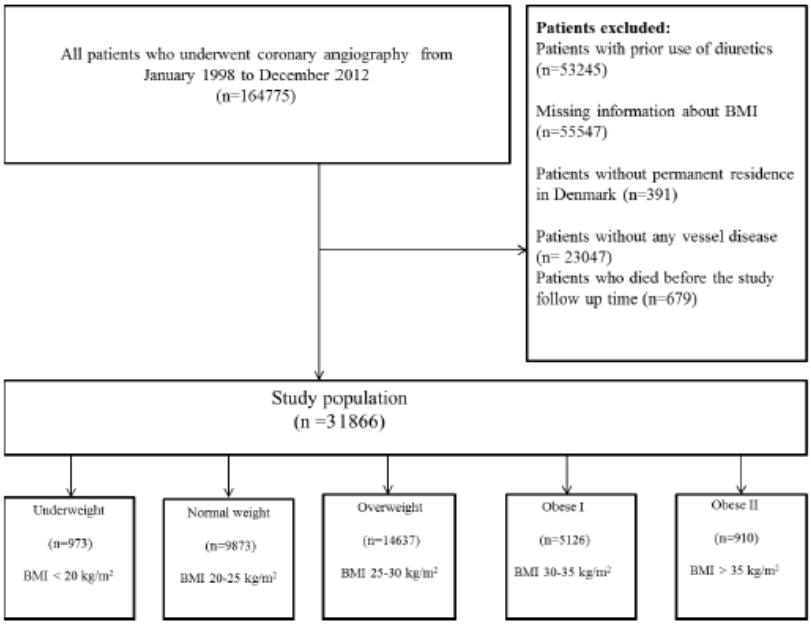


Figure 2: Unadjusted cumulative incidence curve for heart failure and different BMI groups

BMI: Body mass index

HF: Heart failure

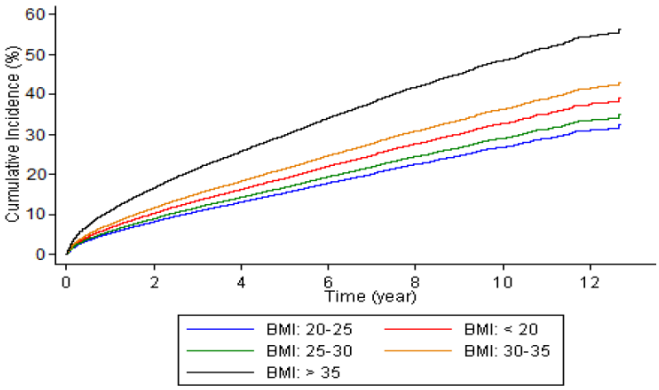
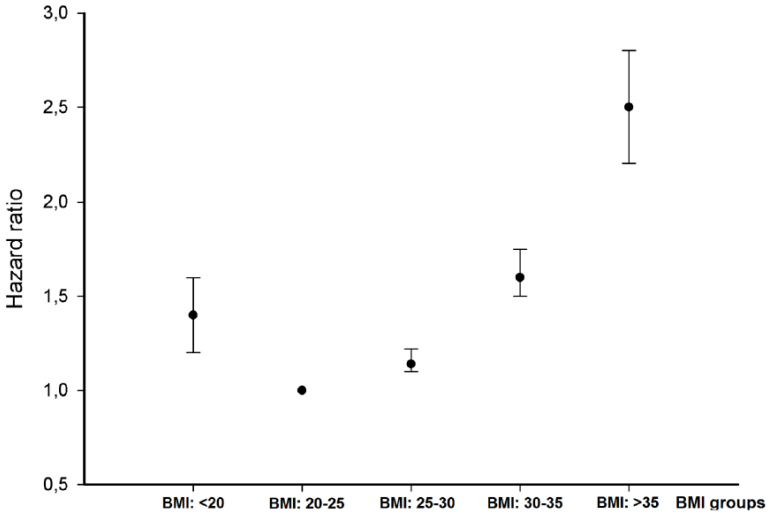


Figure3: The risk of heart failure determined by use of loop diuretics



Adjusted for chronic obstructive pulmonary disease, renal disease, liver disease, Arrhythmia, degree of vessel disease, diabetes, hyperlipidemia, hypertension, smoking status, cerebral vascular disease, malignancy, family disposition for ischemic heart disease and indication for coronary angiography as well as age and sex.

Figure 4: The cumulative risk of mortality in patients with HF and different BMI.

BMI: Body mass index

HF: Heart failure

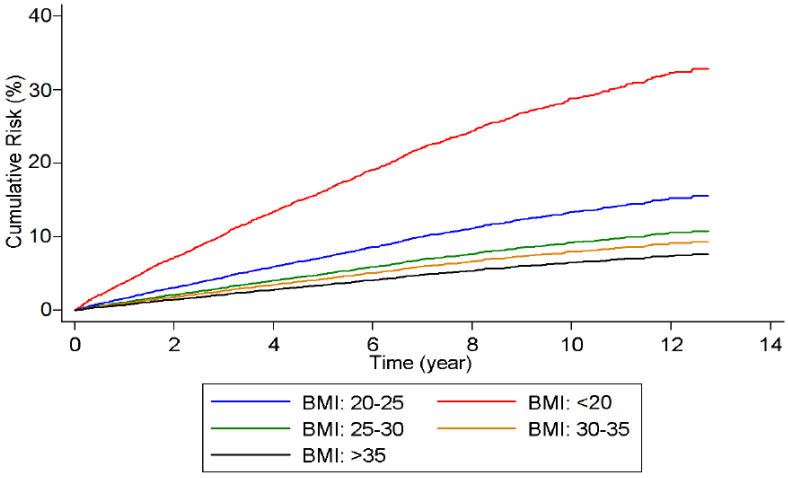
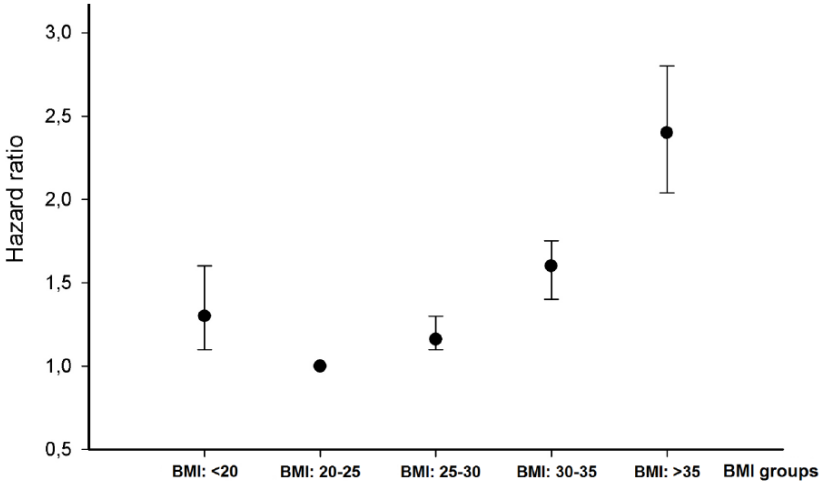


Figure5: Association of BMI and risk of HF (combination of loop diuretics, beta blocker and angiotensin converting inhibitor)



Adjusted for chronic obstructive pulmonary disease, renal disease, liver disease, Arrhythmia, degree of vessel disease, diabetes, hyperlipidemia, hypertension, smoking status, cerebral vascular disease, malignancy, family disposition for ischemic heart disease, and indication for coronary angiography as well as age and sex.

ISSN (online): 2246-1302
ISBN (online): 978-87-7112-753-9

AALBORG UNIVERSITY PRESS