The Association of Body Mass Index and 20-Year All-Cause Mortality Among Patients With Stable Coronary Artery Disease

Anan Younis, MD [a,1*], Arwa Younis, MD [a,1], Ronen Goldkorn, MD [a], Ilan Goldenberg, MD [a,b,c], Yael Peled, MD [a], Boaz Tzur, MD [a], Robert Klempfner, MD [a,b]

[a]The Leviev Heart Center, Sheba Medical Center, Tel Hashomer, 52620 Ramat Gan, Israel
[b]Sakler School of Medicine, Tel Aviv University, Ramat Gan, Israel
[c]Heart Research Follow-up Program, University of Rochester, Rochester, NY USA

Background	Limited data exist regarding the long-term association of body mass index (BMI) and all-cause mortality among patients with stable coronary artery disease (CAD). Accordingly, the aim of this study is to explore the association between BMI and long-term all-cause mortality among patients with stable CAD.
Methods	Our study included 15,357 patients with stable CAD who were enrolled in the Bezafibrate Infarction Prevention (BIP) registry between February, 1990 and October1992, and subsequently followed-up through December 2014.
Results	5,051 (33%) patients were classified as normal weight (BMI 18.5–24.99 kg/m^2), while 7,841 (51%) patients were classified as overweight (BMI 25–29.99 kg/m^2), and 2,465 (16%) as obese (BMI$\geq$30). Kaplan-Meier survival analysis showed that at 20 years of follow-up the rate of all-cause mortality was significantly higher among obese patients (67%) compared to overweight (61%) and normal weight (61%); log rank p-value for the overall difference <0.001. Multivariable analysis showed that obese patients had an independently 12% greater mortality risk compared to normal weight patients (HR = 1.12; 95% CI 1.02–1.23; p = 0.02), whereas, overweight patients experienced a similar mortality risk as normal weight patients (HR = 0.99; 95% CI 0.92–1.06; p = 0.76). The mortality risk associated with obesity was pronounced among patients younger than 65 years (p-value for interaction<0.05).
Conclusions	Our findings indicate that obesity is independently associated with increased risk for long-term mortality among patients with stable coronary artery disease, whereas overweight does not appear to confer an additional risk in this population.
Keywords	BMI • Obesity • Stable coronary artery disease • Prognosis • All-cause mortality • Long-term outcomes

Introduction

There is a worldwide increasing prevalence of overweight and obesity.[1] The World Health Organization (WHO) estimates that more than 1.3 billion adults worldwide are overweight, defined by the WHO as a body-mass index (BMI) of 25–29.99 kg/m^2, and a further 600 million are obese (BMI≥30 kg/m^2).[2] There is a strong correlation between obesity and a number of risk factors for coronary artery disease (CAD) including hypertension, dyslipidaemia and insulin resistance and an association with greater risk for cardiovascular death in the general population.[3–5]

In a recent large scale meta-analysis of prospective studies that included 10,625,411 participants with a median follow up of 13.7 years, overweight and obese patients had an increased all-cause mortality risk.[6] This study, however, excluded subjects with baseline presence of chronic diseases such as ischaemic heart disease.

Several epidemiologic studies have demonstrated that higher BMI was associated with improved survival among patients with established CAD or the CAD equivalents such as advanced renal disease and diabetes or in patients with heart failure.[7–13] This relationship has been known as the ''Obesity Paradox'' phenomenon''.[8,11,12] Most of these studies focussed on patients admitted with an acute coronary syndrome or those undergoing percutaneous coronary intervention (PCI) [8–11,14–16] or had a relatively short follow-up period. [7–9,11,14] Other studies, including mainly patients after PCI, have shown that the association of higher BMI with lower mortality risk was diminished, thus contradicting the ''Obesity Paradox'' phenomenon.[17–20]

Thus, there is limited and contradictory data regarding the very long-term association of BMI and all-cause mortality among patients with stable CAD.

Accordingly, the aims of our study are: (1) to evaluate the long-term association of BMI and all-cause mortality among patients with stable CAD in a large cohort of patients with a 20-year follow-up period and (2) to explore the mortality risk associated with BMI in selected patient subgroups.

Materials and Methods

Study Population

The present study population comprised patients who were screened for participation in the Bezafibrate Infarction Prevention (BIP) trial between February 1990 and October 1992 and enrolled in the BIP Registry. The design and rationale of the BIP Registry and study were published previously.[21,22]

Of the 15,524 screened patients, only 3,090 (20%) proceeded to be randomised in the prospective interventional 6-year BIP study that compared Bezafibrate to placebo. As the intervention period ended more than 15 years ago, we decided to include these subjects in our analysis cohort. Briefly, the BIP Registry included 15,524 patients aged 40 to 74 years with stable CAD fulfilling the following inclusion criteria: (1)

documented myocardial infarction (MI) in the previous 5 years; (2) symptomatic stable angina pectoris and either an ischaemic myocardial perfusion imaging study or ≥60% stenosis of one of the major coronary arteries demonstrated by coronary angiography; or (3) documented percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) operation in the preceding 6 months.

Exclusion criteria were diabetes mellitus (DM) requiring the use of insulin, severe heart failure, unstable angina, hepatic or renal failure, and current use of lipid-modifying drugs. All medical examination and biochemical blood-tests, historical medical data, as well as data on drug therapy, were prospectively recorded and all vital signs measured. After exclusion of those patients with missing BMI values and those with BMI<18.5 kg/m^2, the final data set for the current study comprised 15,357 patients. The study was approved by the Institute's internal review board and was performed according to the principles expressed in the Declaration of Helsinki.

BMI Measurement and Classifications

Patient's weight and height were measured during the first screening visit by study personnel using health care grade equipment. Body mass index was calculated as the ratio between weight (in kilograms) and squared height (in metres). The study patients were classified into three BMI categories according to the WHO classification.[23] Thus, those with BMI of 18.5–24.99 kg/m^2 were classified as normal weight, while those with BMI of 25–29.99 kg/m^2 were classified as overweight, and patients with BMI ≥30 kg/m^2 were considered as obese.

Metabolic syndrome components definition:

We defined metabolic syndrome (MetS) and its components according to the National Cholesterol Education Program–Third Adult Treatment Panel (NCEP).

Thus patients who presented with two, three or four of the following five risk factors were defined as having two, three and four components of the MetS respectively according to the NCEP:

1. Central obesity defined as waist circumference greater than established ethnicity specific values. Since the data regarding waist circumference were not available, for purposes of this analysis we used the accepted BMI above 30 as a criterion for classifying patients as obese;
2. Low high-density lipoprotein (HDL) <1.3 mmol/l among women, and <1.03 mmol/l among men;
3. Elevated fasting plasma triglycerides (TG) ≥1.7 mmol/l, or specific treatment for this lipid abnormality;
4. Elevated systolic blood pressure ≥130 mmHg, or diastolic value ≥85 mm Hg, or treatment of previously diagnosed hypertension;
5. Elevated fasting plasma glucose (FPG) ≥5.6 mmol/l or previously diagnosed diabetes mellitus.

Laboratory Methods

Blood samples were drawn after at least 12 hours of fasting. Cooled samples, collected in the 18 participating centres using standard equipment and procedures, were transferred to the study's central laboratory. All analyses were

performed on a Boehringer Hitachi 704 random access analyser using Boehringer diagnostic kit (Roche Diagnostics Corporation (Formerly Boehringer Mannheim Corporation), Indianapolis, IN, USA).

Primary Endpoint

The primary endpoint of this study was all-cause mortality at 20 years. Mortality data were obtained by matching the patient's identification numbers with their vital status in the National Population Registry of Israel. It should be emphasised that each match record was checked for correct identification by matching the study recorded date of birth during enrolment with the date of birth stored at the national registry. Patients with missing values or inconsistent matching were excluded from the present analysis (n = 167).

Statistical Analysis

Continuous variables are expressed as means ± standard deviation (SD), and categorical data are summarised as frequency (%). The clinical characteristics of the patients at baseline by the different BMI groups were compared with the use of the one-way ANOVA for continuous variables with post hoc analysis and Tanhane's test as needed, and the Chi square (with Z test and Bonferroni correction test), for categorical variables. Kaplan–Meier survival analysis was used to graphically present survival estimates of subjects classified according to the different BMI groups and the subsequent long-term survival probability, cumulative event rates were compared using the log rank test. Multivariate Cox regression was used to assess the independent effect of BMI on the primary endpoint of all-cause mortality. The following covariates were introduced using the best subset method, following a univariate analysis of all relevant variables: age, gender, estimated glomerular filtration rate (eGFR)< 60 ml/min/$1.73m^2$, and diagnosis of DM, New York Heart Association score (NYHA) >2, previous MI, past cerebrovascular accident (CVA), history of hypertension (HTN), chronic obstructive lung disease (COPD), high density lipoprotein concentration (HDL), low density lipoprotein concentration (LDL), triglycerides (TRIG), and fasting blood glucose (FBG), use of: anti-platelets, beta blockers (BB), nitrates, calcium channel blockers (CCB) and diuretics. Proportionality of hazard assumption was verified using Schoenfeld residuals and the log minus log (LML) method. We additionally performed a sensitivity analysis excluding subjects randomised to the BIP randomised study (n = 3,090).

In order to further explore the independent risk associated with overweight and obesity based on the different classifications of BMI in selected patient subgroups (including age [$\geq$65 years], sex, prior MI, renal dysfunction [eGFR <60 ml/min/1.73m ^{2}], and NYHA functional class 1–2, we performed interaction term analysis by the introduction of a BMI-by-risk-subgroup interaction-term to the multivariate adjusted Cox model (covariates as above). Interaction

analysis is graphically presented in the form of a Forest plot. We further calculated the independent risk probability using BMI as a continuous covariate and plotted the function for patients below 65 years versus older patients.

Statistical significance was accepted for a two-sided p<0.05. The statistical analysis was performed with IBM SPSS version 20 (Armonk, NY, USA) and SAS version 9.2 (SAS institute Inc., Cary, NC, USA).

Results

Based on the WHO classification of obesity 5,051 (33%) patients were classified as normal weight (BMI 18.5–24.99 kg/m^2, while 7,841 (51%) were classified as overweight (BMI 25–29.99 kg/m^2), and further 2,465 (16%) as obese (BMI $\geq$30).

Baseline characteristics of the study patients according to the three different BMI groups are presented in Table 1. As expected, overweight and especially obese patients had an adverse clinical and biochemical profile including higher incidence of DM, HTN, and dyslipidaemia compared to those with normal weight. Patients classified as obese were younger, had less male predominance, less past MI, and higher rates of NYHA class >2, compared to those who were overweight or normal weight.

Compared to patients classified as obese, overweight patients were less likely to have DM, HTN, and had lower raters of TRIG, FBG, and had higher levels of HDL.

Obese patients also were more likely to have two, three or four components of MetS than those with overweight.

Obese patients were more likely to receive beta blockers, nitrates, and calcium channel blockers, and diuretics compared to their counterparts with overweight or normal weight.

Long-Term Mortality by the Different BMI Groups

Kaplan-Meier survival analysis showed that at 20 years of follow-up the rate of all-cause mortality was significantly higher among obese patients (BMI $\geq$30[67%]) compared to those who were classified as overweight (BMI 25–29.99[61%]) and normal weight (18.5–24.99[61%]; overall log rank p < 0.001; Figure 1).

Notably, separation in the event rates between obese, overweight and normal weight patients appeared after approximately 4 years and tended to persist thereafter.

Consistently, adjusted for age, gender and major comorbidities, BMI $\geq$30 was associated with approximately 12% independently increased mortality risk (HR = 1.12; 95% CI 1.02–1.23; Table 2), whereas, BMI 25–29.99 was associated with non-significant risk of mortality (HR = 0.99; 95% CI 0.927–1.106; Table 2). When we introduced medications to the multivariable model, consistent results were obtained. Notably, when assessing the mortality risk associated with BMI as a continuous variable, each 1-unit increase was associated with a 1.5% greater adjusted mortality risk (p = 0.001). Consistent results were obtained when subjects randomised to the interventional BIP trial (n = 3,090) were excluded.

**Table 1** Baseline characteristics of the study population according to the different 3 BMI groups.

	18.5≤ BMI<24.99	25≤BMI<29.99	BMI ≥30	P value
Demographics	N = 5051 (33%)	N = 7841 (51%)	N = 2465 (16%)	
Age (years) $	60 ± 7	60 ± 7	59 ± 7 * **	<0.001
Male	4125 (82%)	6509 (83%)	1784 (72%) ***	<0.001
Medical history and clinical characteristics				
HTN	1426 (28%)	2628 (34%) *	1077 (44%) ***	<0.001
DM	851 (17%)	1472 (19%) *	627 (26%) ***	<0.001
COPD	160 (3%)	204 (3%)	85 (4%)	0.055
Past MI	3723 (74%)	5633 (72%)	1737 (71%) ***	0.006
Past CVA	97 (1.9%)	130 (1.7%)	42 (1.7%)	0.530
NYHA >2	247 (5%)	441 (6%)	205 (9%) ***	<0.001
Laboratory values				
CHO mmol/l	5.74 ± 1.01	5.82 ± 1.01 *	5.88 ± 1.06 *	<0.001
Creatinine umol/l	102.57 ± 24.76	102.57 ± 16.80	99.03 ± 15.03 ***	<0.001
HDL mmol/l	1.01 ± 0.28	0.96 ± 0.26 *	0.96 ± 0.23 *	<0.001
LDL mmol/l	4.01 ± 0.88	4.03 ± 0.88	4.01 ± 0.93	0.244
TRIG mg/dl	1.59 ± 0.91	1.83 ± 1.03 *	2.01 ± 1.08 ***	<0.001
FBG mg/dl	6.11 ± 2.44	6.33 ± 2.44 *	6.94 ± 2.94 ***	<0.001
2 components of MetS	1699 (34%)	2467 (32%)*	649 (26%) ***	<0.001
3 components of MetS	1238 (25%)	23,400 (31%)*	843 (34%) ***	<0.001
4 components of MetS	510 (10%)	1282 (16%)*	644 (26%) ***	<0.001
Medications				
Beta blockers	1600 (32%)	2817 (36%) *	990 (40%) ***	<0.001
Nitrates	2465 (49%)	3889 (50%)	1340 (54%) ***	<0.001
CCB	2408 (48%)	3985 (51%) *	1339 (54%) ***	<0.001
Anti-platelet agents	3043 (60%)	4695 (60%)	1336 (54%) ***	<0.001
Diuretics	723 (14%)	1133 (14%)	518 (21%) ***	<0.001

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVA, cerebral vascular accident; CHO, total cholesterol; DM, diabetes mellitus; FBG, fasting blood glucose; HDL, high density lipoprotein; HTN, hypertension; LDL, low density lipoprotein; MI, myocardial infarction; MetS, Metabolic Syndrome; NYHA, New York Heart Association; TRIG, triglycerides.

$Continuous variables are reported as mean ± standard. Categorical variables are reported as numbers (%).

*p-value < 0.05 comparing obese (BMI ≥30), or overweight (BMI 25-29.99) to normal weight (BMI 18.5-24.99).

**p-value < 0.05 comparing obese (BMI ≥ 30) to overweight (BMI ≥ 30) patients.
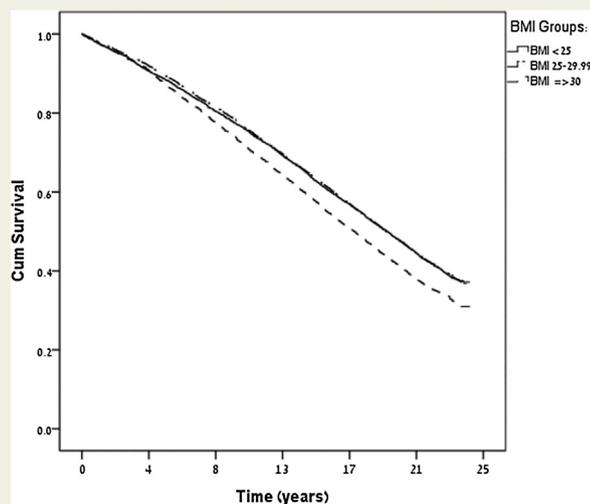
Fig. 1 Kaplan Meier 20-year survival estimates according to the 3 body mass index (BMI) groups.

Additional independent predictors for long-term mortality included: increased eGFR<60 ml/min/1.73m^2, the presence of DM, HTN, NYHA class >2, and a history of past MI, use of nitrates and diuretics.

Subgroup Analysis

We further explored the independent association between BMI ≥30 respectively, and long-term mortality in selected subgroups of patients (Figure 2). In obese patients, the increased mortality risk was similar across all subgroups, except there was a more pronounced effect in patients younger than 65 (HR = 1.17; 95% CI 1.06–1.30, p for interaction = 0.02).

We presented the associated mortality risk against BMI as a continuous variable in patients 65 years or older vs. younger patients (Fig. 3).

**Table 2** Independent predictors of 20-year all-cause mortality outcome.

	adjusted HR	95% CI for lower	95% CI for upper	P-value
BMI ≥30$	1.121	1.020	1. 233	0.02
BMI 25–29.99$	0.99	0.927	1.066	0.87
BMI (per unit increment)^	1.015	1.006	1.025	0.001
Age (per year increment)^	1.079	1.073	1.084	<0.001
Male Gender	1.233	1.117	1.360	<0.001
DM	1.271	1.150	1.404	<0.001
HTN	1.134	1.062	1.212	<0.001
Past MI	1.390	1.290	1.498	<0.001
eGFR<60 ml/min/1.73m^2	1.061	0.992	1.135	0.08
NYHA class >2	1.225	1.070	1.403	0.003
Fasting glucose mmol/l^	1.081	1.062	1.099	<0.001
HDL mmol/l^	0.623	0.506	0.767	<0.001
Anti-platelets	0.937	0.879	0.999	0.04
Beta blockers (BB)	0.840	0.787	0.897	<0.001
Nitrates	1.202	1.129	1.280	<0.001
Diuretics	1.570	1.446	1.705	<0.001

Abbreviations: BMI, body mass index; CI, 95% confidence interval; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension; IFG, impaired fasting glucose; MI, myocardial infarction; NYHA, New York Heart Association.

Hazard ratios are further adjusted to: Sex, Age, eGFR<60 ml/min/1.73m^2, hypertension (HTN), chronic obstructive pulmonary disease (COPD), cerebrovascular accident (CVA), diabetes mellitus (DM), past myocardial infarction (MI), NYHA class >2, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides, fasting blood glucose (FBG), use of: anti-platelets, nitrates, beta blockers (BB), calcium channel blockers CCB, and diuretics.

^denotes covariates introduced as continuous variables into the Cox model.

$hazard ratios compared to BMI 18.5–24.99 (normal weight patients).
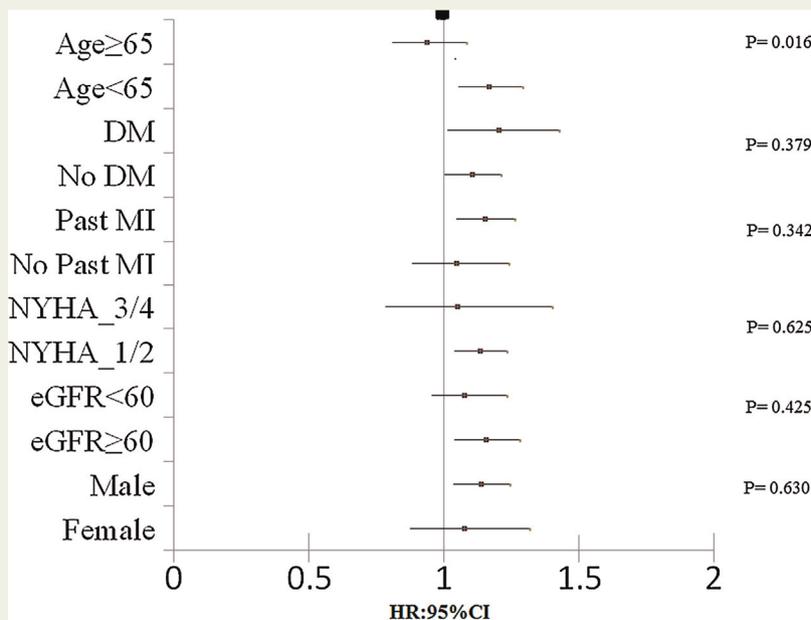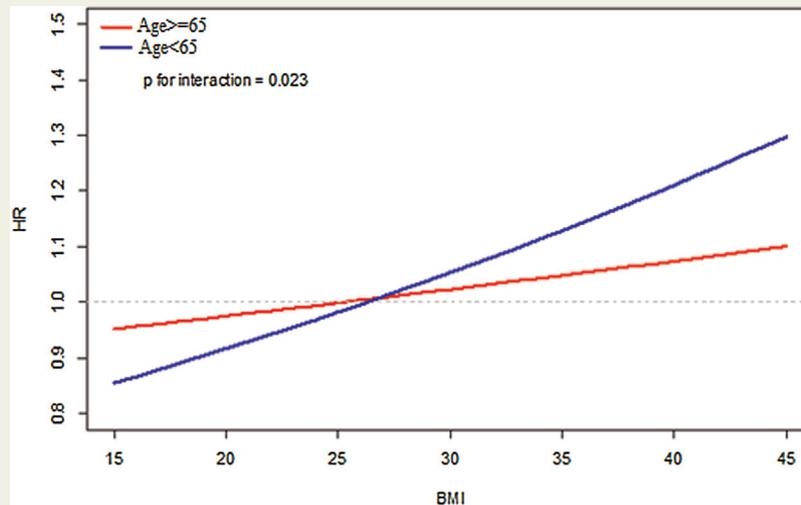

Fig. 2 Adjusted Hazard ratios of all-cause mortality for body mass index (BMI) ≥30 vs. BMI 18.5–24.99 in selected subgroups of patients for the 20-year mortality outcome.

Discussion

The primary results of our study are: (1) BMI ≥30 is associated with almost 12% greater all-cause mortality risk at 20 years of follow-up and the associated risk is independent of other important predictors of mortality; (2) BMI ≥30 is associated with consistent increased risk of mortality which is similar in most subgroups with a more pronounced effect

Fig. 3 Adjusted hazard ratios for 20-year all-cause mortality outcome for body mass index (BMI) as a continuous variable among patients 65 years or older vs. those younger than 65.

among those who are younger than 65; (3) BMI 25–29.99 confers no additional mortality risk.

Previous studies considering the short-term association of BMI and MACE, and all-cause mortality among patients with CAD, showed an inverse relationship thus supporting the "Obesity Paradox" phenomenon.[7,9,11,14,15,24]

On the contrary, the present study showed an increased risk of all-cause mortality with obesity. These results are consistent with previous studies that considered the long-term effect of BMI on all-cause mortality and mainly cardiovascular mortality and morbidity among patients with CAD.[17–20]

Our study focussed on patients whose recruitment took place between 1990 and 1992 and the majority of the patients were without history of revascularisation at the time of their enrolment. Therefore, our study is the largest to evaluate this unique group of patients with stable CAD and without revascularisation given that previous studies focussed on the relation of BMI with all-cause mortality in patients with acute coronary syndrome or those undergoing revascularisation by PCI.[7,9,11,14–19]

Of the few studies that considered the impact of obesity on mortality among patients with stable CAD, one study showed that obesity did not result in increased cardiovascular and all-cause mortality over a 5–10 year period of follow-up.[25] Another study which focussed on middle aged men with stable CAD and a mean follow-up of 10 years showed consistent results with ours regarding both obese and overweight patients.[26] Thus our study expands on these results and includes both men and women in a larger cohort of patients with 20-year follow-up. Moreover, our study is unique in examining the interaction of BMI as both a categorical and continuous variable and mortality among sub groups of risk.

An important finding of our study is the pronounced effect of obesity on mortality among patients younger than 65, thus demonstrating that the association between obesity and mortality changes across the lifespan. In accordance with our findings, Stevens and colleagues [27] demonstrated that the relative risk of all-cause and cardiovascular mortality associated with an excess body mass is greater for younger and middle-aged individuals than for older individuals. A potential hypothesis could be that of a selective survival effect of healthier, older individuals, in that unhealthy individuals with a higher BMI may have already died from the ill effects of obesity[28]. Furthermore, obese individuals are more likely to survive a heart attack than normal weight individuals suggesting another potential explanation for the weak relationship with all-cause and particularly cardiovascular mortality observed in older populations. It is possible that obesity provides protection in the period following an acute event or procedure [11,14,24] yet is associated with increased risk thereafter [18,19]. Excess weight may provide a protective effect following an acute event by its association with a greater fat mass, given that adipose tissue was shown to be a major reservoir of adult stem cells with potential to develop into cardiomyocytes or endothelium[29]. Moreover, the perception of increased risk associated with obesity might lead to more aggressive management of these patients possibly resulting in better short-term outcomes[30]. Our study uniquely demonstrates that obese patients had higher number of metabolic syndrome components than both groups of normal as well as overweight patients, highlighting obesity as a conditional risk for the development of cardiovascular risk factors such as diabetes, dyslipidaemia, and hypertension which are major components in the constellation known as the metabolic syndrome.[31,32] Therefore, the mortality risk associated with obesity may be driven by the higher incidence and prevalence of MetS among these patients.

Limitations

First, although our study had the advantage of being a large prospective study with long-term follow-up, it is a

retrospective analysis and not all confounders can be accounted for. Second, we have no data regarding clinical events and management after the patients' screening period. Third, only all-cause mortality was measured and thus, although this was a cardiovascular cohort, with documented cardiovascular disease at baseline, we are unable to determine what contribution cardiovascular deaths made to our findings. In addition, only a single measure of BMI was made at baseline and this has some limitations in relation to a 20-year follow-up study. Fourth, although BMI may be a useful risk predictor on a population level, it is not a direct measure of body composition (muscle mass vs. fat mass). Moreover, BMI makes it difficult to distinguish between either location or type of fat which may attenuate its prediction ability. Data regarding fat distribution such as waist circumference, hip circumference and thigh diameter are lacking. However, BMI has the advantage of being easy to estimate, highly accurate and more generally available, while waist circumference is more prone to inter-observer variation.

Conclusions

In patients with stable coronary artery disease, obesity (BMI $\geq$ 30), but not overweight (BMI 25-29.99), was associated with significantly increased risk of all-cause mortality over 20-year follow-up. These results were consistent in all subgroups except for age where risk was significantly greater among patients younger than 65. Conversely, overweight is not associated with increased risk of all-cause mortality in this population.

Acknowledgments

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