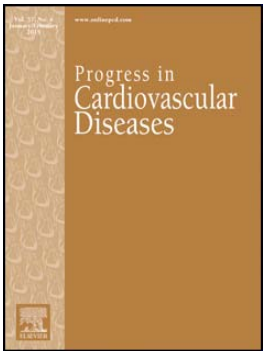

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The Interaction of Cardiorespiratory Fitness with Obesity and the Obesity Paradox in Cardiovascular Disease

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Disclosures:

Dr. Lavie served as a speaker and consultant for the Coca-Cola Company (but on physical activity, exercise fitness and not on their products) and is the author of the book 'The Obesity Paradox.'

Key Words:

Obesity, body composition, obesity paradox, cardiorespiratory fitness, physical activity, exercise, cardiovascular disease

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Abstract

Overweight and obesity are well-established risk factors for most cardiovascular diseases (CVD), including coronary heart disease (CHD), heart failure (HF), and atrial fibrillation. Despite the strong link between excess adiposity and risk of CVD, growing evidence has demonstrated an obesity paradox in patients with CVD. This phenomenon is characterized by a better prognosis in overweight and mildly obese CVD patients than their leaner counterparts. Moreover, the worst outcomes are often incurred by underweight CVD patients, followed by those of normal weight or severely obese. The obesity paradox is now a well-established phenomenon across different types of CVD, and it occurs regardless of age and ethnicity of patients, and severity of CVD. Physical inactivity and low cardiorespiratory fitness (CRF) have long been recognized as major risk factors for CVD. In contrast, high levels of physical activity (PA) and CRF largely neutralize the adverse effects of excess adiposity and other traditional CVD risk factors, including hypertension, metabolic syndrome, and type-2 diabetes. Higher CRF also results in better CVD outcomes across different BMI groups and significantly alters the obesity paradox in patients with HF and CHD. Prognostic benefits of overweight/obesity tend to be limited to unfit patients with HF and CHD, and the obesity paradox usually disappears with improved levels of CRF. Nevertheless, increased PA and exercise training, to maintain or improve CRF, are effective, safe, and proven strategies for primary and secondary prevention of CVD in all weight groups. In this review, we discuss the current concepts of individual and combined contributions of fatness and fitness to CVD risk and prognosis. We then examine the influence of fitness on the obesity paradox in individuals with CVD.

Abbreviations

ACLS = Aerobics Centers Longitudinal Study

ACS = Acute coronary syndrome

AF = Atrial fibrillation

BMI = Body mass index

CAC = Coronary artery calcium

CCLS = Cooper Center Longitudinal Study

CHD = Coronary heart disease

CKD = Chronic kidney disease

CPX = Cardiopulmonary exercise testing

CRF = Cardiorespiratory fitness

CV = Cardiovascular

CVD = Cardiovascular disease

DM = Diabetes mellitus

ET= Exercise training

FHS = Framingham heart study

HF = Heart failure

HFpEF = Heart failure with preserved ejection fraction

HFrEF = Heart failure with reduced ejection fraction

HTN = Hypertension

LA = Left atrial

LV = Left ventricular

LVH =Left ventricular hypertrophy

MET = Metabolic equivalent

MS = Metabolic syndrome

MI = Myocardial infarction

PA = Physical activity

6MWD = Six-minute walk distance

T2DM = Type-2 diabetes mellitus

VA =Veterans affairs

VO_2max = Maximal oxygen consumption

WC = Waist circumference

%BF = Percent body fat

Overweight and obesity are well-established risk factors for cardiovascular disease (CVD) and mortality. Numerous studies have confirmed the strong association of overweight and obesity with increased prevalence of most CVDs, including coronary heart disease (CHD), atrial fibrillation (AF) and heart failure (HF).[1–4] Two main factors underlie the excess risk of CVD in obesity. 1) Obesity shows strong association with other major CVD risk factors, such as hypertension (HTN), atherosclerosis, metabolic syndrome (MS), type-2 diabetes mellitus (DM; T2DM), dyslipidemia and obstructive sleep apnea. 2) Increased adiposity can independently induce alterations in the cardiac structure and function.[5,6] Despite the strong relationship between obesity and development of CVD, multiple studies, mostly published in the last 15 years, have demonstrated an 'obesity paradox,' which is characterized by a better short- and intermediate-term prognosis in overweight or mildly obese patients with CVD compared to their leaner or normal-weight counterparts.[5–8]

The global epidemic of obesity has mainly been attributed to poor dietary choices characterized by excessive calorie intake[9,10] and to massive declines in occupational physical activity (PA) in both men and women and household management in women during past decades.[11,12] Moreover, numerous studies assessing occupational and leisure-time PA, and cardiorespiratory fitness (CRF) have revealed a strong, inverse, graded and independent association of PA/CRF with both CVD and overall mortality, regardless of race and gender.[13] Physical inactivity and low CRF are now recognized as major risk factors for CVD and stroke.[14,15] Moreover, improved CRF has been linked to better prognosis and lower risk of mortality after the onset of CVDs.[13]

The relative and joint contributions of fatness and fitness to health remain poorly understood. But, growing evidence suggests that improved CRF largely neutralizes the adverse effects of increased adiposity, as well as other traditional CVD risk factors, including HTN, MS, and T2DM.[8,16–18]

In this review, we discuss the current concepts of individual and combined contributions of fatness and fitness to CVD risk and prognosis. We then examine the relationship between CRF and the obesity paradox in individuals with CVD.

Obesity as a Risk Factor for CVD and Mortality

Weight gain and obesity lead to various alterations in the central and peripheral hemodynamics, including increased total and central blood volume, decreased systemic vascular resistance, and a rise in left ventricular (LV) stroke volume, cardiac output, LV filling pressures and pulmonary artery pressures.[5–7,19] A complex interaction between these hemodynamic alterations and several other mechanisms, such as HTN, neurohormonal and metabolic abnormalities results in cardiac remodeling and dysfunction in obesity.[20] Obese individuals are more likely to have LV remodeling (concentric remodeling and LV hypertrophy[LVH]), left atrial (LA) enlargement, and greater right ventricular mass and end-diastolic volume.[21–24] Furthermore, obesity has been associated with LV diastolic dysfunction, subclinical LV systolic dysfunction (low myocardial strain), and reduced right ventricular ejection fraction.[6,25–28]

Mortality: In the general population, the association between BMI and risk of mortality is non-linear, and it usually follows a U-shaped pattern. There exists a significant variation among epidemiologic studies regarding what constitutes a 'healthy' BMI. A meta-analysis of 230 cohort studies with a combined sample size of 30.3 million participants reported higher risk of mortality in underweight, overweight and obese individuals.[29] In the analysis of all participants, the lowest risk of mortality was observed among those with a BMI around 25, while among never smokers those with a BMI of 23-24 had the lowest risk of mortality. A recent study by Afzal *et al*. has broadened our understanding of 'healthy' BMI and its dynamic nature.[30] The investigators compared the BMI-mortality relationships from 3 different Danish cohorts enrolled at different times over the past three decades. The study revealed that the BMI value associated with the nadir of all-cause mortality risk increased by

3.3 kg/m^2 (from 23.7 to 27 kg/m^2) from 1976 to 2003-2013. Moreover, over the past three decades, the hazard-ratio of all-cause mortality related to BMI ≥30 vs. BMI of 18.5 to 24.9 kg/m^2 decreased from 1.3 to 1.0.

HF: Multiple epidemiological studies have demonstrated a strong association between overweight/obesity and HF. In the Framingham Heart Study (FHS), every 1 kg/m^2 increment in BMI was found to increase the risk of HF by 5% in men and 7% in women.[3] Other obesity parameters, such as waist circumference (WC) or waist-to-hip ratio, also predict the risk of future HF. In a meta-analysis of 28 prospective studies (>600.000 participants), every 10 cm increase in WC was associated with a 29% higher risk of HF.[31] Obesity tends to show a stronger association with HF with preserved ejection fraction (HFpEF) than HF with reduced ejection fraction (HFrEF).[32,33] Pandey *et al*., using data from 3 major cohort studies (N=51,451), recently demonstrated that higher BMI had a strong dose-dependent association with the cumulative incidence of only HFpEF but not HFrEF.[34]

CHD: Obesity and related comorbidities such as HTN, T2DM, dyslipidemia, systemic inflammation play a significant role in the pathogenesis of atherosclerosis, the hallmark finding of CHD.[35] Consistently, overweight and obese individuals tend to have a higher prevalence of CHD compared to their leaner counterparts.[36] Data from the FHS demonstrated after adjustment for other covariates that approximately 23% of CHD in men and 15% of CHD in women were attributable to excess adiposity.[4] Acute coronary syndromes (ACS) occur at earlier ages in overweight and obese individuals compared to those with a normal BMI. A large retrospective cohort study (n=111,847) showed that the age at first non-ST-elevation myocardial infarction (MI) in individuals with grade 1, grade 2 or grade 3 obesity were 6.8, 9.4, 12.0 years earlier, respectively, compared to that in normal weight patients.[37] The independent impact of obesity on the risk of ACS has not been consistently confirmed across epidemiologic studies. For example, a large population-based cohort study (n= 61,299 and 12 years of follow-up) from Norway found that obese and metabolically healthy individuals did not have excess risk of MI when compared

with normal weight and metabolically healthy individuals.[38] However, these results were challenged by two meta-analyses which showed that overweight and obese individuals are at increased risk of CVD and mortality even in the absence of metabolic abnormalities.[39,40]

AF: There exists substantial evidence on the relationship between obesity and risk of AF. In a meta-analysis of 16 studies with a combined sample size >123,000, obesity was associated with ~50% higher risk of AF than normal weight.[41] Among the FHS participants, every 1-unit increase in BMI was found to increase the risk of AF by 4%.[42] Studies with a longer duration of follow-up period have revealed a more obvious relation between obesity and AF risk. A population-based cohort study (n=12,850) with a median follow-up period of 26 years demonstrated that compared to their normal weight counterparts, overweight and obese young men had 2-fold and 3-fold increased risk of future AF, respectively.[1] Moreover, increased BMI strongly predicts the risk of progression from paroxysmal AF to permanent AF.[43]

Obesity Paradox in CVD

Despite the strong relation between excess adiposity and development of CVDs, a large body of evidence has demonstrated an obesity paradox in patients with CVD. This phenomenon is characterized by a better prognosis in overweight and mildly obese patients with CVD, compared to their leaner counterparts. Also, the worst outcomes are usually observed in underweight CVD patients, followed by those with normal weight or severe obesity.[5,6] The obesity paradox in CVD derives from a complex interaction between several potential mechanisms (**Table**). Relative contribution of each mechanism to the obesity paradox remains poorly understood. However, growing evidence suggest that muscle mass and strength and CRF are the major determinants of the prognostic implications of obesity in CVD.[44–47]

HF: The obesity paradox is a well-established phenomenon in patients with HF. It is observed across different ethnicities and regardless of the acuity (acute vs. chronic), etiology (ischemic vs. non-

ischemic), type (HFpEF vs. HFrEF), and severity (advanced vs. non-advanced) of HF.[6–8,48] Several studies have suggested a U-curve shaped relationship between BMI and adverse outcomes in HF.[49–51] For instance, the poorest prognosis was usually reported in underweight HF patients and to a lesser extent in severely obese ones and a nadir of risk with overweight and mild obesity. The protective effect of obesity is often lost in severely obese HF patients. Nagarajan *et al*. found in 501 consecutive patients with advance HF that a BMI of ≥40 kg/m^2 was associated with 2.5-times higher risk of mortality compared to a BMI of 30.1 to 39.9 kg/m^2.[52] Some studies, but not all, suggested a sex-specific interaction between obesity and prognosis in HF. A retrospective cohort study by Vest *et al.* in 3,811 mostly advanced HF patients demonstrated an obesity paradox in regards to all-cause mortality with the unadjusted data.[50] However, when the authors adjusted the results for other confounders (including CRF and other variables), the overweight/obesity survival benefit only remained significant in female patients. Only a few studies have examined the impact of obesity parameters other than BMI on HF prognosis. Clark *et al.* reported the best survival in HF patients with high BMI and high WC and the worst prognosis in those with normal BMI and normal WC.[53,54]

CHD: In a meta-analysis of 40 studies and >250,000 patients with CHD, Romero-Corral *et al.* reported more favorable CV and total mortality outcomes in overweight and mildly obese patients than those of normal weight and underweight groups.[55] These results were confirmed by another meta-analysis with a larger sample size (89 studies, 1.3 million patients with CHD).[56] In this study, overweight and obesity were associated with lower risk of short-term (<6 months) and long-term (≥6 months) mortality. However, the survival benefit of obesity in CHD was lost after five years. Moreover, patients with grade II/III obesity had a lower risk of short-term mortality, but higher risk of long-term mortality. Several studies examined the relative and combined prognostic implications of BMI and other adiposity parameters in patients with CHD. In a systematic review of 6 studies with nearly 16,000 subjects, BMI was inversely correlated with mortality.[57] However, central obesity was a predictor of higher mortality

even in normal weight (BMI<25 kg/m^2) individuals. A similar analysis in patients with CHD reported the highest risk of mortality in normal weight subjects with central obesity compared with subjects with other weight patterns.[58]

AF: An obesity paradox exists for outcomes in AF as well. A post hoc analysis of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study (n=2,492) demonstrated lower risk of mortality in overweight and obese AF patients compared with the normal weight ones.[59] Similar results were observed in regards to CVD and all-cause mortality among Japanese patients with non-valvular AF and a contemporary cohort of outpatients with AF in the US.[60,61] Sandhu *et al.* recently reported a post hoc analysis of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial which examined the impact of BMI and WC on outcomes in AF patients (n=17,913).[62] The study revealed an inverse association between BMI and risk of all-cause mortality and the composite end-point, which included stroke, systemic embolism, MI, and all-cause mortality. Interestingly, WC had an inverse relationship with adverse outcomes in women, but not in men.

CRF and Risk of CVD and Mortality

Physical inactivity and low CRF are well-recognized risk factors for CVD.[14,63–65] Mainly because of the simplicity of data-collection, self-reported PA has been the most commonly studied indicator of CRF. However, it should be noted that PA and fitness are two closely-related measures with very distinct definitions. PA refers to a collection of behaviors with several domains such as occupational, domestic, transportation, and leisure-time PA.[14] In contrast, CRF is a health-related component of physical fitness, and it is defined as the ability of the respiratory, circulatory and muscular systems to supply oxygen during sustained PA.[66] In simple terms, high CRF indicates the presence of highly integrated and well-functioning oxygen transport and utilization systems. An individual's CRF is determined by an interaction

of several factors, such as PA, age, sex, ethnicity, muscle mass, adiposity, genetics, and CV and respiratory health.[67] Moreover, PA and ET can modify CRF, and improvements in CRF predict lower risk of mortality.[68] CRF is ideally measured by cardiopulmonary exercise testing (CPX) which requires specialized laboratory equipment and trained personnel. CRF is usually reported as metabolic equivalents (METs) or maximal oxygen consumption (VO_2max, ml O_2/kg.min).[67] In clinical practice and research studies, several other techniques are commonly used as surrogates for CRF assessment, such as 6-minute walk test and exercise tolerance on a regular treadmill test.

Increased CRF has been associated with lower blood pressure levels and delay and prevention of development of HTN.[69,70] Moreover, it leads to an improvement in other cardiometabolic risk factors and MS components.[71,72] Higher CRF has been associated with several changes in the CV structure and function, such as larger LV chamber size, less concentric LV remodeling, lower estimated LV filling pressures, improved diastolic function, greater LA volume.[73,74] Data from the FHS revealed that higher PA levels measured by accelerometer were associated with lower arterial stiffness and greater LV mass, aortic root, and LA size.[75] In the Coronary Artery Risk Development in Young Adults (CARDIA) study higher baseline CRF was associated with favorable global longitudinal strain, better diastolic function, and lower LV mass even after 25 years of follow-up.[76,77] Consistently, regular exercise can result in regression of LVH findings on echocardiography.[78]

Mortality: Numerous studies have confirmed the strong, inverse and graded relationship of PA and CRF levels with lower risk of CVD morbidity and mortality, and overall mortality in apparently healthy individuals or those with documented CVD. In general, high CRF provides a protective effect regardless of race, age and gender, and independent of other traditional risk factors, including smoking, DM, HTN, BMI and lipid panel.[13,67,79] Interestingly, in many circumstances, individuals with high CRF and CVD risk factors or CVD have better survival than their counterparts without these conditions but with low CRF.[48] Almost 3 decades ago, Blair *et al.* in their landmark study (n=13,354, follow-up >8 years)

demonstrated that higher CRF estimated with treadmill exercise test was a strong and independent predictor of lower risk of all-cause and CVD mortality in both men and women.[80] In a meta-analysis of 33 studies with a combined sample size over 100,000 participants (with no known CHD and major risk factors at baseline), Kodama *et al.* demonstrated that every 1-MET increase in CRF was associated with 13% and 15% reduction in all-cause and CVD mortality, respectively.[81] Higher levels of CRF have also been linked to lower risk of fatal and non-fatal stroke and death from cancer, independent of obesity measures.[82,83] In the Cooper Center Longitudinal Study (CCLS) with over 60,000 participants with no known CVD at baseline, the addition of a single measure of CRF to other traditional CVD risk factors resulted in a significant improvement in both 10-year and 25-year risk classification for CVD mortality.[84] Maintenance and improvement of CRF levels carry significance from a prognostic standpoint.[85] In the Aerobics Centers Longitudinal Study (ACLS), individuals who maintained or improved their CRF over a period of 6.3 years were found to have a lower risk of all-cause and CVD mortality compared to those with a loss in their CRF.[86] Moreover, the association between changes in weight and risk of all-cause, and CVD mortality became insignificant after adjusting for potential confounders and alterations in CRF.

Several reports have suggested that the greatest benefits of risk reduction are achieved with transitioning from a sedentary lifestyle to modest amounts of exercise or from the lowest levels of CRF to the next highest CRF.[67] In a large prospective observational cohort study (>55,000 participants without documented CVD, 15 years of follow-up), Lee *et al.* found marked reduction in the risk of death from all causes and CVD with leisure-time running even at low doses (5 to 10 minutes/day) and speed (<6 miles/h).[87]

HF: Recent studies have demonstrated a dose-dependent inverse association between levels of leisure-time PA and HF risk.[34,64] Reports from CCLS showed that high levels of objectively measured CRF in mid-life predicts a significantly lower risk of HF hospitalizations and mortality later in old age.[88,89] Furthermore, this protective effect of CRF on HF risk is modifiable and independent of antecedent

burden of traditional cardiovascular risk factors[90] and likely related to favorable effects of CRF on the cardiac structure and function.[77] Similarly, a prospective cohort study from Finland (n=1,853 men without HF at baseline, mean follow-up of 20.3 years) reported 21% reduction in risk of multivariable adjusted risk of new-onset HF with every 1-MET increment in the baseline CRF.[91] Moreover, several CPX parameters such as VO_2max and the slope of minute ventilation/carbon dioxide production (a measure of ventilatory efficiency) independently predict outcomes in patients with established HF.[19,92] Adjusted VO_2max of <14 mL/kg.min has long been recognized as a relative indication for heart transplantation in patients with advanced HF.[93]

CHD: Gander *et al.*, using data from the ACLS, demonstrated that CRF is an independent determinant for future CHD risk even after controlling for a well-established CHD risk calculator, such as the Framingham Risk Score.[94] The investigators found that CHD incidence decreases by 20% with each 1-unit increase in the maximally achieved MET. In some but not all studies, low baseline CRF levels were found to predict incident coronary artery calcification (CAC), a finding of subclinical atherosclerosis.[76,95] Moreover, low CRF has been independently associated with CVD events, even after adjustment for CAC detected by computed tomography.[96]

AF: Increasing PA and higher CRF have been shown to reduce the incidence of AF. However, the relationship between PA and AF appear to follow a U-shaped pattern with a possible increase in the AF rate with the highest levels of PA.[97] Mozaffarian *et al.,* in a population-based prospective study of 5,446 older adults, demonstrated a graded inverse relationship between leisure-time PA and incident AF.[98] Another population-based study which included >36,000 AF-free Swedish women at baseline found that moderate amount of exercise (≥4h/week) compared to minimal to no exercise (<1h/week) was linked to a 15% lower risk of new-onset AF after 12 years of follow-up.[99] A retrospective cohort study of nearly 70,000 adults who underwent physician-referred treadmill testing demonstrated that every 1-MET increment in the CRF at baseline was associated with a 7% lower risk of AF during a median follow-up of

5.4 years.[100] In this study, the protective effect of higher CRF was more pronounced in obese and older individuals. The inverse relationship between higher CRF and incident AF was also confirmed in other studies using VO_2max to estimate CRF.[101]

CRF also significantly affects the risk of arrhythmia recurrence in patients with AF. In a prospective study of 1,415 AF patients enrolled in a tailored exercise program, Pathak *et al.* observed that every 1-MET increase in baseline CRF reduced the risk of arrhythmia recurrence by 20%.[102] The degree of CRF gain from the baseline fitness during exercise program was a predictor of decreased risk of arrhythmia recurrence. Moreover, the protective effect of CRF gain was augmented when participants achieved ≥10% weight loss (**Figure 1**).

Contribution of Veterans Affairs (VA) Cohort Studies

The majority of epidemiologic studies on CRF from several institutions and different parts of the US and the world include middle-aged and relatively healthy cohorts. In addition, many of these cohorts lack data on comorbidities and medications of the participants. In this regard, several relatively large prospective epidemiologic studies from the Washington, DC and Palo Alto, CA VA Medical Centers have filled this void. These studies mostly consist of middle-aged or older veterans referred for an exercise tolerance test for clinical reasons. The equal access to care provided by the Veterans Health Administration independent of a patient's financial status, a unique feature of this cohort, permits epidemiological evaluations while minimizing the influence of disparities in medical care. Moreover, the existence of well-established electronic health records within the VA Healthcare System enables detailed observation of prior history, comorbidities, medications, and alterations in health status. These attributes, coupled with the ability to consider conditions with high short-term mortality rates such as muscle-wasting disease, minimize the possibility of reverse causality, and support the validity of the CRF and mortality relationship for all ages and the age-specific exercise thresholds for risk assessment.

In general, these studies have strongly confirmed the preventive and therapeutic aspects of CRF. For example, they have shown that the incidence of HTN is inversely related to CRF and fit veterans have markedly reduced rate of progression from pre-HTN to HTN.[103] Similarly, chronic kidney disease (CKD) incidence was 22% lower for every 1-MET increase in exercise capacity and this translated into 40% to 60% less risk of CKD in moderate-fit (peak METs achieved 6.5) and high-fit (peak METs achieved 7.7) individuals compared to the least-fit (peak MET level achieved 4.8).[104] The incidence of AF was also significantly and progressively attenuated by 20% to 63% for veterans with an exercise capacity ≥7.0 METs.[105] Finally, in over 20,500 veterans free from CVD at the time of the exercise testing, the risk of having a major CVD event was 16% lower for each 1-MET increase in exercise capacity and was 30% to 68% lower for those with an exercise capacity ≥6 METs (**Figure 2**).[106] In a separate study, the incidence of HF in a group of more than 20,000 veterans free of HF at baseline, adding CRF status to traditional risk factors resulted in reclassification of HF risk in 37% of the participants.[107]

VA-based studies have also confirmed the independent, inverse and graded association between CRF and CVD[79,106,107] and all-cause mortality in both blacks and whites[108,109] and those with specific comorbidities such as HTN,[110,111] pre-HTN,[112] T2DM,[109,113] dyslipidemia,[114,115] and obesity.[116] They have also established an age-specific fitness classification and age-specific CRF/MET threshold that can be used to classify CRF categories and risk association more precisely and that are unique to veterans.[117] In hypertensive veterans, mortality risk was cut by approximately 50% to 70% for those with a peak MET level >7 METs regardless of 2 or more additional risk factors.[110] In veterans with T2DM, the exercise capacity-mortality risk association was inverse, independent, and graded.[109,113] When considering BMI, the inverse and graded association was evident in all BMI categories. But the impact of CRF was more potent in those with a BMI ≥25 kg/m2.

The interactive effects of statins and CRF were also assessed in over 10,000 dyslipidemic veterans. Increased CRF was inversely and independently associated with mortality risk in veterans

treated (n=5,033) and not treated (n=5,010) with a statin. Interestingly, survival benefits of CRF were similar to those observed with statin therapy. When increased CRF and statin therapy were combined, survival benefits were additive.[115] Similarly, the mortality risk reduction associated with moderate increases in CRF was similar to that achieved by statin therapy in veterans with dyslipidemia and HTN.[114] In diabetic veterans, statin therapy also resulted in improved survival, which was further enhanced when increased CRF fitness and statin therapy were combined.[118]

Interaction of CRF and Obesity

A complex interplay between fitness and fatness contribute to an individual's CVD and mortality risk profile. Several key features characterize this interaction. 1) High levels of CRF largely negate the adverse effects of excess adiposity, which is also referred as the 'fat and fit' phenomenon.[8,85] 2) Habitual physical inactivity is a significant contributor to the increased CVD risk in obese individuals since sedentary lifestyle is more prevalent in obese than leaner people.[13] 3) Exercise training (ET) and increased PA, with the goal of maintaining or improving CRF, are efficient and safe strategies for primary and secondary prevention of CVD in all weight groups.

CVD Risk Factors: Physically inactive obese individuals, compared to their physically active counterparts, are more likely to have insulin resistance and higher levels of adiposity-related inflammation. Lee *et al.* examined the relative and combined impact of changes in CRF and fatness on major CVD risk factors (HTN, MS, dyslipidemia) in the ACLS participants (n=3148, 6-year follow-up).[119] The investigators demonstrated an inverse association between CRF and the incidence of each outcome. Importantly, improving fitness attenuated, but not eliminated, the increased risks related to weight gain. Moreover, weight loss somewhat mitigated the increased risks associated with loss of CRF.[120,121]

CVD and Mortality: Several large-scale studies have confirmed the marked contribution of physical inactivity to the CVD risk in obese individuals. In the Nurse's Health Study, obese and inactive

women were found to have 39% higher risk for CHD events and 62% greater risk of CVD mortality compared to obese women who were active.[122,123] The adverse effects of obesity on coronary health were moderately attenuated, but not eliminated, by PA. And being lean did not counteract the CHD risk associated with physical inactivity.[123] Physical inactivity usually shows a stronger association with abdominal obesity than BMI-based general obesity.[124] However, the excess risk associated with physical inactivity appears to be more pronounced with general obesity than abdominal obesity.[124] This differential impact was attributed to the possibility of more co-linearity between physical inactivity and abdominal obesity.[13]

Barry *et al.,* in a meta-analysis of 10 prospective studies, examined the mutual influence of CRF and BMI on all-cause mortality.[125] The investigators found that compared to fit individuals; unfit individuals had two times higher risk of death, regardless of BMI. Moreover, the mortality risk was similar for normal weight-fit, overweight-fit, and obese-fit individuals. Farrell *et al.,* using the data from the CCLS (n=36,836 men), examined the additive effect of different adiposity components [BMI, WC, percent body fat([%BF)] and their interaction with CRF in the mortality risk.[126] The authors observed 5%, 37%, and 87% higher risk of death in individuals who were exposed to 1, 2, or 3 adiposity components, respectively, compared to those who did not have any exposure. And being fit was a predictor of improved survival within each of these four adiposity exposure groups. Moreover, adjustment of the results for BMI did not significantly alter the inverse association between exercise capacity and mortality risk.

Kenchaiah *et al.* examined the joint contribution of BMI and PA for the risk of incident HF in participants of the Physicians Health Study, a prospective cohort study of 21,000 men.[127] The investigators observed that physical inactivity augmented the excess HF risk related to obesity. In fact, compared to the reference group (lean and active individuals), the risk of HF was higher by 49% in the overweight and active, 78% in the overweight and inactive, 168% in the obese and active, and 293% in

the obese and inactive groups. More recently, Pandey *et al*. examined the inter-relationship between BMI and objectively measured CRF in mid-life among participants of the CCLS (n=19,485) and demonstrated that mid-life CRF accounted for a significant proportion of BMI associated risk of HF in otherwise healthy adults. Furthermore, CRF change but not BMI change with aging was significantly associated with downstream risk of HF. Taken together, these findings highlight the important contribution of CRF towards obesity-related risk of HF.[128]

Interaction of CRF and the Obesity Paradox

Several studies have suggested that CRF significantly alters the prognostic implications of fatness in patients with CHD and HF.[8,129] Key features of this interaction can be summarized as follows. 1) Higher CRF is associated with improved outcomes in all weight groups, and the prognostic benefits of overweight/obesity disappear in fit patients. 2) The obesity paradox is usually limited to CHD and HF patients who are unfit. These findings highlight the more prominent role of CRF, compared to BMI, in determining the prognosis of patients with CVD.[19]

CHD: Goel *et al.* examined the collective impact of CRF and adiposity parameters in 855 CHD patients referred for cardiac rehabilitation at the Mayo Clinic.[47] Their analysis revealed a nearly three-fold increased risk of mortality in subjects with low-CRF, even after adjustment for BMI and waist-to-hip ratio. The investigators observed an inverse association between BMI and risk of death only in subjects with low CRF but did not note a significant difference in mortality risk among fit individuals across different adiposity groups. McAuley *et al.* investigated the interaction of CRF and the obesity paradox in nearly 10,000 male ACLS participants with known or suspected CHD.[130] The study demonstrated after 13 years of follow-up that only those participants in the bottom tertile of age- and sex-related CRF had an obesity paradox which was present with BMI, WC, and %BF. However, among participants with high fitness (tertiles 2 and 3), no significant differences were observed in mortality risk across BMI, WC, %BF categories. Kokkinos *et al.* found in male veterans who were referred for exercise treadmill testing that

low BMI was associated with high mortality in only low-fit and moderate-fit subgroups, but not in those with high fitness.[116] The authors concluded that CRF significantly affects the paradoxical BMI-mortality risk association and that lower BMI levels do not increase the risk for premature death as long as they are associated with high fitness. Moreover, their findings suggest that the paradoxically higher mortality risk observed with lower body weight as represented by lower BMI is likely the result of an unhealthy reduction in body weight and, perhaps most importantly, considerable loss of lean body mass.

HF: Several studies have confirmed the substantial influence of CRF on the prognostic value of obesity in patients with HF. Our research in a cohort of 2,066 patients with chronic HFrEF demonstrated that an obesity paradox was present only in HF patients with poor CRF (VO_2max<14 ml/kg.min).[46] The worse outcomes were observed in leaner HF patients with poor CRF. Contrarily, individuals with high CRF had a better prognosis and were not affected by an obesity paradox (**Figure 3**). Clark *et al.* observed similar results in 1,675 HFrEF patients who underwent CPX at a single university center.[131] Piepoli *et al.* reported a strong obesity paradox in 4,623 Italian patients with HFrEF referred for CPX.[132] However, the prognostic differences between the BMI classes disappeared after inclusion of VO_2max as a covariate; suggesting that the prognostic contribution of VO_2max overwhelms that of BMI. Prognostic influence of CRF in HF patients with severe obesity (BMI≥40 kg/m^2) is still not well known since these patients were either underrepresented or entirely excluded in studies.

Zafrir *et al.* evaluated the collective impact of BMI and 6-minute walk distance (6MWD) in 543 advanced HF patients.[133] Consistent with other reports, the study showed a strong obesity paradox in the entire study population during 40 months follow-up. However, the obesity paradox disappeared in the high physical capability group, when study subjects were categorized based on 6MWD. As a novel approach, the authors also calculated the multiplication product of BMI and 6MWD (BMI*6MWD [kilogram/meter]). Compared to the lowest quartile of BMI*6MWD product, patients in the higher

quartiles had a declining pattern of mortality (31% lower in 2nd quartile, 36% lower in 3rd quartile, 60% lower in 4th quartile), after adjustment for other covariates (**Figure 4**).

Mechanisms of CRF-Mediated Alteration in Risk and Prognosis of CVD in Obesity

Mechanisms of CRF-mediated alteration of CVD risk and prognosis in individuals with excess adiposity are still poorly understood. Several factors appear to play a role in the protective effects of high CRF and PA in overweight/obese individuals with known or at risk for CVD. As mentioned above, PA and higher CRF lower blood pressure and improve cardiometabolic risk profile which can explain, to some extent, the protective effects of high CRF in obesity.[69–72] However, studies have repeatedly demonstrated that high CRF remains as the strongest predictor of improved outcomes in all weight groups even after adjustment for other major CVD risk factors, suggesting the potential contribution of several other mechanisms for CRF-related favorable results.

Body Composition: Body fat distribution, particularly the distribution of excess visceral fat depots, is a strong predictor of CVD, independent of total adiposity.[134] Exercise training can substantially influence the body fat distribution.[135] Fit individuals tend to have less amount of visceral fat depots compared to unfit individuals with same BMI.[136] Johnson *et al.* reported that aerobic ET for 4 weeks resulted in a significant reduction in hepatic lipid concentration even in the absence of any changes in the body weight or WC.[137] In a meta-analysis of 15 small size studies (n=852), ET markedly reduced the volume of visceral adipose tissues at varying degrees depending on gender, and the type and intensity of training.[138]

ET and PA strongly correlate with increased muscle mass and strength which are some of the hallmark findings of high CRF.[139,140] Increased muscle mass and strength predicts improved outcomes in patients with CVD. For instance, in a retrospective cohort of 771 Japanese patients with acute HF, Kamiya *et al.* found a strong, independent association between muscle mass (assessed with mid-upper

arm circumference) and improved survival.[44] Moreover, muscle mass was found to have a complementary prognostic value in HF patients when added to BMI (**Figure 5**). In contrast, sarcopenia and decreased amount of appendicular lean mass are considered as significant predictors of poor outcomes in the general population and CVD patients, regardless of BMI.[19] Sarcopenia is a common condition in older adults and those with chronic diseases. [141] In the general population, sarcopenic obesity was associated with a 24% higher risk of mortality compared to non-sarcopenic obesity.[142] Sarcopenia has been linked to impaired exercise capacity, muscle strength and quality of life in patients with HFpEF.[141] We still need further research to identify the potential mechanisms underlying the link between muscle mass and CVD prognosis.

Insulin Resistance: Insulin resistance is implicated in the pathogenesis of several CVD risk factors and diseases such as T2DM, HTN, HF, etc. PA and ET substantially alter obesity-related insulin resistance. In the Multi-ethnic Study of Atherosclerosis, PA was found to have a strong inverse correlation with insulin resistance.[121]

Inflammation: Low-grade chronic inflammation due to excess adiposity is a major contributor to the CV risk profile and disease prognosis.[85] And obesity-related inflammation, assessed by the levels of cytokines and adipokines, has been shown to decrease in response to PA.[120] Moreover, increased CRF was associated with lower levels of white blood cell counts in patients with MS, suggesting an attenuated inflammatory response in fit individuals.[143]

Hematologic: Excess adiposity has been linked to increased platelet reactivity, which potentially contributes to the increased CV event risk in overweight/obese individuals.[144] Keating *et al.,* in a small prospective randomized study of overweight subjects with CHD, demonstrated that four months of ET and weight loss resulted in a significant decline in platelet reactivity.[145]

Endothelial Dysfunction: Obesity-related endothelial dysfunction plays a role in the pathogenesis of CVD. There exists substantial evidence from animal studies regarding the beneficial impact of exercise on obesity-related endothelial dysfunction.[146] A small study (n=42) by La Favor *et al.* recently demonstrated that eight weeks of exercise in obese individuals reduced endothelial dysfunction to levels similar to that of lean individuals.[147]

Oxidative Stress: Oxidative stress is involved in the pathogenesis of insulin resistance, type-2 DM, and CVD. Bianchi *et al.* found that a structured program of nutrition and ET for 12 weeks, when accompanied by weight loss and improved CRF, resulted in a marked decline of reactive oxygen species in sedentary individuals with obesity.[148]

Conclusions

Overweight and obesity are well-established risk factors for most CVDs, including CHD, HF, and AF. Despite the strong link between excess adiposity and risk of CVD, overweight and mildly obese patients with CVD usually have a better prognosis than their leaner counterparts. This obesity paradox is now a well-established phenomenon across different types of CVDs, and it occurs regardless of age and ethnicity of patients and severity of CVD.

Physical inactivity and low CRF are major risk factors for CVD. Numerous studies have confirmed that being normal-weight is not synonymous with being healthy. Because unfit normal-weight individuals usually have a higher risk of all-cause and CVD mortality than normal-weight fit individuals and in some cases even compared to obese but fit people.[149] Despite its strong prognostic role in CVD and mortality risk, CRF is often underutilized as a CVD risk factor, because of difficulties in measuring CRF and lack of widely accepted definition and staging of CRF.[85] Indeed, CRF significantly modifies the relationship between adiposity and mortality in the general population and individuals with known CVD. Increased PA and higher CRF are significant predictors of improved CVD outcomes in all BMI groups.

Several studies have shown that prognostic implications of obesity disappear in fit CVD patients and the obesity paradox mainly affects those with low CRF.

Regular PA and structured ET constitute a fundamental aspect of non-pharmacological management of patients with or at risk for CVD. From a primary prevention standpoint getting patients out of their sedentary behaviors can provide the most benefit regarding prevention of the onset of CVDs.[13] There also exists robust evidence for the efficacy of ET as a therapy for secondary prevention in patients with established CVD. A meta-epidemiological study by Naci *et al.* which included 305 studies with nearly 340,000 participants demonstrated that ET interventions were at least as effective as many drug therapies for secondary prevention of CHD, HF and DM.[150] ET in patients with CVD should ideally include both aerobic-type exercise to increase overall CRF and skeletal muscle training, and resistance ET to maintain lean muscle mass and improve muscular fitness.[19,45]

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Figure/Table Legends

Table:

Title: Mechanism of the Obesity Paradox in CVD

Figure 1:

Title: Outcomes of AF Freedom According to CRF Gain and Weight Loss

Caption: Kaplan-Meier curve for total AF-free survival (multiple ablation procedures ± drugs) according to weight and CRF trends in 1,415 patients with AF. AF, atrial fibrillation; MET, metabolic equivalent; WL, weight loss. Reprint from Pathak *et al*. with permission from the publisher.[102]

Figure 2:

Title: Adjusted Risk for Major Adverse CV Events According to Fitness Categories in US Veterans

Caption: The bar graph demonstrates the adjusted hazard ratios for major adverse CV events (during 11 years of follow-up) according to fitness categories in comparison to the reference group (least fit subjects). CRF categories were determined based on age-specific predicted CRF thresholds. The figure was drawn based on data from Kokkinos *et al.*.[106]

Figure 3:

Caption: Kaplan-Meier analysis according to BMI categories in the low-CRF group (oxygen consumption <14 mL O_2/kg.min) **(A)** and the high-CRF group (oxygen consumption ≥14 mL O_2/kg.min) **(B)**. BMI, body mass index. Reprint from Lavie *et al*. with permission from the publisher.[46]

Figure 4:

Title: Joint Impact of BMI*SMWD Product on Mortality

Caption: Adjusted hazard ratio for all-cause mortality according to the product of BMI and physical capacity assessed by the SMWD test. SMWD, six-minute walk distance. The image was drawn based on data from Zafrir *et al*.[133]

Figure 5:

Title: Combined Impact of BMI and Muscle Mass in Heart Failure

Caption: Kaplan-Meier curve for survival according to combined BMI and MUAC categories in patients with HF. BMI, body mass index; MUAC, mid-upper arm circumference. Reprint from Kamiya *et al*. with permission from the publisher.[44]

Table: Mechanisms of the Obesity Paradox in CVD
Increased muscle mass and strength
Implications related to CRF
Higher energy reserves
Better nutritional status
Earlier presentation of CVD
Compression of morbidity in lean individuals
Reverse epidemiology of detrimental effects of cachexia and frailty
Better tolerability of CVD medications
Genetic factors
Changes in cytokines and neuroendocrine profiles
Immune modulation
Mitochondrial function augmentation

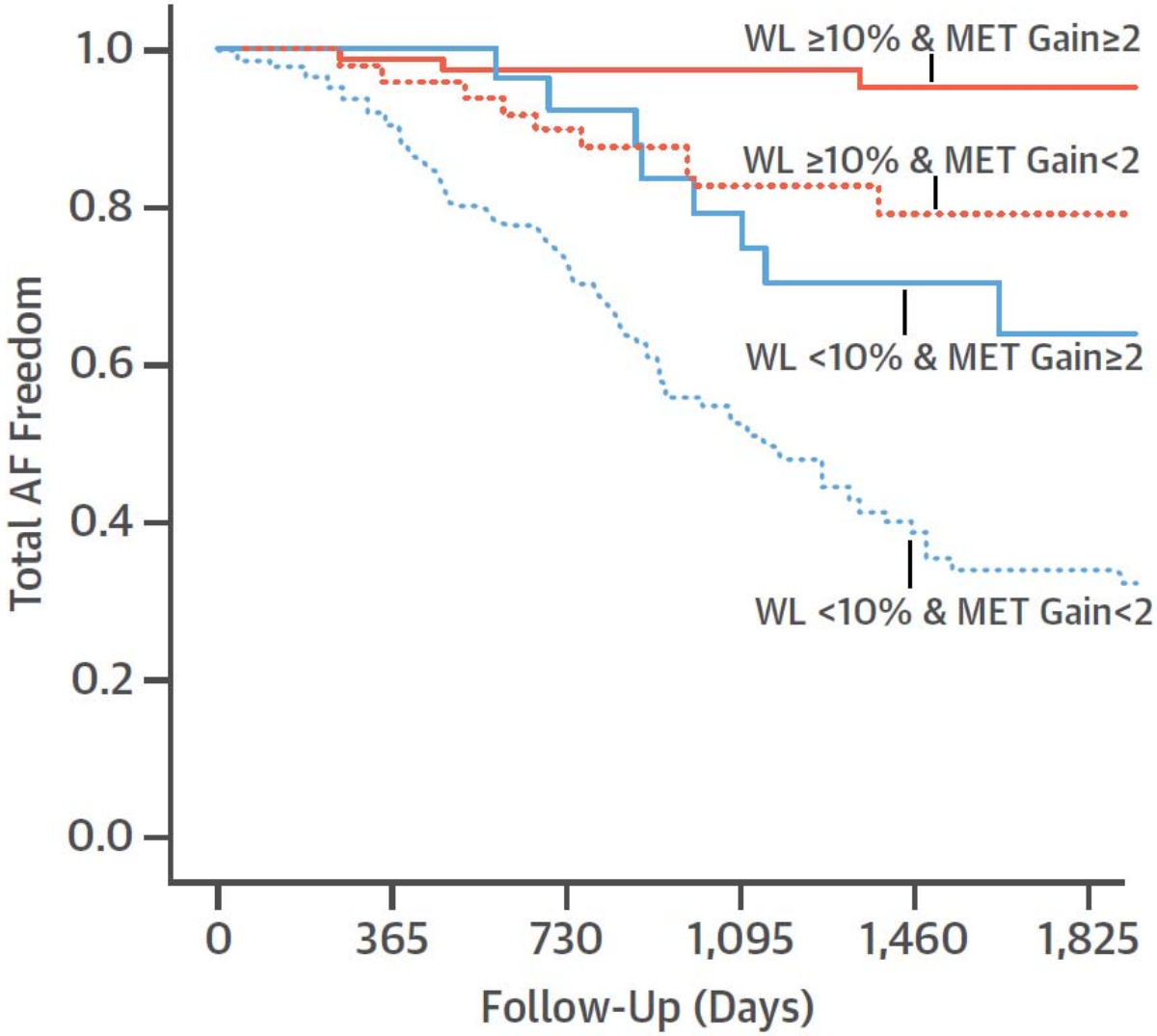

Figure 1

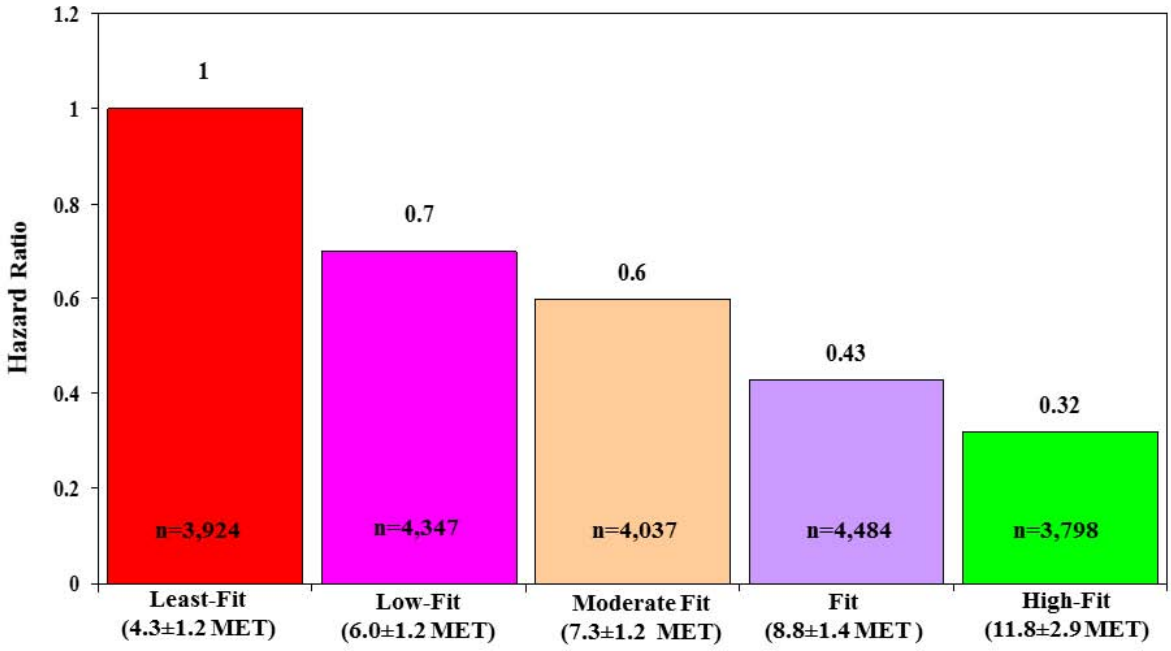

Figure 2

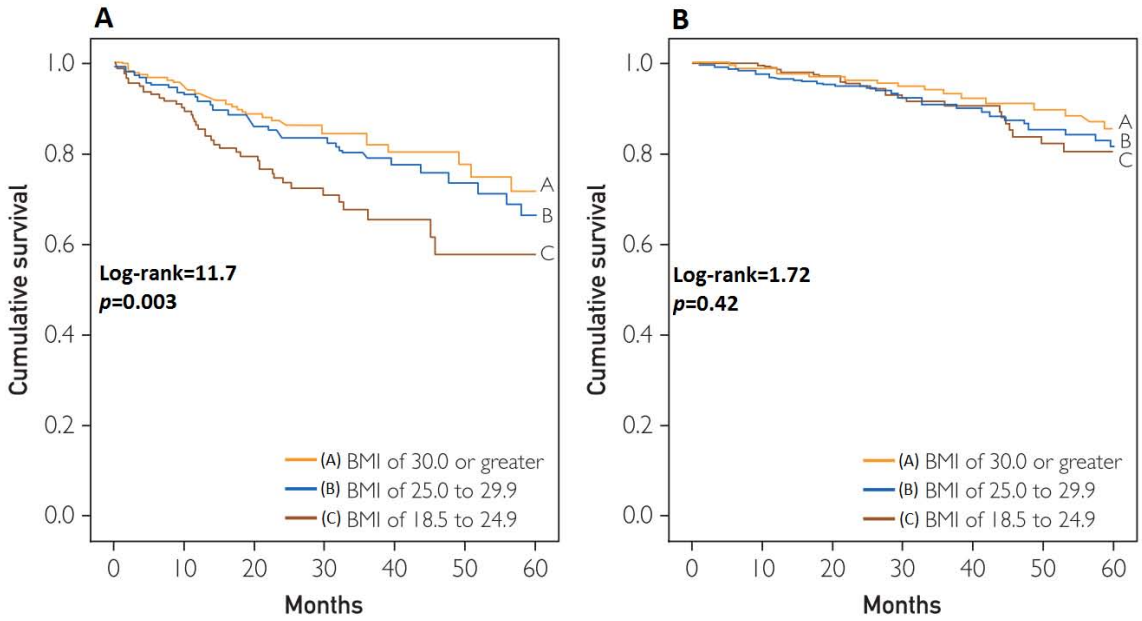

Figure 3

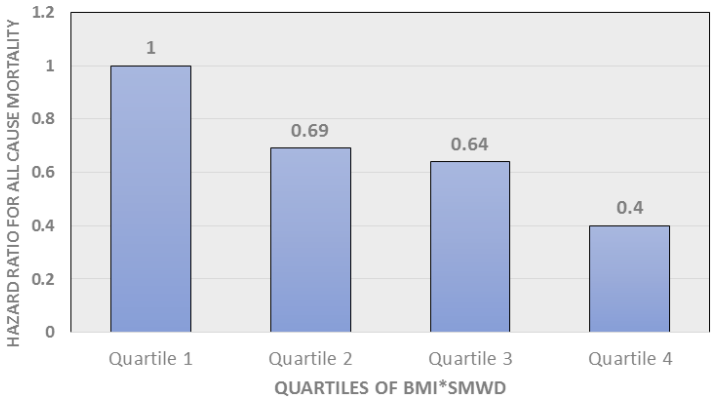

Figure 4

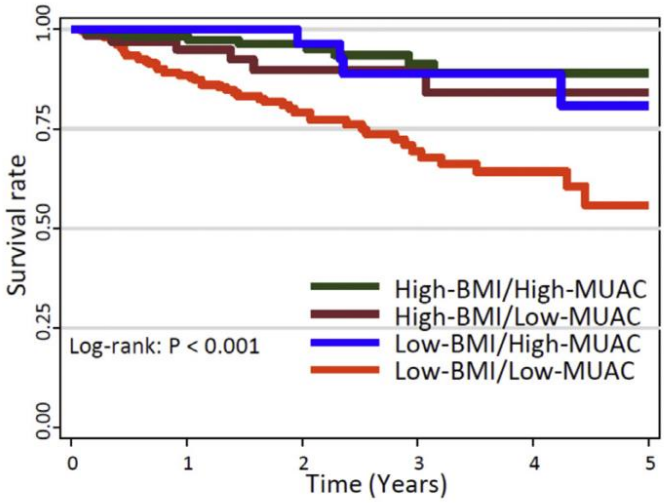

Figure 5