ADDITION OF CARDIORESPIRATORY FITNESS WITHIN AN OBESITY RISK CLASSIFICATION MODEL IDENTIFIES MEN AT INCREASED RISK OF ALL-CAUSE MORTALITY

By

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Abstract

Health organizations recommend that body mass index (BMI) and waist circumference (WC) be measured together to estimate a person's obesity-related health risk. When BMI and WC are high, a person's risk of death and disease increases. Cardiorespiratory fitness (CRF) is a measure of a person's ability to perform aerobic exercise. Despite the fact that CRF reduces health risk, even in people with high BMI or WC, measurement of CRF is not currently recommended alongside BMI and WC in healthcare settings. We sought to determine whether CRF will improve our ability to predict risk of death when both BMI and WC are already considered.

We analyzed data from 31 267 adult male participants of the Aerobics Center Longitudinal Study (ACLS), a prospective study established in 1970 to examine associations between lifestyle factors and health risk. Baseline characteristics were recorded during medical examinations taking place at the Cooper Clinic in Dallas, Texas between 1974 and 2002. Participant follow-up continued until either death or December 31st, 2003. Participants were first categorized by BMI according to whether they were normal BMI, overweight, or obese. They were then grouped according to whether their WC was high or normal based on their BMI category. CRF was assessed by a treadmill exercise test performed to voluntary exhaustion. Participants with the lowest 20% times on treadmill were classified as unfit, while the remaining 80% were classified as fit.

Our primary results are that, for most combinations of BMI and WC, unfit men were at significantly higher risk of mortality compared with fit men within the same BMI and WC group. Higher mortality risk due to low fitness was observed in males with normal BMI regardless of WC, in males who were overweight with normal WC, and in males who were obese with high WC.

Our observations add support to the idea that CRF should be measured in healthcare settings along with BMI and WC to help identify and manage health risk associated with overweight and obesity.

Statement of Co-Authorship

T. Alexander Ricketts and Robert Ross were responsible for conception and design of the research undertaken.

Steven Blair was responsible for the acquisition of the data.

Alexander Ricketts and Robert Ross were responsible for analysis and interpretation of the data.

Alexander Ricketts was responsible for drafting of the manuscript.

Robert Ross, Xuemei Sui, Carl J. Lavie, and Steven Blair were responsible for critical revision of the manuscript for important intellectual content.

Thesis Contributions

This thesis is a secondary analysis of the Aerobics Center Longitudinal Study, which was designed to prospectively investigate the associations between lifestyle factors and cardiovascular risk factors, morbidity, and mortality. Due to the nature of the study, the data was collected by the Cooper Clinic physicians and staff beginning in the early 1970s.

In January of 2015, I travelled to the University of South Carolina to meet with Dr. Steven Blair and Dr. Xuemei Sui, both of whom have worked extensively with the ACLS cohort. I was able to learn much about the ACLS cohort from Dr. Blair, as well as the field of physical fitness epidemiology in general. Dr. Sui guided me through learning the statistical methods I would use in the current report, which were novel to me at the time. After learning as much as I could, I returned to Kingston and performed the statistical analysis on my own, which is the analysis presented in this document.

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List of Abbreviations

BMI	Body mass index
WC	Waist circumference
CRF	Cardiorespiratory fitness
ACLS	Aerobics Center Longitudinal Study
CVD	Cardiovascular disease
VAT	Visceral adipose tissue
CHD	Coronary heart disease
VO_{2Max}	Maximal oxygen uptake
METs	Metabolic equivalents

Chapter 1. Introduction.

Obesity is a well-recognized condition of excess body fat accumulation, which has the potential to reach a point of detriment to health [1]. Obesity is usually a result of chronic positive energy balance, where more calories are consumed than are expended [2]. Obesity, typically measured by body mass index (BMI), increases risk of all-cause [3, 4] and cardiovascular disease (CVD) [4] mortality, as well as risk of type 2 diabetes and CVD [5]. Worldwide, the prevalence of obesity has increased drastically over the last several decades [6], emphasizing the importance of research devoted to the identification and management of obesity-related health risk.

The distribution of obesity has been recognized as an important determinant of health risk. Individuals with an android (upper body) form of obesity are characterized by increased fat deposition in the abdomen, and are at greater risk of mortality, CVD, and type 2 diabetes than individuals who store their fat in the lower body [7-11]. This difference in risk appears to be explained by accumulation of visceral (intra-abdominal) adipose tissue (VAT), which is associated with increased levels of cardiometabolic risk factors, inflammation, and insulin resistance [12]. To estimate abdominal obesity in healthcare settings, waist circumference (WC) is recommended as a simple measurement that correlates with directly measured visceral adipose tissue [13].

Health organizations worldwide recommend that BMI and WC be measured in combination to estimate obesity related health risk [14]. This recommendation is supported by evidence demonstrating the independent associations of BMI and WC with all-cause mortality [15, 16]. Including WC alongside BMI has been shown to improve prediction of cardiometabolic risk [17, 18], CVD, and diabetes [19]. Furthermore, the combination of BMI and WC improves prediction of visceral adipose tissue accumulation [18], which itself is associated with increased risk of all-cause mortality [20, 21].

A single WC threshold of 102 cm is currently recommended for the identification of adult Caucasian males at elevated health risk within each BMI category [14]. This threshold was originally intended to replace a BMI of >30 kg/m^2 as a means of identifying white male adults as obese [22], because WC was decided to be more easily measurable and interpretable by the average person. Use of the same 102 cm threshold for each BMI category classifies very few individuals with normal or overweight BMI, and almost all individuals who are obese, with high WC [17].

In response to this issue, Ardern and colleagues proposed the use of WC values specific to each BMI category in order to better identify individuals at increased risk of coronary heart disease (CHD) mortality [23]. These BMI-specific WC thresholds were developed and cross-validated using large representative samples, and more evenly distribute individuals between normal and high WC categories within BMI groups.

Obesity risk classification models do not currently recommend the measurement of cardiorespiratory fitness (CRF) to estimate obesity-related health risk. CRF has been firmly established as a strong predictor of all-cause and cardiovascular disease mortality [24, 25], independent of commonly measured cardiometabolic risk factors [26], BMI [27, 28], and WC [29].

A recent report by Farrell and colleagues showed that having elevated BMI, WC, and percent body fat together predicted greater all-cause mortality risk, and that being fit was protective in males with elevated levels of those measures [30]. The authors were limited by few participants in some categories, and were unable to analyze the effect of CRF across specific combinations of BMI, WC and percent body fat.

It remains unclear whether addition of CRF to an obesity risk classification model will improve our ability to predict risk of all-cause mortality. While CRF clearly adds to risk estimates when considered alongside BMI and WC alone, it remains to be established whether CRF is protective beyond the

combination of BMI and WC. The goal of this research is therefore to determine whether the addition of CRF improves prediction of all-cause mortality across a range of BMI and WC groups. If CRF does improve mortality risk prediction in a combined BMI and WC model, healthcare practitioners may be provided with another measure of identifying and managing obesity-related health risk in clinical settings.

Chapter 2. Literature Review.

2.1 The Obesity Pandemic

Obesity is a well-recognized state of excess accumulation of body fat, often to the point where health may be impaired [1]. The etiology of obesity usually involves a prolonged state of chronic positive energy balance consequent to decreased energy expenditure relative to energy intake, resulting in hypertrophy and hyperplasia of adipose tissue. The exact causes of the obesity pandemic continue to be debated, but it is generally agreed that the etiology of obesity is multifactorial [31]. The most important factors contributing to the obesity pandemic are an environment which has reduced energy expenditure and physical activity demands in combination with a relative inability to adjust energy intake to match energy expenditure in that same environment which promotes an overabundance of inexpensive, calorically dense food [2]. The important role of physical activity in obesity management has been demonstrated in an analysis by Church and colleagues. They report a significant decrease in occupational physical activity over the last several decades, and that this decrease predicted changes in obesity levels in a nationally representative sample [32].

Worldwide, the prevalence of overweight and obesity has increased across all regions, with 2.1 billion individuals classified as overweight or obese in 2011 [6]. Prevalence of overweight and obesity has increased by 27.5% for adults, and 47.1% for children over the last 33 years. Although higher in developed countries, prevalence has increased in both developed and developing countries. While some national data has indicated a slowing of obesity prevalence in developed countries over the last decade [33], current global trends indicate further increase [6].

Since 1985, the number of individuals with a body mass index of ≥30.0 kg/m^2 in Canada has tripled to 18% of the total population [34]. Alarmingly, within the last decade the number of overweight and obese individuals overtook the number of normal weight individuals within the Canadian

population. These numbers are projected to increase to 34.2% of the population classified as overweight and 21.2% classified as obese by the year 2019 [34].

While there is some indication of the rising obesity trend slowing in the United States [33], the prevalence of obesity in the United States remains enormous. 35.5% of American males and 35.8% of American females are classified as obese [33]. Of the 671 million individuals with obesity worldwide, the United States accounts for approximately 13% [6]. This should be contrasted against the countries with the next greatest obesity prevalence, China and India, who together account for 15% of people with obesity worldwide.

It should be noted that these prevalence values are most likely conservative estimates of the true prevalence of obesity. Most large-scale epidemiological studies use self-reported BMI. Self-reported BMI is limited by the fact that participants usually under-report weight and over-report height [35]. For example, while the paper by Twells et al reports an obesity prevalence of 18% [34], recent data from the Canadian Health Measures Survey indicates that this prevalence is actually 26% based on measured BMI [36].

2.2 Obesity, Morbidity, and Mortality

Epidemiological evidence supports the independent association of obesity with health outcomes. Obesity increases risk of all-cause mortality, CVD mortality and cancer mortality, as well as risk of morbidities such as incident CVD and diabetes [3-5, 37]. A meta-analysis of 26 studies found that obesity, classified as a BMI ≥30 kg/m^2, was associated with a 26% greater risk of all-cause mortality compared with normal BMI (18.5-24.9 kg/m^2) [4]. A later analysis from the Prospective Studies Collaboration found a similar mortality-obesity relationship in 57 studies, with 29% increased all-cause mortality risk for every 5 kg/m^2 above a BMI of 22.5-25 kg/m^2 [37]. More recently, Flegal and colleagues, in a meta-analysis of 2.88 million participants from 97 studies found that overall obesity is associated

with 18% higher all-cause mortality risk. However, class 1 obesity was not at increased risk of all-cause mortality, while class 2 and 3 obesity were together associated with 29% greater all-cause mortality risk [3].

Much of the excess mortality associated with obesity is due to mortality from CVD [38, 39]. In the meta-analysis of 26 studies, obesity was associated with a 52% and 45% higher risk of CVD-mortality in females and males, respectively [4]. When considering CHD mortality, the risks relative to the normal BMI group are 1.62 for females and 1.51 for males. Results from the Prospective Studies Collaboration involving 57 studies show a 39% increased risk of mortality from both ischaemic heart disease and stroke for every 5 kg/m^2 increase in BMI above a BMI of 25, after adjustment for study, sex, age, and baseline smoking status [37].

Large meta-analyses show that the relationship of obesity with cancer mortality is slightly weaker than the association with CVD-mortality. For example, the Diverse Studies Collaboration indicated a 10% increased risk of cancer-mortality in females who are obese, but a non-significant increase in cancer mortality risk in males who are obese [4]. The Prospective Studies Collaboration has shown a 12% increased risk of cancer for every 5 kg/m^2 increase in BMI above 25 kg/m^2 [37].

Obesity has also been associated with morbidities such as CVD, diabetes, and cancer incidence [5]. A meta-analysis of 89 studies found that obesity was associated with an increased relative risk of diabetes of 6.7 for males and 12.4 for females compared to a normal BMI. The same meta-analysis found increased risks for hypertension, coronary artery disease, congestive heart failure, and stroke. Furthermore, the cancers most influenced by obesity appeared to be colorectal, endometrial, kidney, and pancreas.

2.2.1 The Importance of Obesity Distribution

The seminal work of Jean Vague was the first to recognize the importance of distribution of excess body fat, noting the association of upper body (android) obesity with a host of metabolic aberrations, including type 2 diabetes, atherosclerosis, and gout [7]. This contrasted greatly with the lower body (gynoid) form of obesity, which was not as frequently associated with these health problems. Vague's work would be extended by Per Bjorntorp and colleagues, who in a large sample of males and females used waist-to-hip ratio as an index of abdominal obesity to demonstrate the association of metabolic risk factors with abdominal fat accumulation [8]. This agreed with and added to the findings of Kissebah and colleagues, who had published a smaller-scale paper on the same topic almost simultaneously [40]. Throughout the 1980s, the Bjorntorp group provided evidence to establish abdominal obesity as a predictor of cardiovascular disease mortality, and type 2 diabetes, independent of BMI [9-11].

Abdominal adipose tissue is defined according to different depots, or areas, of fat deposition: abdominal visceral adipose tissue (VAT) and abdominal subcutaneous adipose tissue. Imaging studies have been conducted to quantify the respective contributions of visceral and subcutaneous abdominal adipose tissue in the development of metabolic abnormalities. In both males and females who were obese, Ross and colleagues demonstrated that VAT independently predicted insulin resistance, even after control for nonabdominal adipose tissue, abdominal subcutaneous adipose tissue and cardiorespiratory fitness (CRF) [41, 42]. By employing a matching strategy the authors were able to show a significant difference in glucose metabolism between individuals with high and low VAT and similar abdominal adipose tissue; no such difference was observed between individuals with high and low abdominal subcutaneous adipose tissue matched for VAT. In both men and women, it appears that metabolic risk factors predictive of CVD and diabetes are elevated when VAT area is greater than 100 cm^2, and greatly elevated beyond 130 cm^2 [43].

The current working model for the contribution of VAT to cardiometabolic risk is the "lipid spillover" theory [12]. In this model, dysfunctional subcutaneous adipose tissue is unable to expand to accommodate increased fat storage in the context of positive energy balance. As a result, subcutaneous adipose tissue cannot act as a "metabolic sink" and excess lipid spills over and accumulates in undesirable (ectopic) locations. These ectopic fat depots include VAT, liver fat and pancreatic fat. It is the excess fat storage in these ectopic depots which is hypothesized to produce the harmful metabolic consequences of insulin resistance, inflammation, and impaired insulin secretion, increasing cardiometabolic risk and risk of type 2 diabetes [12].

Prospective data lends support to the association of VAT with higher mortality risk. In the first report on directly measured VAT and all-cause mortality, Kuk and colleagues observed that VAT is a strong, independent predictor of all-cause mortality in men [21]. In a model including VAT, liver fat, and subcutaneous abdominal fat, only VAT remained a strong predictor of mortality after adjustment for age, length of follow-up, and the other fat depots. Further adjustment for smoking, BMI, and cardiovascular risk factors did not alter results. A more recent report by Britton and coworkers has added to these findings, demonstrating that VAT is associated with increased risk of incident CVD, cancer, and all-cause mortality after adjustment for age and sex; although VAT was no longer associated with all-cause mortality when cardiovascular risk factors and BMI were included in the model [20]. This report also demonstrated that the addition of VAT to CVD risk algorithms improved CVD risk prediction by 16%.

2.2.2 Waist Circumference and Morbidity and Mortality

Although imaging techniques represent the gold standard for assessing VAT accumulation, these techniques are expensive, and in the case of computerized tomography involve radiation exposure, making them poor choices as clinical measures. In their 1994 report, Pouliot and colleagues compared

various anthropometric indices of abdominal obesity by their associations with VAT and CVD risk [13]. Waist circumference (WC) and abdominal sagittal diameter were better correlates of both VAT and cardiovascular risk factors than waist-to-hip ratio. The ease of measurement of WC led the authors to conclude that WC was the best anthropometric measure of abdominal obesity for use in clinical settings.

Epidemiological evidence clearly supports the independent association of WC with all-cause mortality [15, 16], CVD [44, 45] and diabetes [46] risk. In a 2013 meta-regression analysis involving 689 465 patients and 48 421 deaths, a WC of 100 cm compared to 80 cm in women and 115 cm compared to 95 cm in men was associated with a 32% increased risk of all-cause mortality [15]. The relationship between WC and all-cause mortality was shown to be linear, and was strengthened after adjustment for BMI. Adding further support to the association of WC with all-cause mortality is a 2014 meta-analysis of 650 000 adults by Cerhan and colleagues, where each 5-cm increment in WC was associated with a 7% increased mortality risk in males and a 9% increased mortality risk in females [16]. This analysis demonstrated a positive linear relationship between 5-cm WC increments and all-cause mortality across a wide range of BMI groups stratified according to 2.5 kg/m^2 increments. In agreement between these two meta-analyses is the observation that WC is associated with higher mortality risk independent of BMI, and the conclusion that both BMI and WC be used to estimate risk rather than attempt to establish one as a superior marker to the other.

A collaborative analysis from the Emerging Risk Factors Collaboration investigated the association of WC with fatal and nonfatal CVD in 221 934 adults [45]. Each 12.6 cm higher WC (baseline value) was associated with a 32% increased risk of coronary heart disease (CHD), a 25% increased risk of ischaemic stroke, and a 27% increased risk in CVD after adjustment for age, sex, and smoking status. Another meta-analysis demonstrates a 10% increase in future CVD risk for every 5-cm increase in WC

after adjusting for age, cohort year, or treatment [44]. Finally, a 2012 meta-analysis demonstrated a 63% higher risk of developing type 2 diabetes for every 1 standard deviation increase in WC [46].

It is important to note that many different measurement protocols exist for the measurement of WC, which could influence the association between WC and adverse events. A 2008 review by Ross and colleagues noted that 101 (84%) of 120 studies measured WC at the umbilicus, midpoint between 12th rib and iliac crest, and at the point of minimal WC [47]. Other measurement points include the iliac crest, the last rib, 1 inch above the umbilicus, 1 cm above the umbilicus, and at the point of largest abdominal circumference. The reviewers concluded that WC measurement protocol did not appear to substantially influence the association between WC and CVD, diabetes, CVD mortality and all-cause mortality.

2.2.3 Guidelines for the Identification of Obesity

In response to the large impact of obesity on health risk worldwide, health organizations have established guidelines for the identification, treatment and management of overweight and obesity. These were initially established in 1997 by the World Health Organization [1] and in 1998 by the National Institutes of Health/National Heart, Lung and Blood Institute [48]. The 1998 clinical use guidelines were updated in 2013 in a joint report from the American Heart Association/American College of Cardiology [14].

A combination of BMI and WC has been recommended for the identification of individuals as overweight and obese, and to estimate the health risk related to a patient's level of obesity [14]. As BMI categories increase, health risk is said to increase. Within each BMI category, as WC crosses a threshold value health risk is said to increase further. The initial NIH guidelines used standard thresholds of 18.5-24.9, 25.0-29.9, and ≥30.0 kg/m^2 to classify adults as normal weight, overweight, and obese, respectively. Obesity can be further subdivided into obese class 1, obese class 2, and obese class 3;

corresponding BMI values are 30.0-34.9, 35.0-39.9, and ≥40.0 kg/m^2. The recommended WC threshold indicating abdominal obesity was 102 cm in men, and 88 cm in women. Greater risk is associated with high WC for individuals with BMI values up to class 1 obesity, while risk is considered to be significantly elevated in class 2 and 3 obesity regardless of WC. The 2013 update to the guidelines recommended that both these measures be used to identify individuals at increased health risk, and that those same thresholds be used until sufficient evidence emerged to justify use of different thresholds.

2.2.4 Evidence Supporting the Combined Use of BMI and WC

The first support of the NIH clinical guidelines BMI and WC thresholds came from an analysis by Janssen and colleagues on 14, 924 adult participants from the third National Health and Nutrition Examination Survey (NHANES) cohort [17]. Participants were categorized first by BMI as normal BMI, overweight, or obese, and then classified according to whether they were above or below the 102/88 cm WC thresholds. Individuals with high WC in each BMI group had higher levels of metabolic risk factors, and greater prevalence of cardiometabolic disease than those with low WC in the same BMI group. While this report demonstrated that the addition of WC to BMI improved prediction of metabolic risk, whether the opposite was true was investigated in a later report from the same group. In the same cohort, participants were grouped according to the NIH BMI and WC thresholds. After classifying according to low or high WC, risk of metabolic disorders increased with increasing BMI [49]. However, when classified as continuous variables, the addition of BMI to WC did not improve the prediction of the metabolic syndrome; therefore, for a given WC value, individuals who are normal BMI, overweight, and obese are at similar levels of cardiometabolic risk.

As previously stated, the utility of WC is believed to be its ability to predict visceral fat accumulation for a given BMI. To support this assumption, Janssen and colleagues characterized the independent contributions of BMI and WC to the prediction of nonabdominal, abdominal subcutaneous,

and visceral fat [50]. This study found that when added to BMI, WC improves prediction of abdominal fat, almost exclusively through prediction of visceral fat. This finding was supported by the observation that within each BMI category, the high WC (NIH thresholds) category was associated with greater quantities of visceral adipose tissue. These findings support the above observations concerning the utility of WC in discerning additional health risk reported previously by Janssen et al [17, 49].

Perhaps the best evidence to date supporting the use of BMI and WC in combination to estimate VAT accumulation and associated cardiometabolic risk comes from the INSPIRE ME cohort. In the largest international study to use directly measured VAT, Nazare and colleagues examined the relationship between BMI, WC, and VAT in over 4000 males and females [18]. There was substantial variation in both WC and VAT for a given BMI increment (1 kg/m^2). Furthermore, within each BMI unit, increasing tertiles of WC were associated with increasing amounts of VAT. In a similar fashion, increasing tertiles of WC were associated with higher cardiometabolic risk score within each of 3 BMI categories. These results echo previous findings from the cross-sectional International Day for the Estimation of Abdominal Adiposity study, which found that increasing tertiles of WC were associated with increased risk of CVD and diabetes for a given BMI category, including lean individuals with a BMI <25 kg/m^2 [19].

While BMI and WC together have been shown to predict VAT and cardiometabolic risk, there is also evidence to suggest that the combination of BMI and WC improves prediction of adverse events. The meta-analysis involving 650 000 participants conducted by Cerhan and colleagues demonstrate that within 2.5 kg/m^2 increments of BMI, WC is associated with all-cause mortality in a strong, linear fashion [16]. Adjusting for BMI only strengthened the relationship between WC and mortality. WC was also shown to predict mortality due to respiratory disease, CVD, and cancer after adjusting for BMI in this cohort.

Adding further support to the notion that both BMI and WC be measured together to better estimate health risk is a 2010 report on changes in BMI and WC and risk of all-cause mortality [51]. In 12 584 men and 14 041 women, changes in BMI were inversely associated with mortality, whereas changes in WC were positively associated with mortality. The associations of BMI and WC change with mortality were stronger after adjusting for each other. These results emphasize the importance of reducing abdominal fat mass for a given BMI, and that redistribution of fat mass towards the abdomen is a risk factor for mortality.

2.3 Limitations to Single WC Thresholds

Limited data supports the notion that the single 102/88 cm threshold optimally identifies individuals as abdominally obese with elevated health risk. These thresholds were initially proposed by Han and colleagues as a means of identifying Caucasians with a BMI of 30.0 kg/m^2, as WC was deemed to be more readily understandable by the average person [22]. Linear regression was used to identify the WC values which correlated with a BMI of 25.0 and 30.0 kg/m^2 in males and females, to produce WC action levels identifying increasing need for obesity treatment. These thresholds were therefore not produced based on their ability to identify individuals at greater risk based on adverse events, but to identify individuals with elevated BMI. Later analyses would provide population-based evidence that these thresholds did indeed identify individuals at greater health risk, but did not confirm that the 102/88 cm WC thresholds optimally identified individuals at greater risk [17].

Another limitation of the 102/88 cm threshold is evident when examining the 2002 study by Janssen and colleagues [17]. Very few individuals with normal BMI also had a WC >102/88 cm, and very few individuals who were obese had a WC <102/88 cm. This is a product of the selection method for the 102/88 cm thresholds. As a BMI of 30 was correlated with a WC of 102 cm in men and 88 cm in women, it can be expected that very few individuals who are obese will have WC values below this threshold,

and very few individuals with normal BMI will have WC values above this threshold. The implication of this relationship between threshold and BMI is that in analyses involving both BMI and WC, very few individuals will appear in certain groups, which may limit investigations that use these thresholds.

To address the need for WC thresholds that optimally identified individuals with increased health risk based on outcomes, Ardern et al performed analyses based on Framingham CHD risk index to produce WC thresholds specific to each BMI category [23]. These thresholds better identified individuals at increased risk for CHD. These BMI-specific WC thresholds were then cross-validated using a large representative sample. It was concluded that a single WC threshold for all BMI categories is insufficient to accurately identify individuals at increased risk, and that multiple WC thresholds specific to BMI categories should be instead used.

2.4 Cardiorespiratory Fitness

Cardiorespiratory fitness (CRF) is a measure of physical fitness which reflects an individual's ability to perform maximal aerobic exercise involving large muscle groups. Physiologically, CRF reflects the capacity of the cardiovascular and respiratory systems to deliver oxygen to working muscles, and the capacity of those muscles to utilize that oxygen to perform work [52]. CRF is an attribute rather than a behaviour; physical activity is the behaviour which influences CRF. CRF is measured objectively by exercise testing, while physical activity is often determined by self-report, at least in large epidemiological studies. Therefore CRF may serve as a reliable indicator of recent physical activity patterns.

CRF is typically assessed by measurement of maximal oxygen capacity, or VO_{2max}, by maximal exercise testing [52]. The gold standard for CRF measurement is direct measurement of gas exchange during a maximal exercise test. In large epidemiological studies it is common for CRF to be measured

indirectly by using maximal exercise test time for a standard test protocol. The indirect method has a high correlation with directly measured VO_{2max} in both males [53] and females [54].

More recently, longitudinal algorithms have been developed using both directly [55] and indirectly [56] measured CRF which may be used to estimate VO_{2max}. This method may be well suited for clinical settings where time constraints may prohibit direct exercise testing. To estimate CRF, these algorithms make use of age, BMI, resting heart rate, and self-reported physical activity, all of which are quickly and easily recorded during a standard clinical visit [55, 56].

2.4.1 Factors Associated with Cardiorespiratory Fitness

There are several modifiable and non-modifiable predictors of CRF. CRF is recognized as having a large heritable component: the HERITAGE Family Study has estimated the maximal genetic and non-genetic heritability of VO_{2max} to be approximately 50% [57]. Additionally, the VO_{2max} response to chronic exercise training also appears to be heritable, with a maximum heritability estimate of 47% [58].

A recent report from the Cooper Clinic Longitudinal Study has helped to identify factors associated with CRF in a large cohort [59]. In 20,000 men and women, age, sex, BMI, and physical activity together explained 56% of the variance in CRF. The addition of other clinical factors such as smoking and cholesterol improved the model, but only by 2%. The substitution of WC with BMI did not change the model to any significant degree.

These findings largely agreed with a report by Laukkanen and colleagues on measures associated with CRF in Finnish men with and without CVD [60]. Physical activity components (frequency, intensity, and duration) were directly related to CRF, while CVD was inversely associated with VO_{2max}. Cardiovascular function, carbohydrate intake, age, and body composition were also found to influence variability in CRF.

2.4.2 Cardiorespiratory Fitness and Cardiometabolic Risk Factors

Studies investigating the association of CRF and mortality report lower levels of cardiometabolic risk factors with increasing levels of CRF [24, 26]. Recent reports using directly [61] and indirectly [62] measured CRF have further explored the relationship between CRF and cardiometabolic risk. Cardiovascular risk factors, prevalence of metabolic syndrome, and 10-year Framingham risk decrease with increasing quintiles of CRF [62]. Furthermore, every 5 mL/kg O2 decrease in CRF is associated with a 56% increase in clustered cardiometabolic risk factors [61]. Finally, CRF thresholds of 12 metabolic equivalents (METs) in men and 10 METs in women have been identified, below which cardiometabolic risk factors are significantly elevated [61].

2.4.3 Cardiorespiratory Fitness and Morbidity and Mortality

CRF is now recognized as an important prognostic indicator of health risk. In their landmark 1989 report, Steven Blair and colleagues clearly demonstrated that CRF, objectively assessed by maximal exercise test time on treadmill, was strongly and inversely associated with all-cause mortality in a large cohort of males and females [24].

Numerous prospective longitudinal studies consistently associate CRF with clinical endpoints including CVD mortality [24, 63-65], cancer mortality [24, 66-68], and incidence of CHD [69], myocardial infarction [70], stroke [71, 72], and sudden cardiac death [73]. While many studies have been performed with predominantly white male populations, the benefits of increased CRF have been shown to apply to female [74, 75], African American [76], and older [77, 78] populations.

The relationship of CRF with all-cause mortality has been characterized in a recent meta-analysis involving 100,000 males and females by Kodama and colleagues [25]. Every 1 MET increase in CRF was associated with a 13% decrease in relative risk of all-cause mortality and a 15% reduction in risk of CVD mortality.

2.4.4 Changes in Cardiorespiratory Fitness and Health Risk

Given the large genetic component of CRF [57], it is possible that the mortality risk reduction due to high CRF is conferred through genetic predisposition rather than an effect of physical training during the life cycle. Reports on changes in CRF and mortality risk help to emphasize the importance of improving CRF through physical activity, as a change in CRF will be due to lifestyle factors rather than heredity [79]. A 1995 report by Blair and colleagues showed that improving CRF was associated with a 44% reduction in mortality compared with individuals who stayed unfit [79]. Even within the fit category, further increases in CRF were associated with reduction in mortality risk. These findings are in agreement with those of another cohort of Norwegian men [80], and are unchanged within the same cohort when reanalyzed in a 2011 report with larger sample size and greater follow-up [81].

2.4.5 Cardiorespiratory Fitness, Common Cardiometabolic Risk Factors, and Risk

Not only is CRF associated with morbidity and mortality, but this association remains even when considering commonly measured cardiometabolic risk factors such as blood pressure and smoking. In 1996, Blair and colleagues first described the relation of CRF to all-cause and CVD mortality within strata of other common risk factors [26]. The most compelling observation was that mortality risk for individuals who had high fitness and 2-3 risk factors (smoking, high cholesterol, and /or high blood pressure) was lower than for individuals with low fitness and 0 risk factors. This and a later report [28] demonstrated CRF was independently associated with mortality risk, and that the strength of association of CRF with mortality was at least as strong as other cardiometabolic risk factors.

The benefit of including CRF alongside traditional risk factors has been demonstrated in a report by Gupta et al, using data from the Cooper Center Longitudinal Study [82]. In 66, 000 males and females, adding CRF to traditional cardiovascular risk factors resulted in a 10% improvement in net reclassification. This means that 10% more individuals were reclassified correctly than if fitness were not measured. An individual is correctly classified if they are moved into a higher risk category and a

cardiovascular event occurs, or if they are moved into a lower risk category and a cardiovascular event does not occur. The addition of CRF to traditional risk factors therefore improves risk prediction for CVD mortality, and is a strong and independent predictor of morbidity and mortality.

2.4.6 Cardiorespiratory Fitness, Disease, and Mortality Risk

The benefit of high CRF is not limited to healthy/asymptomatic individuals. Reports from the Aerobics Center Longitudinal Study and elsewhere consistently demonstrate that mortality risk is lower in individuals with high CRF despite conditions such as hypertension [83-87], CVD [76, 88], diabetes [89-91], the metabolic syndrome [92], diabetes and CVD [93], and coronary artery disease [94]. Despite the presence of conditions which predispose to early mortality, CRF consistently emerges as a protective attribute.

2.4.7 Cardiorespiratory Fitness, Obesity, and Health Risk

Many researchers have investigated the independent effects of obesity and CRF on mortality. Considerable evidence suggests that CRF either completely eliminates or at the very least attenuates obesity-related risk of all-cause mortality and mortality due to CVD [28, 78, 95-97]. Furthermore, this has been shown not only in the general, healthy population, but also in those with hypertension [85, 98, 99], diabetes [89], the metabolic syndrome [100], CHD [101], and pre-diabetes [102].

Barry and colleagues have conducted a meta-analysis on the relative contributions of CRF and obesity, as determined by BMI, to risk of all-cause mortality [27]. They found that individuals that were fit (highest 80% of age- and sex-standardized time on treadmill values) had eliminated excess risk of mortality due to a BMI of >30 kg/m^2, but individuals that were unfit had increased mortality risk. In agreement with this analysis is a pair of studies from the Aerobics Center Longitudinal Study (ACLS) on changes in CRF and BMI [81, 103]. Changes in CRF over time predicted both increased risk of all-cause and CVD-mortality, as well as increased risk of hypertension, dyslipidemia, and development of the

metabolic syndrome, even after adjustment for changes in BMI. After adjusting for changes in CRF, changes in BMI were no longer associated with risk of all-cause and CVD-mortality, but were still associated with development of cardiometabolic risk factors.

Fewer studies have investigated the relative contributions of WC and CRF to mortality risk. In their often cited 1999 study, Lee and colleagues reported that fit men were at no higher risk of all-cause mortality due to elevated WC, while unfit men with a high WC had 147% increased mortality risk relative to fit men with low WC [29]. Similar findings of CRF eliminating mortality risk due to elevated WC have been reported in females [104], older adults [78], and adults with prediabetes [102], coronary heart disease [101], or hypertension [99].

Cross-sectional analyses reveal that CRF modifies the association of obesity with cardiometabolic risk. For a given level of obesity, CRF has been associated with reductions in inflammatory biomarkers, improvements in glucose metabolism and lipid concentrations [52]. For a given level of BMI or WC, individuals who are fit have lower amounts of total and abdominal adipose tissue [50]. When matched for BMI, individuals who are fit have lower amounts of visceral adipose tissue and lower levels of cardiometabolic risk factors than individuals who are unfit [105, 106]. Furthermore, CRF is associated with lower values of cardiometabolic risk factors, as well as lower risk of developing the metabolic syndrome, for a given amount of WC and VAT [107]. It should be noted that not all studies demonstrate lower values of cardiometabolic risk factors when individuals are matched for VAT accumulation, suggesting that some of the protective effect of CRF may act through reduction of VAT [105].

A growing amount of data suggests that physical activity interventions which increase CRF result in improvements in cardiometabolic risk factors, even with no change in body weight [108]. Exercise without weight loss has been shown to reduce WC and cardiometabolic risk factors while

simultaneously preserving lean mass and improving CRF [109]. These findings have led several investigators to call for a new line of thinking concerning effective obesity management: even if weight loss is not achieved, cardiometabolic risk factors can still be reduced consequent to adoption of a healthful diet and physically active lifestyle [110, 111].

2.4.8 Multiple Measures of Obesity, CRF, and Mortality

To date, only a single study has examined the protective effect of CRF on all-cause mortality when multiple measures of obesity are considered together. In an analysis from the Cooper Center Longitudinal Study, Farrell and colleagues classified a large cohort of males according to whether their BMI was above 30 kg/m^2, WC above 102 cm, and percent body fat above 25% [30]. The subjects were considered to be either positive or negative for each of the three obesity measures. Increasing number of positive obesity measures was associated with increasing risk of all-cause mortality. When CRF was included, males who were fit had reduced mortality risk regardless of whether they had multiple positive measures of adiposity.

A limitation of this study was that the authors were unable to investigate the effect of addition of CRF across specific combinations of BMI and WC due to few cases of mortality in some combined groups of BMI, WC and percent body fat [30]. It is therefore unclear whether addition of CRF improves the prediction of mortality risk across the various categories of a combined BMI and WC model.

2.5 Summary of Literature

The available literature clearly supports the association of obesity with increased risk of morbidity and mortality, in particular the abdominally obese phenotype characterized by increased WC. While these conclusions are formed from prospective data using clinical endpoints, the majority of studies investigating the association of obesity with health risk do not take into account any role of CRF. This is despite the large amount of prospective, longitudinal data demonstrating the ability of CRF to

predict morbidity and mortality risk independent of measures of obesity. Studies looking to accurately identify individuals at increased obesity-related health risk must consider CRF alongside measures of obesity.

While the literature demonstrates that CRF substantially attenuates the relationship between obesity and health risk, there are important gaps that must be addressed. Most of the literature concerning the relative contributions of CRF and obesity has focused on whether CRF predicts health risk beyond BMI or WC alone. This method of analysis does not take into account widely-recommended obesity risk management guidelines, which emphasize the combined measurement of BMI and WC to estimate obesity-related health risk. In fact, only a single study has reported on the ability of CRF to protect against increased mortality risk in a combined BMI and WC model, and in that study the authors were unable to investigate the effect of CRF across specific combinations of BMI and WC.

The use of BMI-specific WC thresholds developed by Ardern and colleagues may be superior to a single 102 cm WC threshold for analyses involving BMI, WC and CRF, as they result in better distribution of participants among normal and high WC categories for a given BMI group, allowing further stratification by CRF. Furthermore, the BMI-specific WC thresholds were developed according to their ability to predict risk of CHD, while the single 102 cm threshold has no such basis in risk prediction. It is a weakness that these validated BMI-specific WC thresholds are not more widely utilized in the literature.

Further inquiry is therefore needed into the whether CRF improves prediction of mortality risk when added to a combined BMI and WC model. This analysis would be best strengthened through the use of prospective, longitudinal data providing a large number of adverse events and objective measurements of BMI, WC, and CRF. If CRF improves risk prediction beyond BMI and WC, further support will be given to the notion that the measurement of CRF deserves an equal place alongside BMI and WC in healthcare settings. Healthcare practitioners may be provided with another option for both

identifying patients at increased risk, and a measure that can be targeted to manage and reduce obesity-related health risk in their patients.

Chapter 3. Addition of Cardiorespiratory Fitness Within an Obesity Risk Classification Model Identifies Men at Increased Risk of All-Cause Mortality

3.1 Abstract

Background: Guidelines for identification of obesity-related risk stratify disease risk using specific combinations of body mass index (BMI) and waist circumference (WC). Whether the addition of cardiorespiratory fitness (CRF), an independent predictor of disease risk, provides better risk prediction of all-cause mortality within current BMI and WC categories is unknown.

Objective: To determine whether the addition of CRF improves prediction of all-cause mortality risk classified by established categorization of BMI and WC.

Design: Prospective observational data from the Aerobics Center Longitudinal Study (ACLS).

Participants: A total of 31,267 men (mean age 43.9 [SD, 9.4] years) who completed a baseline medical examination during 1974-2002. Participants were grouped according to the following BMI- and WC-specific threshold combinations: Normal BMI of 18.5-24.9 kg/m^2, WC threshold of 90 cm; overweight BMI of 25.0-29.9 kg/m^2, WC threshold of 100 cm, and obese BMI of 30.0-34.9 kg/m^2, WC threshold of 110 cm. Participants were classified by CRF as unfit or fit. Unfit was defined as the lowest fifth of the age-specified distribution of maximal exercise test time on treadmill among the entire ACLS population.

Main Outcome Measure: All-cause mortality.

Results: 1,399 deaths occurred over an average length of follow-up of 14.1 ± 7.4 years, for a total of 439, 991 person-years of observation. Males who were unfit and normal BMI with WC<90 cm and ≥90 cm had 95% (1.95, 1.34-2.83) [Hazard ratio, 95% confidence interval] and 163% (2.63, 1.58-4.40) higher mortality risk than males who were fit, respectively (p<.05). Males who were unfit and overweight had 41% (1.41, 1.04-1.90) higher mortality risk with a WC <100 cm (p<.05), but were at no greater risk (1.30, 0.92-1.84) if their WC was ≥100 cm (p=.14). Males who were unfit and obese were not at increased

mortality risk (1.37, 0.90-2.09) with a WC <110 cm (p=.14), but were at 111% (2.11, 1.31-3.42) increased risk with a WC ≥110 cm (*p*<.05).

Conclusions: For most of the BMI and WC categories, inclusion of CRF allowed for improved identification of males at increased mortality risk.

3.2 Introduction

Health organizations worldwide recommend that body mass index (BMI) and waist circumference (WC) be combined to estimate obesity related health risk [14], as these measures have independent associations with all-cause mortality [16], and the addition of WC to BMI has been shown to improve evaluation of cardiometabolic risk [18], cardiovascular disease (CVD), and diabetes [19].

At present, a single 102 cm WC threshold is recommended for the identification of adult Caucasian males at elevated health risk within each BMI category [14]. However, the 102 cm threshold was originally intended as a replacement of BMI measurement to identify white male adults with a BMI of ≥30.0 kg/m^2 [22]. Use of the 102 cm threshold classifies very few individuals with normal and overweight BMI, and almost all individuals who are obese with high WC based on this cut-point [17]. In response, Ardern and colleagues proposed the use of WC values specific to each BMI category to identify CHD mortality risk that were developed and cross-validated using large representative samples [23].

Currently, obesity risk classification models also do not include cardiorespiratory fitness (CRF), which is well established as a strong predictor of morbidity and mortality [24, 25] independent of BMI and WC [27-29]. A recent report has demonstrated the protective effect of CRF against all-cause mortality, even when BMI, WC, and percent body fat are elevated [30]. In that study, however, the authors were unable to analyze the effect of the addition of CRF across specific combinations of BMI and WC due to sample size limitations. Therefore, whether the addition of CRF improves prediction of

mortality risk within a combined BMI and WC model has potentially important implications for obesity risk management. Should CRF improve risk prediction, healthcare practitioners may be provided with a measure which, when used in combination with BMI and WC, may be used to better predict and manage obesity-related health risk in clinic.

To investigate this question, we classified a large cohort of males enrolled in the Aerobics Center Longitudinal Study (ACLS) according to BMI- and WC-specific thresholds as validated by Ardern and colleagues [23] and examined whether the addition of CRF improved the prediction of all-cause mortality within groups classified by the combination of BMI and WC.

3.3 Methods

3.3.1 Study Population

The ACLS is a prospective longitudinal study established in the 1970s to examine associations between health behaviours, risk factors for chronic disease, and morbidity and mortality [24]. The ACLS study population consists of patients attending the Cooper Clinic in Dallas, Texas for preventive medical examinations. These patients were volunteers, either self-referring or were referred to the Cooper Clinic by employers or health care providers. The ACLS cohort consists of predominantly white, well-educated, United States residents, from all 50 states, and from middle to upper socioeconomic stratum. Study participants were aware of the purpose of the study, and provided written consent prior to study participation. The ACLS protocol was subject to annual review by the Cooper Institute's Institutional review board.

All males with BMI measurements between 18.5-34.9 kg/m^2 and a complete set of baseline data were included for the current analysis. Males with a BMI ≥35.0 kg/m^2 and all females were excluded from analysis due to few events within some groups for all-cause mortality. Participants were excluded based on presence of CVD or cancer at baseline, or an abnormal exercise test electrocardiogram. These

conditions reduce exercise test time on treadmill, and increase likelihood of mortality during follow-up, thereby increasing the likelihood of demonstrating an exaggerated CRF-mortality relationship [26]. Additionally, participants with less than one year of follow-up, or who failed to achieve 85% of age-predicted exercise test maximal heart rate were excluded from analysis. Participants who died within one year of follow-up, or who failed to achieve the predicted heart rate were presumed to be more likely to have pre-existing conditions which would again increase the likelihood of demonstrating an exaggerated CRF-mortality relationship [24]. Using these criteria, 31 267 males were included in the final analysis, having completed baseline medical examinations at the Cooper Clinic between 1974 and 2002.

3.3.2 Data Collection

After providing written consent (See Appendix 1), patients underwent a full preventive medical examination including examination by a physician, fasted blood chemistry analysis, personal and family health history assessment, anthropometry, resting blood pressure and electrocardiography measurement, and a maximal graded treadmill exercise test. Examinations were performed by trained technicians following standardized measurement protocols. Cigarette smoking (current smoker or not), alcohol intake (heavy drinking defined as >14 alcoholic drinks per week), and physical inactivity (defined as no reported physical activity during the previous 3 months) were determined by self-report from the patient's personal history. Parental history of CVD was determined from family health history. Presence of hypertension was defined as blood pressure >140/90 mm Hg, or previous physician diagnosis of hypertension. Presence of hypercholesterolemia was defined as total cholesterol >240mg/dL, or previous physician diagnosis of hypercholesterolemia. Presence of diabetes was defined as fasting glucose >126 mg/dL, previous physician diagnosis of diabetes, or reported insulin use.

3.3.3 Mortality Surveillance

Mortality follow-up occurred from the date of baseline examination until the date of death, or December 31, 2003 for survivors. The National Death Index and state death certificates were used to

determine survival status. Deaths were classified using the *International Classification of Diseases, Ninth Revision* for deaths occurring before 1999, and the *International Statistical Classification of Diseases, 10th edition*, for deaths occurring from 1999 to 2003.

3.3.4 Measurement and Classification of BMI, WC and CRF

Height and weight were measured using a stadiometer and physician's scale; BMI was calculated according to the formula Weight (kg)/Height $(m)^2$. In this analysis, participants were classified according to standard BMI categories for normal (BMI 18.5 to <25.0 kg/m^2), overweight (BMI 25.0 to <30.0 kg/m^2), and obesity (BMI 30.0 to <35.0 kg/m^2).

WC was measured at the level of the umbilicus. In this analysis participants were classified as abdominally obese according to BMI-specific thresholds derived by Ardern et al [23]. The Ardern thresholds for males are as follows: normal BMI (18.5-24.9), WC threshold of ≥90 cm; overweight BMI (25.0-29.9), WC threshold of ≥100 cm; and obese BMI (30.0-34.9) WC threshold of ≥110 cm. For the analysis involving WC alone without BMI, a WC threshold of 96 cm was used. This value was determined by Ardern et al to represent the optimal threshold for all males studied regardless of BMI.

CRF was determined using a modified Balke maximal treadmill exercise test [24, 112]. Treadmill speed was initially set at 88 m/min. Treadmill grade was initially set at 0% for the first minute, was increased to 2% for the second minute, and was increased by 1% for each minute thereafter. If the patient reached 25 minutes, treadmill speed was then increased by 5.4 m/min each minute. The treadmill test continued until the patient reached volitional fatigue. Patients were discouraged from using the treadmill hand supports to help reduce misclassification of CRF.

Maximal exercise test time on treadmill has been found to correlate highly with measured maximal oxygen uptake in males [53]. Metabolic equivalent (MET) levels were determined from end of

test treadmill speed and grade to allow for comparison between patients. Patients were classified as fit or unfit based on the upper 80% (fit) and lower 20% (unfit) of the age-standardized CRF ACLS time on treadmill distribution in the entire ACLS population. While there are no current consensus definitions of low fitness, our approach has been a standardized method in the ACLS. Previous ACLS reports using this method have demonstrated that low fitness by this definition independently predicts risk of morbidity and mortality [24, 28, 29]. Classification according to CRF level (fit or unfit) further stratified the six combined BMI and WC groups, resulting in twelve groups in total for analysis.

3.3.5 Rationale for the use of BMI-specific thresholds

The 94 and 102 cm thresholds proposed by Han and colleagues were originally designed to identify males with a BMI of ≥25.0 kg/m^2 and ≥30.0 kg/m^2 respectively, providing action levels for obesity treatment [22]. However, this results in very few individuals with a normal BMI with a WC over the 102 cm threshold, and few individuals who are obese with a WC under the 102 cm threshold [17]. Indeed, in the ACLS cohort described here, only 15 males were classified as having normal BMI with a WC >102 cm (data not shown). The Ardern WC thresholds more evenly distribute individuals with high and normal WC within BMI categories, allowing group comparisons in mortality risk. The Ardern thresholds were also designed to maximize sensitivity and specificity for Framingham CHD risk, optimally identifying individuals at high risk of future CHD events. This is in contrast to the Han and Lean thresholds, which were developed according to association with BMI, and not according to risk of events.

Together the BMI categories and WC thresholds were used to create 6 groups for analysis: normal BMI with WC <90 cm, normal weight with WC ≥90 cm, overweight BMI with WC <100 cm, overweight with WC ≥100 cm, obese with WC < 110 cm, and obese BMI with WC ≥110 cm.

3.3.6 Statistical Analysis

Group differences in baseline characteristics were compared using t-tests and analysis of variance for continuous, and X^2 tests for categorical variables. Tukey's studentized range test was used post hoc to determine group differences in baseline characteristics between males who were unfit and males who were fit within each BMI and WC group. Cox proportional hazards models were then used to estimate hazard ratios and 95% confidence intervals of all-cause mortality risk for males who were unfit compared with the fit reference group within each of the combined BMI and WC groups, and when CRF was added to BMI or WC alone. Each model was fully adjusted for age, year of baseline examination, and the following behaviours and conditions which predispose to early mortality: smoking, alcohol intake, physical inactivity, diabetes, hypertension, hypercholesterolemia, and parental history of CVD. Models were checked to ensure that they did not violate the proportional hazards assumption. Statistical significance was set at $p < 0.05$.

3.4 Results

A total of 1,399 deaths occurred in 31,267 males followed for an average of 14.1 ± 7.4 years with a range of 1.0 to 29.3 years, for a total of 439, 991 person-years of observation. Baseline characteristics for study participants according to survival status are presented in **Table 3.1**. Mean age at baseline was 43.9 ± 9.4 years. Decedents were older, had greater WC, lower CRF, and higher blood pressure, blood cholesterol, and blood glucose than survivors ($p < .05$). Survivors had greater CRF and time on treadmill than decedents ($p<.05$). Decedents were more likely to smoke, be physically inactive, and to have diabetes, hypertension, or parental history of CVD ($p < .05$). Survivors were more likely to consume alcohol in excess of 14 alcoholic drinks per week ($p <.05$).

Baseline characteristics for study participants according to CRF within each BMI and WC group are presented in **Table 3.2**. Participants who were unfit within each BMI and WC group were generally younger, with higher BMI and WC, but had lower CRF and time on treadmill ($p<.05$). Unfit individuals

were more likely to be current smokers, physically inactive, and to have diabetes, hypercholesterolemia, or hypertension (p <.05).

For most BMI and WC groups, being unfit was associated with a higher risk of all-cause mortality after adjusting for covariates (**Table 3.3**)**.** For males with normal BMI, being unfit was associated with a 95% higher risk (1.95, 1.34-2.83) [Hazard ratio, 95% confidence interval] of all-cause mortality (p<.05) for males with a WC <90 cm, and a 163% higher risk (2.63, 1.58-4.40) of all-cause mortality (p<.05) for males with a WC ≥90 cm. For males who were overweight, being unfit was associated with a 41% higher risk (1.41, 1.04-1.90) of all-cause mortality for males with a WC <100 cm (p<.05), while there was no significant increase in risk (1.30, 0.92-1.84) for males who were unfit and overweight with a WC ≥100 cm (p=.14). Males who were unfit and obese were not at higher risk of all-cause mortality (1.37, 0.90-2.09) with a WC <110 cm (p=.14), but were at 111% higher risk (2.11, 1.31-3.42) with a WC ≥110 cm (p<.05).

When grouped by BMI or WC alone, males who were unfit were at significantly greater mortality risk compared with males who were fit within each group (**Table 3.4**). When considering BMI alone, males who were unfit were at 110%, 41%, and 65% greater risk of all-cause mortality compared with males who were fit if they had normal, overweight, or obese BMI, respectively. When grouped according to WC alone, males who were unfit were at 53% and 79% greater risk of all-cause mortality if they had WC <96.0 cm or WC ≥96.0 cm, respectively.

Table 3.1. Baseline characteristics for all study participants and according to survival status.

	All Participants (n=31 267)	Survivors (n=29 868)	Decedents (n=1399)
Age (y)	43.9 ± 9.4	43.5 ± 9.2*	51.1 ± 10.6
BMI (kg/m^2)	26.2 ± 3.1	26.2 ± 3.1	26.2 ± 3.2
WC (cm)	92.7 ± 9.5	92.7 ± 9.5*	94.1 ± 10.0
CRF (METs)	12.1 ± 2.4	12.2 ± 2.3*	10.8 ± 2.4
Time on Treadmill (min)	18.9 ± 4.7	19.0 ± 4.7*	16.2 ± 5.1
Fasting Glucose (mg/dL)	99.7 ± 54.2	99.5 ± 55.1*	104.3 ± 28.1
Fasting Total Cholesterol (mg/dL)	207.7 ± 43.6	207.3 ± 43.6*	216.3 ± 42.2
Resting SBP (mmHg)	120.4 ± 12.8	120.3 ± 12.7*	124.0 ± 14.5
Resting DBP (mmHg)	80.9 ± 9.3	80.8 ± 9.3*	82.4 ± 10.1
Current Smoker (%)	16.6	16.2*	26.7
Heavy Alcohol Intake (%)	8.1	8.2*	5.5
Physically Inactive[a] (%)	22.7	22.5*	26.9
Diabetes[b] (%)	3.8	3.6*	7.3
Hypercholesterolemia[c] (%)	27.2	27.1	29.2
Hypertension[d](%)	28.3	27.7*	39.6
Parental History of CVD (%)	26.9	26.2*	41.5

Abbreviations: BMI, body mass index; WC, waist circumference; CRF, cardiorespiratory fitness; SBP, systolic blood pressure; DBP diastolic blood pressure; CVD cardiovascular disease.

Data presented as mean ± standard deviation, unless otherwise indicated. * indicates a significant difference between survivors and decedents ($p<.05$).

[a] Defined as no self-reported leisure-time physical activity within 3 months of baseline examination, as reported on the standardized medical history/health habits questionnaire.

[b] Defined as history of physician diagnosed diabetes, use of insulin, or measured fasting glucose level ≥126 mg/dL.

[c] Defined as history of physician diagnosis or measured fasting total cholesterol level ≥240 mg/dL.

[d] Defined as history of physician diagnosis or measured resting systolic blood pressure ≥140 mmHg or measured resting diastolic blood pressure ≥90 mmHg

Table 3.2. Baseline characteristics according to fitness status within each combined body mass index and waist circumference group.

	Normal BMI				Overweight BMI				Obese BMI			
	Normal WC		High WC		Normal WC		High WC		Normal WC		High WC	
	Unfit	Fit	Unfit	Fit	Unfit	Fit	Unfit	Fit	Unfit	Fit	Unfit	Fit
N	307	9217	176	2459	879	10860	569	2814	674	1966	520	783
Age (y)	41.6 ± 9.5	41.9 ± 9.8	44.0 ± 9.6	45.9 ± 9.4	41.9 ± 8.3*	44.1 ± 9.1	44.6 ± 8.8*	47.2 ± 9.0	42.4 ± 8.4	44.9 ± 8.7	44.5 ± 8.5*	47.2 ± 9.2
BMI (kg/m^2)	22.8 ± 1.5	23.0 ± 1.3	24.0 ± 0.8	24.1 ± 0.8	27.0 ± 1.3*	26.7 ± 1.2	28.5 ± 1.1*	28.2 ± 1.2	31.7 ± 1.2*	31.4 ± 1.1	32.9 ± 1.3*	32.6 ± 1.4
WC (cm)	83.8 ± 5.2	83.0 ± 4.6	93.4 ± 3.1	92.8 ± 3.0	94.5 ± 4.2*	92.7 ± 4.8	104.2 ± 3.8*	103.2 ± 2.9	104.4 ± 4.6*	103.1 ± 5.8	114.9 ± 6.5*	113.6 ± 3.3
CRF (METs)	8.9 ± 1.1*	13.7 ± 2.3	8.7 ± 1.2*	12.2 ± 1.8	9.0 ± 1.0*	12.2 ± 1.8	8.7 ± 1.1*	11.1 ± 1.5	8.8 ± 1.0*	11.1 ± 1.4	8.5 ± 1.1*	10.4 ± 1.3
Time on Treadmill (min)	12.1 ± 2.4*	22.1 ± 4.3	11.7 ± 2.7*	19.2 ± 3.7	12.3 ± 2.1*	19.2 ± 3.8	11.6 ± 2.3*	16.8 ± 3.2	11.8 ± 2.1*	16.8 ± 3.0	11.1 ± 2.2*	15.4 ± 2.8
Resting SBP (mmHg)	115.3 ± 13.0	117.5 ± 12.4	119.3 ± 12.5	120.6 ± 13.1	119.9 ± 11.7	120.7 ± 12.5	123.0 ± 12.8	123.1 ± 13.0	125.0 ± 12.5	124.8 ± 12.5	126.1 ± 12.2	127.2 ± 13.0
Resting DBP (mmHg)	79.1 ± 8.7	77.8 ± 8.7	80.1 ± 9.0	81.5 ± 9.3	81.8 ± 8.9	81.1 ± 9.0	84.0 ± 9.4	83.2 ± 9.2	85.6 ± 9.3	85.0 ± 9.3	86.4 ± 9.1	86.5 ± 9.6
Fasting Total Cholesterol (mg/dL)	212.8 ± 40.4*	197.0 ± 46.3	209.8 ± 38.5	216.0 ± 40.5	221.9 ± 44.9*	209.5 ± 42.1	219.5 ± 41.4	215.8 ± 41.1	217.2 ± 39.3	212.7 ± 40.1	222.2 ± 45.6	214.6 ± 40.8
Fasting Blood Glucose (mg/dL)	97.3 ± 17.2	97.6 ± 96.6	102.4 ± 27.9	98.6 ± 13.5	102.1 ± 22.5	99.1 ± 12.9	103.6 ± 21.3	102.4 ± 15.8	105.2 ± 25.7	102.1 ± 16.6	110.8 ± 32.5	105.1 ± 18.7
Current Smoker (%)	41.7*	12.5	38.8*	14.6	36.6*	16.6	31.6*	16.8	25.5*	15.8	23.3*	12.9
Heavy Alcohol Intake (%)	8.5	6.8	9.0	7.9	6.9	8.8	7.7	9.0	6.2*	9.3	8.3	9.8
Physically Inactive[a] (%)	55.7*	14.1	59.6*	20.7	51.1*	19.5	54.1*	28.3	52.1*	23.2	54.8*	32.2
Diabetes[b] (%)	2.0	2.2	6.2*	2.7	4.0	3.2	7.2*	5.0	9.8*	6.1	14.2*	9.2
Hypercholesterolemia[c] (%)	28.0*	17.7	30.9	26.3	37.5*	29.0	37.1	34.6	38.9*	32.8	41.0	37.0
Hypertension[d] (%)	20.5	16.8	32.6*	24.2	30.6	28.2	43.2*	38.7	49.0	44.7	52.5	53.6

Parental History of CVD (%)	22.8	23.6	34.8	30.1	29.8*	26.7	32.9	30.2	27.0	25.7	30.6	28.9

Abbreviations: BMI, body mass index; WC, waist circumference; CRF, cardiorespiratory fitness; SBP, systolic blood pressure; DBP diastolic blood pressure; CVD cardiovascular disease.

Data presented as mean ± standard deviation unless otherwise indicated. * indicates a significant difference between unfit and fit individuals within each BMI/WC group (p<.05).

[a]Defined as no self-reported leisure-time physical activity within 3 months of baseline examination, as reported on the standardized medical history/health habits questionnaire.

[b]Defined as history of physician diagnosed diabetes, use of insulin, or measured fasting glucose level ≥126 mg/dL.

[c]Defined as history of physician diagnosis or measured fasting total cholesterol level ≥240 mg/dL.

[d]Defined as history of physician diagnosis or measured resting systolic blood pressure ≥140 mmHg or measured resting diastolic blood pressure ≥90 mmHg.

Table 3.3. Hazard ratios for all-cause mortality between unfit and fit men within each combined body mass index and waist circumference group.

BMI	WC	Unfit vs. Fit	*p*-value
Normal	<90 cm	1.95 (1.34-2.83)*	0.0005
	≥90 cm	2.63 (1.58-4.40)*	0.0002
Overweight	<100 cm	1.41 (1.04-1.90)*	0.0253
	≥100 cm	1.30 (0.92-1.84)	0.1426
Obese	<110 cm	1.37 (0.90-2.09)	0.1408
	≥110 cm	2.11 (1.31-3.42)*	0.0023

Abbreviations: BMI, body mass index; WC, waist circumference

Data presented as Hazard Ratio (95% Confidence Interval), * indicates $p<.05$.

Model adjusted for age, year of baseline examination, smoking, alcohol intake, physical inactivity, diabetes, hypertension, hypercholesterolemia, and parental history of cardiovascular disease.

Normal BMI: 18.5 to <25 kg/m^2, Overweight BMI: 25 to <30 kg/m^2, Obese BMI: 30 to <35 kg/m^2.

Table 3.4. Hazard ratios for all-cause mortality between unfit and fit men grouped according to body mass index or waist circumference alone.

	Category	Unfit vs. Fit	*p*-value
BMI	Normal	2.10 (1.56-2.83)*	<.0001
	Overweight	1.41 (1.12-1.76)*	0.0030
	Obese	1.65 (1.22-2.24)*	0.0011
WC	WC < 96.0 cm	1.53 (1.18-1.99)*	0.0012
	WC ≥ 96.0 cm	1.79 (1.48-2.15)*	<.0001

Abbreviations: BMI, body mass index; WC, waist circumference

Data presented as Hazard Ratio (95% Confidence Interval), * indicates $p<.05$.

Model adjusted for age, year of baseline examination, smoking, alcohol intake, physical inactivity, diabetes, hypertension, hypercholesterolemia, and parental history of cardiovascular disease.

Normal BMI: 18.5 to <25 kg/m^2, Overweight BMI: 25 to <30 kg/m^2, Obese BMI: 30 to <35 kg/m^2.

3.5 Discussion

Current obesity risk management guidelines do not recommend that CRF be measured along with BMI and WC [14]. Our primary observation is that for most combinations of BMI and WC, males who were unfit were at significantly higher risk of all-cause mortality than males who were fit. These data suggest that the inclusion of CRF within current BMI and WC models may improve the ability of practitioners to identify males at higher mortality risk within most obesity phenotypes.

That individuals who are unfit are at elevated mortality risk in this study after grouping according to BMI and WC is consistent with a previous report demonstrating the protective effect of CRF on all-cause mortality risk when BMI, WC and/or percent body fat is elevated [30]. Our current findings extend these previous observations, as we have demonstrated the ability of CRF to determine mortality risk across a range of combined BMI and WC groups.

Contrary to our expectation, males who were unfit and overweight with WC ≥100 cm and those who were unfit and obese with WC <110 cm were not at higher mortality risk compared with males who were fit within the same BMI and WC group. This does not appear to be a result of group differences in cardiometabolic risk factors, anthropometric measures, or exercise test results (**Table 3.2**). In fact, the trend for all obesity phenotypes appears to be toward a protective role of CRF (**Table 3.3**). This raises the possibility that with more events the effect of CRF would become statistically significant in these two groups. In agreement with previous reports [27-29], all males grouped as unfit were at increased risk of mortality when CRF was added to BMI or WC alone.

Possible explanations for the protective role of CRF for a given obesity phenotype include lower levels of visceral or ectopic fat, and/or lower values of cardiometabolic risk factors [113]. Visceral (intra-abdominal) fat and ectopic fat depots, such as hepatic fat, have been recognized as being detrimental to cardiometabolic health [12, 114]. Cross-sectional analyses show that for a given BMI, males who are fit

have lower levels of visceral fat and lower cardiometabolic risk factor values than males who are unfit [105, 106]. Individuals who are fit have been shown to have lower total and abdominal fat for a given BMI or WC [50]. Furthermore, for a given WC or amount of visceral fat, CRF is associated with lower values of cardiometabolic risk factors [107]. Finally, it has been demonstrated that physical activity interventions which improve CRF are associated with a reduction in both visceral fat and cardiometabolic risk factors, independent of change in weight [109].

Our findings have implications regarding effective obesity management. Health practitioners who measure CRF have another means beside the weight scale to determine whether a patient has effectively reduced health risk following lifestyle modification. Obesity management guidelines solely focusing on loss of weight and WC imply that a failure to reduce these measurements means that treatment has failed [111]. Although these are important goals, our findings suggest that a patient who improves CRF out of the bottom quintile has substantially reduced their mortality risk, despite no change in BMI or WC category. This provides valuable information to the practitioner regarding patient risk, and a positive message to the patient to continue to practice healthy behaviours rather than discontinue them following failure to achieve weight loss. Patients may be counseled that they do not have to reach the CRF levels of an elite athlete, as the majority of risk reduction attributable to increasing CRF occurs by moving from low to moderate levels, specifically out of the bottom quintile of age-and gender-associated risk [24]. In this way it is encouraging that approximately 150 minutes of weekly physical activity consistent with consensus recommendations is associated with substantial increases in CRF for most adults [115]. In fact, participation in moderate intensity physical activity has been shown to improve CRF in as little as 4 weeks [116]. While direct measurement of CRF may not be feasible in clinic, algorithms have been developed to estimate CRF using routinely collected clinical measures, and are associated with all-cause and CHD mortality [117, 118].

Strengths of the current study include a large, well-characterized cohort [24, 26, 28, 78, 81], with considerable follow-up, providing a large number of mortality events for analysis, as well as objectively measured CRF, BMI, and WC. The use of novel BMI-specific WC thresholds [23] permitted analysis of groups stratified according to BMI, WC, and CRF in combination. These analyses were well controlled for confounding factors, such as age, year of baseline examination, smoking, and physical activity. Furthermore, the exclusion of individuals with pre-existing CVD or cancer, with less than one year of follow-up, and those who failed to reach 85% of maximal predicted exercise test heart rate decreased the likelihood of other factors influencing the observed relationship between CRF and mortality for a given BMI and WC [24, 26].

Limitations of the ACLS cohort are well described [24]. The cohort is predominantly white, well-educated, and from middle to upper socioeconomic stratum. Therefore, caution must be exercised when generalizing these findings to other populations. The homogeneity of this cohort does, however, strengthen the internal validity of the present findings. There were relatively few events in some groups despite large sample size, and our novel classification strategy, thereby preventing analyses involving females, cause-specific mortality, and the classification of CRF across a gradient of low, moderate, and high CRF. Unfortunately, there is a lack of sufficient data concerning medication use or dietary patterns, both of which could confound results. The Ardern BMI-specific WC thresholds were developed using risk of CHD to determine the optimal WC that indicated elevated risk [23]. Whether these thresholds are appropriate for all-cause mortality is uncertain, although our mortality data from ACLS supports this concept for all-cause mortality. Finally, the use of categorical analysis could be viewed as a limitation. We believe that the categorization of BMI and WC in this manner reflects how obesity risk estimation models are typically used in clinical settings, which in fact strengthens the current analysis.

In summary, we report that for most BMI and WC groups, inclusion of CRF identifies males at increased mortality risk after classification according to novel BMI-specific WC values. These observations provide further support for the inclusion of CRF as a routine measure in health care settings to help identify and manage obesity-related risk.

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Chapter 4. General Discussion

To summarize the key findings of the study, we show that males who are unfit are at significantly higher risk of all-cause mortality when compared to males who are fit within most BMI and WC groups. Our findings were not universal for all combinations of BMI and WC, as there was no significant increase in mortality risk in males who were unfit and overweight with high WC, and in males who were unfit and obese with normal WC.

Strengths and limitations of the study have already been stated in the manuscript, but to reiterate we were able to investigate our question using a large, well-studied cohort with a large enough number of events to allow an analysis utilizing three stratifying factors (BMI, WC and CRF). Our analysis would not have been possible without using the Ardern BMI-specific WC thresholds, the use of which also strengthened the analysis because they were derived based on their ability to predict risk of adverse events. Our use of objective measures helps to reduce misclassification bias, and the chosen endpoint of all-cause mortality is rather easy to interpret and appreciate.

Although our cohort was homogenous, this strengthens the internal validity of our findings while making it more difficult to generalize our findings to other non-Caucasian or non-male populations. Although we could not perform the analysis in females, other races or socioeconomic statuses, or using disease-specific mortality, previous publications from this cohort suggest the trends for CRF and mortality will be similar to those described here.

Our research raises some interesting questions concerning BMI, WC, and CRF and mortality. Most prospective studies, including the current analysis, make use of baseline measurements to explain outcomes over potentially long follow-up terms. For some cases in this analysis the length of follow-up spanned almost 30 years. Given the fact that these baseline measurements of BMI, WC, and CRF likely

changed in some way over time, it is somewhat remarkable that we see an association with mortality at all.

To expand on our work, what if we investigated the effects of changes in BMI, WC, and CRF on mortality risk? The literature suggests that changes in CRF are more important for predicting health risk than are changes in BMI. Would it not be compelling if an improvement in CRF was associated with a marked decrease in mortality risk, even in the highest risk individuals with elevated BMI and WC? We could also consider the potentially additive effects of lowering WC and improving CRF with no change in BMI on mortality risk. To demonstrate this would provide strong evidence that weight loss should not be the sole determinant of effective obesity management.

Given that even with a very large cohort in our current study we had few events in some groups using only baseline measures, it may be that any one prospective study would not have enough individuals with serial measurements of BMI, WC, and CRF to conduct such an analysis. I would therefore suggest a pooled analysis using serial BMI, WC, and CRF data from multiple cohorts, and through collaboration investigate the relative contributions of changes in multiple measures of obesity and CRF on risk of all-cause mortality.

As mentioned in the manuscript, our research has implications for how we identify individuals at increased obesity-related risk, and how we manage that risk. To estimate obesity-related health risk, our findings suggest that you must measure CRF to obtain a complete picture of your patient's risk. In other words, if a healthcare practitioner measures BMI and WC to estimate health risk, but neglects CRF, then they haven't finished their job.

To manage obesity-related health risk, CRF gives us another measure to determine whether treatment was effective or not. A scenario has already been presented where an individual who improves CRF but not BMI or WC following intervention has effectively reduced their risk of mortality –

the patient is encouraged to continue in a physically active lifestyle, and the practitioner is armed with the knowledge that they have reduced their patient's risk. Consider an alternative scenario: an individual who has decreased their BMI and WC, but remains unfit, is likely still at elevated risk of all-cause mortality. Without measuring CRF, the healthcare practitioner might wrongfully conclude that they have effectively reduced risk, and fail to continue intervention in a patient who needs it.

With these considerations in mind, and an appreciation for the wealth of evidence supporting the notion that CRF is independently associated with morbidity and mortality regardless of cardiometabolic risk factors, BMI, and WC, an important question presents itself: Why aren't we measuring CRF in healthcare settings?

The American Heart Association has published criteria for the evaluation of novel cardiovascular risk markers. CRF is associated with mortality risk, and improves prediction of mortality risk when added to traditional cardiovascular risk factors. These two observations fulfill the first two requirements for novel risk factors. A novel risk marker must also alter risk enough to change clinical treatment strategy and must improve clinical outcomes – whether the patient management guided by the novel marker results in reduced outcomes compared with conventional care. Whether CRF as a novel risk marker fulfills these last two criteria is unclear – these represent excellent targets for future research.

There is some support for CRF influencing treatment outcomes in the literature. The work of Peter Kokkinos and colleagues has demonstrated that the benefit of having moderate CRF is as effective at reducing mortality risk compared with taking statins to reduce cholesterol, and the combination of CRF and statins was more protective than either alone. This is not to say that CRF should be promoted and statin use discouraged in the prevention of mortality – we should make use of any treatment that provides benefit. I believe that at the very least interventions which improve CRF would provide an effective adjunct treatment to drug therapies and an alternative treatment for those who are precluded

from taking statins. A benefit of CRF is that the physical activity which improves it is very cost-effective, much more so than a drug regimen. Physical activity to improve CRF also has a very low risk of adverse events; with the benefits far outweighing the risks.

Time is an important limiting factor to the implementation of routine measurement of CRF in clinical settings. Maximal exercise testing can be a time-consuming process. For example, using a modified Balke protocol a 25-year old male would have to remain on the treadmill for at least 15 minutes to avoid an unfit classification according to ACLS age- and sex-specific time on treadmill distribution. There simply isn't enough time in a primary care setting to perform these tests.

Fortunately, CRF-prediction algorithms have been developed using directly measured CRF which make use of measures commonly collected during a standard visit with a physician. The components of this algorithm are age, BMI, resting heart rate, and a physical activity index. Furthermore, CRF estimated by this method has been shown to predict long term risk of mortality. Such an algorithm could be used feasibly within a clinical setting, and easily attached to a patient's electronic medical record. The algorithm components are also simple enough that a patient could calculate their own estimated CRF with the help of a web- or mobile-based application. In this manner the patient could also track their own progress in between physician visits rather than waiting for an annual check-up.

Another option may be to refer the exercise test to a licensed kinesiologist, similar to how patients are sent to a dietician for detailed nutritional advice. This option may be better than the algorithm because during the exercise test other variables can be collected such as exercise test heart rate and heart rate recovery, which themselves are associated with health outcomes. As the algorithm only estimates maximal oxygen uptake, these other variables would be missed. Another benefit of referred testing over an algorithm is the reliance of the algorithm on self-reported physical activity, which may be prone to bias.

A final consideration is the mechanism by which CRF attenuates mortality risk, independent of obesity. It is suggested that the harmful effects of obesity are related to the accumulation of VAT and other ectopic fat depots which leads to a pro-inflammatory, insulin resistant state associated with poor metabolic profile. Of the factors associated with CRF, physical activity is the only modifiable behaviour which will increase CRF. It is established that VAT is preferentially reduced in response to physical activity, even in the absence of weight loss. It is therefore possible that the mortality benefit seen in individuals with high CRF is due to the effects of the physical activity which increased CRF rather than the CRF itself.

It is probable that physical activity does not explain all of the risk reduction provided by increased CRF. Prospective data examining the separate influence of CRF and physical activity has shown that these two measures have independent relationships with mortality. Their independence could be due to the fact that physical activity is most often measured by self-report in a prospective setting, while CRF is usually objectively measured by exercise test. Further research using objectively measured physical activity obtained using accelerometers may better elucidate the separate and combined associations of physical activity and CRF with health outcomes.

Cardiac output, a product of heart rate and stroke volume, is the limiting factor which determines an individual's maximal oxygen uptake. It is stroke volume which increases in response to exercise training, allowing more oxygenated blood to be pumped with each heartbeat. It is possible that an increased stroke volume would be protective against mortality in situations where the cardiovascular system is challenged such as myocardial infarction and heart failure. This could provide protective benefit independent of any beneficial metabolic effects of energy expended during physical activity to increase CRF.

In summary, we report that for most BMI and WC groups, inclusion of CRF identifies males at increased mortality risk after classification according to novel BMI-specific WC values. Although further research is required, our findings provide further support for the inclusion of CRF as a routine measure in health care settings to help identify and manage obesity-related risk.

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Appendices

Appendix 1. Example of Cooper Clinic consent form for the Aerobics Center Longitudinal Study.

DISCLOSURE AND CONSENT
MEDICAL AND SURGICAL PROCEDURES

TO THE PATIENT: You have the right, as a patient, to be informed about your condition and the risks and hazards involved in the recommended surgical, medical, or diagnostic procedure to be used. You may then make the decision whether or not to undergo the procedure. This disclosure is not meant to scare or alarm you; it is simply an effort to make you better informed so you may give or withhold your consent to the procedure.

CONSENT

I voluntarily consent and authorize Dr. _____, as my Cooper Clinic physician, and such technical assistants and other health care providers as he may deem necessary, to administer an exercise stress test.

Just as there may be risks and hazards in continuing any present condition without treatment, there may also be risks and hazards related to the performance of this procedure. I realize that common to many surgical, medical, and diagnostic procedures is the potential for infection, blood clots in veins and lungs, hemorrhage, allergic reaction, and even death. In addition, I realize that the following risks and hazards may also occur in connection with this particular procedure: disorders of heart rhythm, fall in blood pressure, heart attack.

For the purpose of aiding medical research, I permit the Institute for Aerobics Research and the Cooper Clinic to accumulate and analyze data relating to my evaluation and to contact me for follow-up information regarding my health status in the future.

I have been given an opportunity to ask questions about the procedure and the risks and hazards involved, and I believe that I have sufficient information to give this informed consent. I certify this form is clear to me, that I have read it or have had it read to me, and that I understand its contents.

SIGNATURE: _____
PATIENT OR LEGALLY RESPONSIBLE PERSON

DATE: _____ **TIME:** _____

WITNESS: _____