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Cardiorespiratory fitness and body mass index are related to morbidity and mortality (Manson, 1996). There is a preponderance of evidence supporting this relation in men (Gibbons, 1983; Blair, 1989, 1995,1996; Lee,I, 1993; Barlow, 1995; Kampert, 1996; Dorn, 1997; Lee, C, 1999). The evaluation of the stated risk factors have been virtually unexplored in a cohort of women. The aim of this study is to evaluate whether higher levels of cardiorespiratory fitness attenuate the risk of all-cause mortality in overweight and obese women. In this prospective study, the study population consisted of 7572 women ages 20-89 years, who had a medical examination and achieved at least 85% of their age-adjusted maximal heart rate during a maximal treadmill test were followed for 69,979 woman-years. After adjustment for age, exam year, health status and smoking status, unfit women had a higher risk of all-cause mortality across BMI categories [RR 1.70 95% CI (1.18, 2.43)]. The benefits of cardiorespiratory fitness significantly decrease the risk of all-cause mortality. These data suggest that considering BMI alone is not as an informative predictor of all-cause mortality in women as the concurrent consideration of cardiorespiratory fitness.

CARDIORESPIRATORY FITNESS, BODY MASS INDEX

AND ALL-CAUSE MORTALITY IN WOMEN,

ACLS 1970-1994

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CARDIORESPIRATORY FITNESS, BODY MASS INDEX

AND ALL-CAUSE MORTALITY IN WOMEN,

AEROBICS CENTER LONGITUDINAL STUDY

1970-1994

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INTRODUCTION

Cardiovascular disease remains the leading cause of death of women in the United States and other industrialized countries (Manson,1996). Risk factors associated with cardiovascular disease are highly prevalent in American women, and risk factor reduction is important for women of all ages. Attenuation of progression, and possibly regression of atherosclerosis, through risk factor reduction can occur through an elderly age, which can lessen coronary morbidity and/or mortality.

Risk factors associated with cardiovascular disease include cigarette smoking, hypertension, hypercholesterolemia, glucose intolerance and diabetes mellitus, obesity and body fat distribution, physical activity and cardiorespiratory fitness, as well as less understood risk factors, including hormone replacement therapy, number of pregnancies, alcohol consumption and psychosocial factors.

The trends for physical inactivity and obesity in women should cause alarm. As reported by the Behavior Risk Factor Surveillance System in 1992, 35.8 % of women 18+ years reported no participation in leisure time activity, and the prevalence for physical inactivity is increasing. As a result of physical inactivity, weight gain and obesity develop (Manson, 1996). Unfortunately, obesity is not the endpoint. Obesity greatly increases risks for many serious, chronic morbid conditions, such as hypertension, diabetes mellitus and lipid abnormalities (Manson, 1990). The 26-year follow-up of Framingham data determined obesity to be an independent predictor of cardiovascular disease, particularly among women (Hubert, 1993). It is clearly associated with increased risk for mortality (Solomon, 1997).

Overweight and obesity have traditionally been determined by body mass index (BMI kg/m^2). Overweight is defined as a BMI 25- <30 kg/m^2 and obesity as a BMI > 30 kg/m^2 for women. The rationale for these definitions is based on epidemiological data that show increases in mortality with BMI's above 25 kg/m^2 (National Institutes of Health, 1998). The BMI measurement, however, may not be an accurate measurement of adiposity. One person who is physcially fit and has a lean body mass, may have the same BMI as a person who is unfit with a greater fat-mass. According to the 1998 weight guidelines as determined by the National Institutes of Health, both may be considered obese. Cardiorespiratory fitness is an important mortality predictor and may possibly be confounding the relationship between BMI and mortality (Lee, 1998).

Cardiorespiratory fitness, as measured by maximal treadmill exercise testing, shows a strong, graded, and consistent relationship with lower mortality rates in both men and women, a relationship that is not due to confounding by age or other risk factors (Blair, 1989). This evidence continues to pique researchers' interest regarding cardiorespiratory fitness. Several researchers at the Cooper Institute in Dallas, Texas have initiated studies to further determine the effects of BMI and physical fitness as well as body composition and physical fitness on morbidity and mortality. To date, most studies have included only male subjects. The limited number of women's studies have unstable risk estimates due to low numbers of participants, misclassification due to self-reported data and few deaths during the study period.

Clearly, there is a preponderance of epidemiologic reports regarding cardiovascular risk factors and morbidity and/or mortality in men. Explanations for the exclusion of women are many and diverse (Manson, 1996, p388). The fact remains, that the number one killer of American women is cardiovascular disease and epidemiologic studies must be conducted as recommended by the 1994, Physical Activity and Health Report of the Surgeon General.

The present report aims has several strengths. First, the data presented is unique in that the exposures and outcomes have not been analyzed in a well-designed manner in women. Second, the cohort of women has been expanded from previous ACLS analyses (Blair, 1989). Third, there is minimal bias due to direct assessment of exposures, confounding factors and disease through a clinical medical examination. Fourth, the prospective design allows for extended follow-up time in which chronic disease can develop. Extended follow-up also allows for a larger sample; thereby removal of participants having less than one-year of follow-up can be excluded from analysis. Finally, the prospective design of this study can elucidate a temporal relationship between exposures and mortality.

The results presented in this report are ultimately intended to not only initiate further research regarding cardiorespiratory fitness across BMI stratum and mortality in women, but initiate further research regarding women's health in general.

REVIEW OF LITERATURE

Only recently, has the validity of the US weight guidelines in determining specific outcomes, such as mortality, been challenged. According to the U.S. weight guidelines, healthy weights for men and women are defined as having a body mass index (BMI kg/m^2) from 18.5-25 kg/m^2 (National Institutes of Health, 1998). This measurement alone may not be an accurate predictor of true body fatness or mortality. As a result, these guidelines can be misleading. It is difficult to know how much of the higher morbidity and mortality seen in overweight and obese individuals is due to elevated weight and how much is due to physical inactivity and low-fitness (Blair, 1999). Previous reports, such as the following continue to pique interest in the relation between body mass index, cardiorespiratory fitness and mortality. The first report to be published including specific analyses designed to evaluate the relation of cardiorespiratory fitness across BMI categories and mortality (Barlow, 1995) will be reported later in this review.

Material chosen for this review focuses on the following question: "Do higher levels of cardiorespiratory fitness attenuate risk all-cause mortality in the overweight and obese?" Studies on men will be included due to the limited number of studies regarding women and the specific exposures and outcomes of interest. Outcome variables included in this review include cardiovascular disease mortality and all-cause mortality. Exposure variables include body habitus (BMI) and cardiorespiratory fitness.

The first of these papers, published in 1989, by Blair et al, evaluated the relation of cardiorespiratory fitness to mortality in a prospective cohort of healthy men and women. All participants received a preventive medical examination at the Cooper Clinic in Dallas, Texas during 1970-1981. Those included in the study were residents of the US, had a complete examination, achieved 85% of their age-predicted maximal heart rate on a treadmill exercise test at the baseline clinic visit and were free of known physician diagnosed disease. Fit men and women tended to have lower all-cause mortality rates than unfit individuals in each BMI stratum. The highest mortality rate occurred in individuals from the lowest BMI category, < 20 kg/m^2. Adjustments were made for age, serum cholesterol level, blood pressure, smoking habit, fasting blood sugar, family history of CHD. A significant strength of this study is the direct assessment of exposure and disease during the clinical examination. The sample size of women was small and few deaths reported results in unstable risk estimates. Only one BMI category ($\geq$ 26.9) was used in evaluation of all-cause mortality.

A report published in December, 1993, by IM Lee et al., investigated the nature of the relation between body weight and all-cause mortality in a cohort of men from the Harvard Alumni Study. Participants included 19,297 Harvard alumni who responded to questionnaires and were free of physician-diagnosed disease. In these prospective data, body weight and mortality in men were directly related [BMI $\geq$ 26.0, RR 1.18, 95% CI (1.08-1.28)] even after adjustment for age, smoking and physical activity. Lowest mortality was observed among men weighing 20 % below the US average for men of comparable age and height. BMI was calculated by self-reported measurement, which may have introduced bias. This study failed to account for cardiorespiratory fitness.

Investigators examined the association between BMI and both overall mortality and mortality from specific causes in a cohort of 115,195 women enrolled in the prospective Nurses Health Study (Manson, 1995). The women were aged 30-55, free of known cardiovascular disease and cancer in 1976, and provided data on height and weight in a mailed questionnaire. Questionnaires were mailed every two years to update information. A sub-sample of women was chosen to be weighed in order to validate reported weights by participants. Reported weights were highly correlated with measure weights (Spearman r = 0.96) although they averaged 1.5 kg (3.3 lbs) lower than measured values. Results indicate that body weight and mortality from all-causes are directly related. There was an increased risk with an increase in each BMI category, but the inverse was not significant until BMI was $\geq$32.0 (RR 1.5, 95% CI 1.3-1.7). The lowest mortality rate was observed in women who had a BMI < 19 kg/m^2, which is 15 % less than the U.S. average. Adjustments were made for age, smoking status, menopausal status, oral contraceptive use and postmenopausal hormone use and parental history of myocardial infarction before the age of 60. Again, cardiorespiratory fitness was not considered.

Up to this point, cardiorespiratory fitness has not been considered as a confounding factor in relation to BMI and mortality. As stated earlier, Barlow's, 1995 report, presented the first report designed to evaluate the relation of cardiorespiratory fitness to mortality in individuals classified as normal, overweight and obese, based on

BMI. Participants included men who completed a preventive medical examination at the Cooper Clinic in Dallas, Texas from 1970 to 1989. Those participants with prior history of disease were stratified into an unhealthy group. BMI calculation and physical fitness were assessed as a part of the preventive medical examination. Results suggested that moderate to high levels of cardiorespiratory fitness protects against the increased mortality that is associated with overweight and obesity in men. Moderate to high fit men in BMI categories of ≥27-30 and >30 had lower death rates than their low-fit counterparts. Inverse gradients of mortality across fitness groups were similar for obese and non-obese men. The associations remain after controlling for confounding factors (age, BMI, resting blood pressure, total cholesterol, fasting blood glucose, cigarette smoking and health status). The results supported the hypothesis that moderate to high levels of fitness protect against the increased mortality associated with overweight and obesity.

The Cooper Institute investigators also have evaluated the relationship between changes in physical fitness and the risk of mortality (Blair,1995). The cohort included 9777 healthy and unhealthy men aged 20-82 who completed at least two preventive medical examinations at the Cooper Clinic in Dallas, Texas, from December, 1979 to December, 1989. Unhealthy men had one or more of the following conditions: abnormal resting and exercising electrocardiograms, history of myocardial infarction, stroke, diabetes, or hypertension at both examinations. The investigators observed a reduction in the mortality risk in the total population of men who maintained or improved fitness. The reduction was observed in both healthy and unhealthy men. Men who were initially unfit had a 44 % lower age-adjusted risk of all-cause mortality [RR 0.56, 95 % CI (0.41-0.75)] and a 52 % lower age-adjusted risk of cardiovascular disease mortality [RR 0.48, 95 % CI (0.31-0.74)]. This study did control for several confounding factors. It however, did not relate BMI categories and fitness with mortality. The results do demonstrate that risk can be reduced even at older ages and in those with significant morbidity.

During the summer of 1996, Blair et al proposed to quantify the relation of cardiorespiratory fitness to cardiovascular disease mortality and all-cause mortality within strata of other personal characteristics that predispose to premature mortality (Blair, 1996). In this prospective cohort study, cardiovascular disease and all-cause death rates were presented for low, moderate and high fitness categories by smoking habits, cholesterol level, blood pressure, and health status. Participants included both men and women. Results indicated several independent predictors of mortality among men including low fitness [RR 1.52, 95 % CI (1.28-1.82)]. The only statistically significant predictors of mortality in women were low fitness [RR 2.10, 95 % CI (1.36-3.21)] and smoking [RR 1.99, 95 % CI (1.25-3.17)]. Moderate fitness appears to protect against the influence of the other predictors on mortality as was initially proposed by Barlow in 1995. According to this study, BMI of ≥ 27 kg/m^2 was not an independent predictor of cardiovascular disease mortality and all-cause mortality in women. The sample of women in this report is too small and few deaths have been recorded for reliable analysis.

Kampert re-examined the association between physical activity, physical fitness and mortality in an expanded cohort of men and women in the ACLS. Although results are reported regarding physical activity and cancer mortality, only all-cause mortality among men and women by fitness categories will be reported here as it specifically relates to my research. Low-fit (lowest quintile of fitness) men and women had much higher death rates than did more physically fit individuals. The greatest difference in death rates is between the lowest (referent) group and highest fitness groups, with the most fit groups having a death rate that is > 50 % lower than among less fit individuals [men, RR = 0.52, 95 % CI (0.36-0.74) and women, RR = 0.36, 95 % CI (0.15-0.90)]. Adjustments were made for baseline differences in age, examination year, cigarette smoking, chronic illnesses and electrocardiogram abnormalities. BMI was not considered in this analysis.

Other investigators have investigated the relationship between BMI and mortality. One such study is The Buffalo Health Study, which initially began in 1960. Approximately 2273 men and women aged 15-96, from the general population of Buffalo, New York, were enrolled to study hypertension. In January of 1997, Dorn et al investigated the long-term relationship between BMI and mortality from all causes and specific causes. This study focuses on the 29-year follow-up, after exclusion criteria are met, of 611 white men and 697 white women aged 20-96 and free from known disease at baseline. Results indicate that men < 65 years of age exhibit an association between the highest BMI quartile (>27.5) and all-cause mortality and cardiovascular mortality. Men over age 65 did not exhibit a similar association. There is no association between BMI categories and all-cause mortality and cardiovascular disease mortality in women. However, there was a significant association between BMI quartile 4 (27.1-48.3) and coronary heart disease mortality. All analyses were adjusted for age, education, cigarettes smoked and mean arterial blood pressure. A significant limitation of this study is potential misclassification related to the self-reported data, particularly BMI data. In addition, BMI data was collected only at baseline. No other measurements over time were taken. Once again, cardiorespiratory fitness has not been considered as a confounding factor. The unique strength of this study is the random selection of participants of the general population of Buffalo, New York. The researchers purported that controlling for physical activity is a strength of their study, despite the fact that confounding due to cardiorespiratory fitness is not considered.

The remaining studies regarding all-cause and cardiovascular disease mortality are further analyses of the Aerobic Center Longitudinal Study. Lee et al investigated the validity of the 1995 U.S. weight guidelines, while considering cardiorespiratory fitness in the ACLS male cohort. After adjustment for age, examination year, cigarette smoking, and alcohol intake, fit, overweight men (BMI $\geq$ 27.8) had a similar rate of all-cause mortality as physically fit men of normal weight (BMI 19.0 to < 25.0) and had a lower risk of all-cause mortality than unfit and normal weight men. Fit men of normal weight (referent group) had the lowest cardiovascular disease mortality while unfit and overweight men experienced the highest cardiovascular disease mortality [RR 2.24, 95 % CI (1.68-2.98)]. Unfit men had substantially higher cardiovascular disease mortality than fit men in each BMI group.

The final study to be reviewed in regard to all-cause mortality and cardiovascular disease mortality investigates body composition. Although, this study goes beyond the scope of my research it lends further support for the need to conduct more advanced research in women, as well as other underrepresented populations. As several studies have mentioned in their limitations, the measurement of obesity is often a factor of concern. In most previous studies, BMI has been considered a surrogate of fatness or adiposity. In August of 1998, Lee et al examined the health benefits of leanness and the hazards of obesity while simultaneously considering cardiorespiratory fitness. The hypothesis initially stated has been strongly supported. Moderate to high cardiorespiratory fitness not only across BMI categories, but also across body composition categories attenuates the risk of all-cause and cardiovascular disease mortality in men. Although most researchers have agreed that obesity is related to a multitude of adverse health effects or health hazards and leanness is generally associated with health benefits, lean men in this study had decreased mortality risk only if they were fit. There is an increased mortality risk for unfit men across all body composition categories. This report purports that obesity does not increase mortality in fit men. Cardiorespiratory fitness truly attenuates the risk of all-cause and cardiovascular disease mortality across body composition categories in men. Adjustments were made for age, examination year, cigarette smoking, alcohol intake and parental history of IHD.

Purpose of this study

This study further analyzes data from the extended Aerobics Center Longitudinal Study (ACLS, 1970-1994) at the Cooper Institute in Dallas, Texas. The intention of this study is to evaluate whether or not higher levels of cardiorespiratory fitness attenuate risk for cardiovascular mortality and all-cause mortality in overweight and obese women.

Hypotheses

1. Women who have a BMI 18.5 - <25.0 and are fit will have the lowest all-cause mortality.

2. Women who have a BMI 25.0 - <30.0 and are fit will have a lower all-cause mortality than women who are unfit in the same BMI category.

3. Women who have a BMI ≥ 30.0 and are fit will have a lower risk of all-cause mortality than women who are unfit in the same BMI category.

4. Women who have a BMI ≥ 30.0 and are unfit will have the highest mortality of all BMI categories and fitness groups.

5. Unfit women in all BMI categories will be at a significantly higher risk of all-cause mortality than their fit counterparts.

6. All-cause mortality will increase with an increase in BMI in both fit and unfit women, respectively.

7. Women having a BMI 18.5-<25.0 who are unfit will have a higher risk of all-cause mortality than women having a BMI 25.0-<30 who are fit.

METHODS

Research Design

This observational study uses a prospective cohort design.

Study participants

Study participants included 7572 women, aged 20-89 years at baseline who completed a preventive medical examination at the Cooper Institute in Dallas, Texas, between December 6, 1970 and December 31, 1994. All study participants were residents of the United States, had complete data from the medical examination, and achieved at least 85% of their age-predicted maximal heart rate (220-age in years) during the treadmill test. Patients not achieving maximal heart rate standard were presumed to be more likely to have pre-existing disease. These conditions would be associated with poorer treadmill test performance and higher risk of death during follow-up. Thus excluding patients with these characteristics attempts to reduce the chance of finding a spurious inverse relationship between fitness and mortality. Approximately 5964 (79%) study participants were apparently healthy at baseline. Women determined to be healthy at baseline had normal resting and exercising electrocardiograms, and no history or evidence of myocardial infarction, stroke, diabetes or hypertension. The 1608 unhealthy women are reported to have one or more of the stated conditions.

Clinical Examination

The baseline evaluation was performed after participants gave their informed written consent for the medical examination and subsequent registration in the follow-up study. The protocol was reviewed and approved annually by the Institutional Review Board. Examinations followed an overnight fast of at least 12 hours and included a personal and family health history, physical examination, a questionnaire on demographic characteristics and health habits, anthropometry, resting ECG, blood chemistry analysis, blood pressure measurement, and a standard maximal exercise test on a motor driven treadmill. All procedures were administered by technicians who followed a standard manual of operations.

Height and body mass were measured on a standard physician's scale and stadiometer. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. [The non-metric conversion formula is calculated as weight in pounds divided by the square of the height in inches multiplied by 704.5.] Subjects were assigned body mass index categories of normal, overweight or obese. These categories correspond to a body mass index 18.5-<25, 25-<30, or > 30, respectively, as specified in1999, by the National Institutes of Health. Cardiorespiratory fitness was measured by using a maximal treadmill exercise test. Treadmill speed was set initially at 88 m/min, the grade was 0% for the first minute, 2% for the second minute, and increased 1% until 25 minutes. After 25 minutes, the grade did not change and speed was measured 5.4 m/min each minute until test termination. Patients were given encouragement to give maximal effort. Total treadmill test time in seconds was the variable used in the analysis. Treadmill time from this protocol is highly correlated with measured maximal oxygen uptake in women (r = .94), which is the most widely accepted index of cardiorespiratory fitness (Blair,1989). Additional examination procedures are published elsewhere (Blair,1989).

Women in the least fit 20% of each age group were classified as physically unfit, and all others as physically fit. All subjects were cross-tabulated by cardiorespiratory fitness level across body mass index categories as follows: 1) normal and fit, 2) normal and unfit, 3) overweight and fit, 4) overweight and unfit, 5) obese and fit, or 6) obese and unfit. The normal and fit group are the comparison group. Additonal analysis reviewed each body mass index category and fitness level as separate indicators of mortality.

Mortality Surveillance

All participants were followed from the baseline examination to the date of death or to 31 December, 1994. The average length of follow-up from the date of baseline examination to the date of death is ~9 years. The observational period included 69, 979 of woman-years of follow-up experience. Deaths among study participants were identified from the National Death Index, and official death certificates of decedents were obtained from the department of vital records in the respective state. The analysis reported is based on 139 deaths among women. The underlying cause of death was coded by a nosologist according to the *International Classification of Diseases* (revised 9th edition, US Government Printing Office, Washington, 1979), with cardiovascular disease (CVD) defined as codes 390-449.9.

Statistical Analysis

Baseline descriptive statistics (mean, standard deviation and frequency) of study participants were performed using univariate and frequency procedures for continuous and categorical variables respectively. This analysis was performed by cross-tabulating body mass index and fitness level, health status, fitness level and body mass index, as well as body mass index and fitness level separately. Crude death rates were calculated to identify an elevated risk of cardiovascular disease, cancer and all-causes of the ACLS female study participants. These rates disregard differences existing between race, age, gender, or other confounding variables. This rate was calculated by dividing the number of deaths from the stated diseases by the total woman-years of follow-up for that disease, and multiplying by 10,000 woman-years. All-cause death rates per 10,000 woman-years (for which a woman-year is 1 woman followed for 1 year) of follow-up, adjusted for age and exam year, were calculated across body mass index and cardiorespiratory fitness categories. Proportional hazards regression was used to examine the associations among cardiorespiratory fitness, body mass index and all-cause mortality. The relative risks (RRs) of all-cause mortality were estimated after adjustment for age and examination year and further adjustment for health status. Women who were normal weight and physically fit were selected as the reference category. The 95% confidence intervals were calculated for each RR. All procedures were performed with Statistical Analysis Systems (SAS) software.

RESULTS

During an average of 9 years of follow-up (69,979 woman-years), there were 139 deaths: 38 from cardiovascular disease, 70 from cancer and 31 from other causes. Baseline characteristics of the subjects across body mass index and cardiorespiratory fitness level are shown in Table 1. Unfit women had a slightly higher body mass index than their fit counterparts with normal, overweight and obese categories [.5, .4, 1.4 higher respectively]; treadmill times were progressively lower in unfit women, indicating lower cardiorespiratory fitness across normal, overweight and obese categories. Fit and normal women had the highest average estimated maximal aerobic power (861.2 seconds), whereas obese and unfit women had the lowest average estimated maximal aerobic power (371.3 seconds).

Table 1 Baseline characteristics (mean ± SD) by body mass index (kg/m^2) and cardiorespiratory fitness level in women

Body Mass Index Category	Normal (18.5-<25)		Overweight (25-<30)	
Fitness level	Fit	Unfit	Fit	Unfit
n	5183	776	826	307
Apparently healthy at baseline (%)	4364(84)	539(69)	606(73)	189(62)
Follow-up (mean woman-years)	9.8±5.1	11.7±5.8	8.0±4.9	10.4±5.9
Follow-up (total woman-years)	47098	9056	6609	3191
Age (years)	42.9±10.7	45.0±10.8	48.6±11.6	47.0±11.0
Height (inches)	64.8±2.3	64.4±2.2	64.2±2.5	64.2±2.4
Weight (pounds)	127.7±13.0	129.3±13.5	157.8±14.8	160.1±14.2
Treadmill time (seconds)	861.2±252.3	427.6±120.1	684.8±186.0	391.5±118.6
BMI (kg/m^2)	21.4±1.7	21.9±1.7	26.9±1.4	27.3±.1.4

continued Table 1

Body mass index category	Obese (>30)		All
Fitness level	Fit	Unfit	
n	194	286	7572
Apparently healthy at baseline (%)	103(53)	163(57)	5964(79)
Follow-up (mean woman-years)	7.4±4.4	9.0±5.6	9.2±5.3
Follow-up (total woman-years)	1445	2580	69979
Age (years)	49.9±12.0	45.2±11.5	44.2±11.1
Height (inches)	63.8±3.1	64.1±2.7	64.6±2.4
Weight (pounds)	193.5±24.7	203.0±30.4	137.1±24.4
Treadmill time (seconds)	623.2±165.2	372.3±123.4	753.9±285.0
BMI (kg/m^2)	33.3±3.4	34.7±4.4	23.1±4.0

Baseline characteristics of women across body mass index categories are shown in Table 2. Women in the normal (18.5-<25 kg/m^2) category had the lowest average body mass index (21.5 kg/m^2), as compared to their counterparts in the overweight and obese categories (27.0 kg/m^2 and 34.1 kg/m^2, respectively). Treadmill times were progressively lower as body mass index increased, indicating lower cardiorespiratory fitness across normal, overweight and obese categories. Normal women had the highest average estimated maximal aerobic power (804.8 seconds), whereas obese women had the lowest estimated maximal aerobic power (473.7 seconds).

Table 2 Baseline characteristics (mean ± SD) by body mass index (kg/m^2)

Body mass index category	Normal (18.5-<25)	Overweight (25-<30)	Obese (>30)	All
n	5959	1133	480	7572
Apparently healthy at baseline (%)	4903(82)	795(70)	266(55)	5964(79)
Follow-up (mean woman-years)	9.4±5.2	8.6±5.3	8.4±5.2	9.2±5.3
Follow-up (total woman-years)	56154	9800	4025	69979
Age (years)	43.2±10.7	48.2±11.5	47.0±11.9	44.2±11.1
Height (inches)	64.7±2.3	64.2±2.5	64.0±2.9	64.6±2.4
Weight (pounds)	127.9±5.0	158.4±14.7	199.1±28.6	137.1±24.4
Treadmill time (seconds)	804.8±280.3	605.3±214.5	473.7±187.8	753.9±285.0
BMI (kg/m^2)	21.5±1.7	27.0±1.4	34.1±4.1	23.1±4.0

Baseline characteristics for women across cardiorespiratory fitness level are shown in Table 3. Unfit women had a higher body mass index than their fit counterparts (3.3 kg/m^2 higher); treadmill times were lower in the unfit women indicating lower cardiorespiratory fitness. Fit women had a higher average estimated maximal aerobic power (830.3 seconds), whereas unfit women had a low average of estimated maximal aerobic power (408.0 seconds).

Table 3 Baseline characteristics (mean ± SD) by cardiorespiratory fitness level

Fitness category	Fit	Unfit	All
n	6203	1369	7572
Apparently healthy at baseline (%)	5073(82)	891(65)	5964(79)
Follow-up (mean woman-years)	8.9±5.0	10.8±5.9	9.2±5.3
Follow-up (total woman-years)	55152	14827	69979
Age (years)	43.9±11.1	45.5±11.0	44.2±11.1
Height (inches)	64.7±2.4	64.3±2.4	64.6±2.4
Weight (pounds)	133.8±20.2	151.6±34.5	137.1±24.4
Treadmill time (seconds)	830.3±252.2	408.0±122.3	753.9±285.0
BMI (kg/m^2)	22.5±3.2	25.8±5.6	23.1±4.0

Crude death rates per 10,000 woman-years were calculated to identify an elevated risk of cardiovascular disease, cancer and all-cause mortality. These rates disregard differences existing between age, race, or other confounding variables. Crude death rates across body mass index categories are shown in Table 4. Unfit women had a higher crude death rate as compared to fit women across normal, overweight and obese categories (27%, 10%, 8% higher, respectively). Interestingly, the crude death rate decreased in the overweight unfit group and increased again in the obese unfit group. Further analysis is needed to determine reason for this pattern.

Table 4 Crude death rates per 10,000 woman-years by body mass index (kg/m^2) and cardiorespiratory fitness level

	Deaths *n*	Woman-Years	Crude Death Rate/10,000
Normal (18.5-<25)			
Fit (n=5183)	65	47,098	14
Unfit (n=776)	37	9056	41
Overweight (25-<30)			
Fit (n=826)	12	6609	18
Unfit (n=307)	9	3190	28
Obese (>30)			
Fit (n=194)	5	1445	35
Unfit (n=286)	11	2580	43

Crude death rates per 10,000 woman-years were calculated specifically for cardiovascular disease, cancer and all-cause mortality across body mass index categories which are shown in Table 5. Deaths from cardiovascular disease, cancer and all-causes were greatest in the obese (>30 kg/m^2) category. Lower death rates were observed in each subsequently lower body mass index category for deaths from cancer and all-causes. Although previous studies have indicated a progressive increase in mortality across body mass index categories, a decrease is shown in the overweight (25->30 kg/m^2) category of women.

Table 5 Crude death rates per 10,000 woman-years by body mass index category (kg/m^2)

	Normal (18.5-<25)		
	Deaths *n*	Woman-years	Crude Death Rate /10,000
CVD	27	56154	5
CA	50	56154	9
All-causes	102	56154	18
	Overweight (25-<30)		
CVD	4	9800	4
CA	12	9800	12
All-causes	21	9800	21
	Obese (>30)		
CVD	7	4025	17
CA	8	4025	20
All-causes	16	4025	40

Crude death rates per 10,000 woman-years were also calculated by cardiorespiratory fitness category as shown in Table 6. Cardiovascular disease, cancer and all-cause mortality rates were lower in the fit women as compared to their unfit counterparts, exhibiting a 3-fold decrease in cardiovascular disease, a 2-fold decrease in cancer, as well as a 2-fold decrease in deaths from all-causes.

Table 6 Crude death rates per 10,000 woman-years by cardiorespiratory fitness level

	Fit			Unfit		
	Deaths *n*	Woman-years	Crude death rate/10,000	Deaths *n*	Woman-years	Crude death rate/10,000
CVD	20	55152	4	18	14827	12
CA	48	55152	8	25	14827	17
All-causes	82	55152	15	57	14827	38

Further calculation determined crude rates per 10,000 woman-years for all-causes across BMI categories by health status and fitness category as shown in Table 7 and Table 8. Healthy-unfit women have a two-fold increased mortality rate across BMI categories as compared to their healthy-fit counterparts. Unhealthy women have a less well-defined benefit of fitness as BMI increases due to few deaths.

Table 7 Crude death rates per 10,000 woman-years of follow-up for all-causes across body mass index (kg/m^2) categories by healthy status at baseline and fitness level

Health status	Healthy					
Fitness level	Fit			Unfit		
Body mass index category	Deaths *n*	Woman -years	Crude death rate /10,000	Deaths *n*	Woman -years	Crude death rate /10,000
Normal (18.5-<25)	47	46390	10	17	7255	23
Overweight (25-<30)	8	5614	14	5	2372	21
Obese (<30)	0	845	0	3	1688	18

Table 8 Crude death rates per 10,000 woman-years of follow-up for all-causes across body mass index (kg/m^2) categories by unhealthy status at baseline and fitness level

Health status	Unhealthy					
Fitness level	Fit			Unfit		
Body mass index category	Deaths *n*	Woman -years	Crude death rate /10,000	Deaths *n*	Woman-years	Crude death rate /10,000
Normal (18.5-<25)	18	8027	22	20	2936	68
Overweight (25-<30)	4	1944	21	4	1284	31
Obese (<30)	5	800	63	8	1297	62

Table 9 presents all-cause mortality rates for cardiorespiratory fitness levels across body mass index categories. Cox proportional hazard regression analysis, adjusted for age, and examination year, showed that fit women had lower death rates than did their unfit counterparts within normal, overweight and obese categories. Unfit normal women had twice the risk of all-cause mortality as did normal, fit women and also had higher risk than overweight and fit as well as obese and fit categories (2.5, 1.5 higher respectively). The all-cause mortality rate of overweight-fit women, and obese-fit women were not significantly different than the normal-fit women. The all-cause mortality of normal-unfit women was significantly different [RR = 2.07, 95% CI (1.37, 3.11)] from that of normal-fit women. No significant difference was observed in the overweight-unfit women [RR = .86, 95% CI (.46, 1.60)] as compared to the normal-fit women. The RR in the overweight-fit women suggests little difference by fitness or due to a higher BMI . Again, a significant difference was observed in the obese-unfit women [(RR = 2.29, 95% CI (1.21, 4.35)] and the normal-fit women. To evaluate further possible bias of confounding factors at baseline, another multivariate model was constructed to adjust for health status and smoking status (Table 9). The results for the multivariate analysis were similar after adjustment. Exclusion of women with less than one year of follow-up made little difference in the results (not shown).

Table 9 Body mass index and relative risks (RR) of all-cause mortality by cardiorespiratory fitness level

Body Mass Index Category and Cardiorespiratory Fitness Level		Woman -years	Deaths *n*	RR of Death (95% CI)[1]	Multivariate RR of Death (95% CI)[2]
Normal (18.5-<25)					
Fit	n=5183	47,098	65	1.00	1.00
Unfit	n=776	9056	37	†2.07 (1.37, 3.11)	†1.92 (1.27, 2.90)
Overweight (25-<30)					
Fit	n=826	6609	12	.86 (.46, 1.60)	.85 (.46, 1.58)
Unfit	n=307	3190	9	1.02 (.50, 2.08)	.96 (.47, 1.96)
Obese (>30)					
Fit	n=194	1445	5	1.51 (.60, 3.78)	1.44 (.57, 3.64)
Unfit	n=286	2580	11	†2.29 (1.21, 4.35)	†2.11 (1.12, 4.02)

[1] Adjusted for age (single year) and examination year.
[2] Adjusted for age (single year), examination year, health status, and smoking status.
† Indicates significance at the .05 level

DISCUSSION

It has been well documented that the relation between body mass index and mortality exists in both men and women. However, few studies have reported the association between cardiorespiratory fitness across body mass index categories and mortality in men and virtually none in women. This report is the first of its kind to evaluate this important relationship.

The major finding is that fitness does attenuate the risk of mortality across body mass indices. Significance was only achieved in the normal-unfit and obese-unfit women as compared to the referent group (normal-fit). The overweight group statistics as a whole was somewhat perplexing. Crude death rates for women indicated an increased risk in mortality progressively, but did not continue to support that trend through the Cox proportional hazard regression analysis. The relative risk in this group shows no difference than the normal weight group and no difference by fitness level. Further analysis is needed to investigate this possible spurious inverse association.

The following hypotheses were supported in these data: 1) women who have a BMI 18.5-<25.0 and are fit have the lowest all-cause mortality, 2) women who have a BMI >30.0 and are fit will have a lower risk of all-cause mortality than women who are unfit in the same BMI category and 3) women who have a BMI >30.0 and are unfit have the highest mortality of all BMI categories and fitness groups. The following hypotheses were not supported by significant findings: 1) the relative risks suggest that women having a BMI 25.0-<30.0 and are fit have a lower all-cause mortality than women who are unfit in the same category, 2) unfit women in only the normal and obese categories were at a significantly higher risk of all-cause mortality; the overweight-unfit women category suggested a lower risk of all-cause mortality, and 3) this study failed to report an increased risk in all-cause mortality in unfit women having a recommended BMI 18.5-<30 as compared to fit women having a BMI 25.0-<30 as was reported in men by Blair et al, 1995.

Some important limitations affect the validity of this report. The primary limitation existing is the small number of deaths recorded to date for women in the ACLS. Another follow-up is needed to possibly support the hypotheses which were not shown to be significant in this report. Other limitations include the sample of women participating in the ACLS were predominantly caucasian and of middle and upper socioeconomic levels. On the other hand, the homogeneity of this group reduces the likelihood of confounding by socioeconomic characteristics (Lee, 1999). Baseline health status is a concern of longitudinal studies. In order to reduce the bias of pre-existing disease, all participants were given a complete medical exam at the inception of the study. Those who did not meet inclusion criteria as stated earlier were eliminated. Further elimination of selection bias involved the elimination of women with less than one year of follow-up. BMI as a measurement of obesity remains controversial and can be considered a limitation. Discrimination between fat-mass and fat-free mass is indeed necessary to truly determine the idea of overweight and obesity and was not considered in this report.

The idea that cardiovascular disease is a man's disease is no longer valid. Cardiovascular disease is not only the number one killer of all men in the United States. It is also the number one killer of women. It is time to regard women's cardiovascular health with the same seriousness as has been given to men's health. Recognition as a public health problem is needed to support further research regarding women's health and promulgating policies to support this effort.

Many of the risk factors are modifiable. Many also have different effects on women as compared to men (Manson, 1996). Women need be aware of these issues in order to make informed decisions. Without research, education and cardiovascular prevention programs, women will continue to be uninformed and misinformed of the implications of the risk factors related to cardiovascular disease morbidity and mortality. Special attention needs to be made regarding the unique effects of some risk factors for cardiovascular disease, which just cannot be observed in men.

In summary, data reported here suggest that cardiorespiratory fitness attenuates the risk of all-cause mortality in women. All women should be encouraged to increase their cardiorespiratory fitness level by engaging in regular, moderate intensity physical activity. This type of exercise aims to benefit all women, even if remaining overweight. Other investigations regarding cardiorespiratory fitness across body mass indices and mortality in women are suggested to further support this claim.

APPENDIX

Table 1 Baseline characteristics (mean ± SD) by body mass index (kg/m^2) and cardiorespiratory fitness levels in women, ACLS, 1970-1994.

Variable	Normal (18.5-<25)		Overweight (25-<30)		Obese (>30)		All
Fitness category	Fit	Unfit	Fit	Unfit	Fit	Unfit	
n	5183	776	826	307	194	286	7572
Apparently healthy at baseline (%)	4364(84)	539(69)	606(73)	189(62)	103(53)	163(57)	5964(79)
Follow-up (mean woman-years)	9.8±5.1	11.7±5.8	8.0±4.9	10.4±5.9	7.4±4.4	9.0±5.6	9.2±5.3
Follow-up (total woman-years)	47098	9056	6609	3191	1445	2580	69979
Age (years)	42.9±10.7	45.0±10.8	48.6±11.6	47.0±11.0	49.9±12.0	45.2±11.5	44.2±11.1
Height (inches)	64.8±2.3	64.4±2.2	64.2±2.5	64.2±2.4	63.8±3.1	64.1±2.7	64.6±2.4
Weight (pounds)	127.7±13.0	129.3±13.5	157.8±14.8	160.1±14.2	193.5±24.7	203.0±30.4	137.1±24.4
Treadmill time (seconds)	861.2±252.3	427.6±120.1	684.8±186.0	391.5±118.6	623.2±165.2	372.3±123.4	753.9±285.0
Serum glucose (mg/dL)	93.2±11.0	93.6±10.3	98.1±19.1	100.7±23.9	103.1±18.3	106.1±34.3	94.8±14.9
Triglycerides (mg/dL)	81.6±79.3	97.5±70.3	119.8±90.8	125.2±73.6	150.0±117.8	141.4±90.8	93.4±83.6
Total cholesterol (mg/dL)	200.2±44.3	208.3±41.1	220.4±44.2	216.4±44.2	225.2±41.5	217.1±44.9	205.3±44.7
Systolic BP (mmHg)	110.8±13.9	114.4±16.7	117.3±14.8	117.7±15.0	124.2±16.4	123.0±15.7	113.0±14.9
Diastolic BP (mmHg)	74.4±9.1	76.1±10.2	78.0±9.0	77.6±9.3	82.8±10.0	81.9±10.1	75.6±9.6
BMI (kg/m^2)	21.4±1.7	21.9±1.7	26.9±1.4	27.3±1.4	33.3±3.4	34.7±4.4	23.1±4.0
Drinks per week #	3.1±4.7	2.7±4.6	2.2±4.1	2.2±4.6	2.0±6.5	1.4±4.2	2.8±4.7
Hydrostatic percent fat	24.0±7.0	27.5±8.1	34.2±6.3	34.7±7.0	40.3±5.2	40.8±5.4	26.4±8.4
Skinfold percent fat	24.0±5.6	25.9±5.9	33.0±4.7	33.3±5.4	36.8±3.9	36.9±4.5	26.3±6.8
Waist girth (cm)	60.1±22.6	65.1±20.8	73.4±26.0	73.5±27.4	84.5±28.5	86.0±31.4	64.5±24.5
Hip girth (cm)	92.5±6.2	90.1±3.8	104.5±5.5	103.3±12.5	119.6±10.1	118.6±8.1	98.5±11.1
Systolic BP (≥140 mmHg) %	4.3	7.7	7.6	8.5	18.6	15.4	6.0
Serum glucose (≥126mg/dL) %	.5	.5	2.8	3.9	7.2	7.7	1.3
Inactive %	26.6	65.5	37.8	61.9	45.9	61.0	35.1
Family history CVD %	25.1	27.0	32.7	25.4	32.0	30.8	26.5
Family history hypertension %	13.4	7.7	16.5	10.7	25.8	14.7	13.4
Family history diabetes %	9.2	3.9	17.3	10.4	16.5	14.7	10.0
Family history congenital HD %	6.0	7.7	6.2	7.5	4.0	7.5	6.3
Family history stroke %	24.1	24.5	20.2	21.5	20.1	23.4	23.5
Abnormal resting ECG %	1.5	4.3	3.3	4.2	4.1	4.2	2.3
Present smoker %	10.9	21.8	7.4	15.7	5.7	15.5	11.8
Past smoker %	33.3	30.4	34.3	30.7	30.6	26.4	32.9

Table 2 Baseline characteristics (mean ± SD) of women by body mass index (BMI-kg/m^2), ACLS, 1970-1994.

Body Mass Index Category	Normal (18.5-25)	Overweight (25-30)	Obese (>30)	All
n	5959	1133	480	7572
Apparently healthy at baseline (%)	4903(82)	795(70)	266(55)	5964(79)
Follow-up (mean woman-years)	9.4±5.2	8.6±5.3	8.4±5.2	9.2±5.3
Follow-up (total woman-years)	56154	9800	4025	69979
Age (years)	43.2±10.7	48.2±11.5	47.0±11.9	44.2±11.1
Height (inches)	64.7±2.3	64.2±2.5	64.0±2.9	64.6±2.4
Weight (pounds)	127.9±5.0	158.4±14.7	199.1±28.6	137.1±24.4
Treadmill time (seconds)	804.8±280.3	605.3±214.5	473.7±187.8	753.9±285.0
Serum glucose (mg/dL)	94.9±124.6	98.8±20.5	104.9±28.9	94.8±14.9
Triglycerides (mg/dL)	83.6±78.4	121.2±86.6	144.8±102.5	93.4±83.6
Total cholesterol (mg/dL)	201.2±44.0	219.4±44.2	220.4±43.7	205.3±44.7
Systolic BP (mmHg)	111.3±14.3	117.5±14.9	123.5±16.0	113.0±14.9
Diastolic BP (mmHg)	74.6±9.4	77.9±9.1	82.2±10.1	75.6±9.6
BMI (kg/m^2)	21.5±1.7	27.0±1.4	34.1±4.1	23.1±4.0
Drinks per week #	3.1±4.7	2.2±4.2	1.6±5.3	2.8±4.7
Hydrostatic percent fat	24.4±7.3	34.3±6.5	40.6±5.3	26.4±8.4
Skinfold percent fat	24.3±5.6	33.0±4.8	36.8±4.3	26.3±6.8
Waist girth (cm)	61.4±22.5	73.4±26.4	85.4±30.2	64.5±24.5
Hip girth (cm)	92.3±6.1	104.4±5.9	119.0±8.8	98.5±11.1
Systolic BP (≥140 mmHg) %	4.8	7.9	16.7	6.0
Serum glucose (≥126mg/dL) %	.5	3.1	7.5	1.3
Inactive %	31.7	44.3	55.0	35.1
Family history CVD %	25.3	30.7	31.3	26.5
Family history hypertension %	12.6	14.9	19.2	13.4
Family history diabetes %	8.5	15.5	15.4	10.0
Family history congenital HD %	6.3	6.6	6.2	6.3
Family history stroke %	34.3	34.1	36.7	23.5
Abnormal resting ECG %	1.9	3.5	4.2	2.3
Present smoker %	12.3	9.5	11.5	11.8
Past smoker %	32.9	33.4	28.1	32.9

Table 3 Baseline characteristics (mean ± SD) by cardiorespiratory fitness level in women, ACLS, 1970-1994.

Fitness category	Fit	Unfit	All
n	6203	1369	7572
Apparently healthy at baseline (%)	5073(82)	891(65)	5964(79)
Follow-up (mean woman-years)	8.9±5.0	10.8±5.9	9.2±5.3
Follow-up (total woman-years)	55152	14827	69979
Age (years)	43.9±11.1	45.5±11.0	44.2±11.1
Height (inches)	64.7±2.4	64.3±2.4	64.6±2.4
Weight (pounds)	133.8±20.2	151.6±34.5	137.1±24.4
Treadmill time (seconds)	830.3±252.2	408.0±122.3	753.9±285.0
Serum glucose (mg/dL)	94.2±13.0	97.9±21.6	94.8±14.9
Triglycerides (mg/dL)	89.0±84.2	113.2±78.0	93.4±83.6
Total cholesterol (mg/dL)	203.8±44.5	212.0±42.8	205.3±44.7
Systolic BP (mmHg)	112.1±14.4	117.0±16.5	113.0±14.9
Diastolic BP (mmHg)	75.1±9.3	77.7±10.3	75.6±9.6
BMI (kg/m^2)	22.5±3.2	25.8±5.6	23.1±4.0
Drinks per week #	2.9±4.7	2.3±4.5	2.8±4.7
Hydrostatic percent fat	25.5±8.0	31.0±9.1	26.4±8.4
Skinfold percent fat	25.6±6.5	30.0±7.2	26.3±6.8
Waist girth (cm)	63.3±23.9	71.7±26.4	64.5±24.5
Hip girth (cm)	97.5±9.9	104.8±15.3	98.5±11.1
Systolic BP (≥140 mmHg) %	5.2	9.5	6.0
Serum glucose (≥126mg/dL) %	1.0	2.8	1.3
Inactive %	28.7	64.0	35.1
Family history CVD %	26.3	27.5	26.5
Family history hypertension %	14.2	9.8	13.4
Family history diabetes %	10.5	7.6	10.0
Family history congenital HD %	6.0	7.5	6.3
Family history stroke %	23.5	23.6	23.5
Abnormal resting ECG %	1.8	4.4	2.3
Present smoker %	10.3	19.1	11.8
Past smoker %	33.4	29.4	32.9

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