Fitness, fatness, and estimated coronary heart disease risk: the HERITAGE Family Study

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ABSTRACT

KATZMARZYK, P. T., J. GAGNON, A. S. LEON, J. S. SKINNER, J. H. WILMORE, D. C. RAO, and C. BOUCHARD. Fitness, fatness, and estimated coronary heart disease risk: the HERITAGE Family Study. *Med. Sci. Sports Exerc.*, Vol. 33, No. 4, 2001, pp. 585–590. **Purpose:** To determine the contributions of fatness and fitness to the estimated risk of future coronary heart disease (CHD). **Methods:** The sample consisted of 212 black and 411 white adult sedentary participants. Percent body fat (%BF) was measured using densitometry, whereas maximal oxygen uptake ($\dot{V}O_{2max}$) was measured on a cycle ergometer. Risk of future CHD was estimated using the revised Framingham Heart Study algorithm. **Results:** For fatness, the odds ratios for risk of future CHD were 1.83 and 1.70 for the moderate and high tertiles, respectively, compared with the low tertile. Similarly, the odds ratios for $\dot{V}O_{2max}$ were 1.29 (NS) and 1.62, for the moderate and low tertiles, respectively. Removing $\dot{V}O_{2max}$ from the full model had no effect; however, removing %BF resulted in a significantly weaker model ($\chi^2 = 10.38$, $P < 0.01$). **Conclusion:** Both fatness and fitness are important predictors of risk of future CHD, based on the Framingham index. **Key Words:** RISK FACTORS, ADIPOSE TISSUE, OBESITY, AEROBIC FITNESS, PREDICTION, CARDIOVASCULAR DISEASE

There is considerable evidence that a sedentary lifestyle, poor aerobic fitness, and associated excess body fatness are risk factors for coronary heart disease (CHD). The report of the U.S. Surgeon General on Physical Activity and Health (32) summarized the evidence linking both physical activity and aerobic fitness to CHD risk, while recent publications by the World Health Organization (36) and the U.S. National Institutes of Health (22) have highlighted the current world-wide epidemic of obesity and its impact on health and longevity. Given that CHD is the leading cause of death in the United States (33) and Canada (12), and that people with a favorable CHD risk profile live longer and have significantly lower medical insurance costs later in life than those with an unfavorable risk profile (9), investigating the relationships between the risk of CHD and potentially modifiable risk factors, including fitness and fatness, are important research directions.

There is controversy as to the independent effects of fatness and physical fitness on mortality or CHD risk. There is evidence that overweight and obesity are associated with a greater risk of all-cause mortality (3,8) and mortality from cardiovascular diseases (CVD) (18,28). On the other hand, high physical fitness levels are associated with lower risk of CVD mortality (4,26) and of CHD in particular (31), whereas an increase in cardiorespiratory fitness resulted in a reduction in CVD mortality risk in men in one study (5). Further, it has been suggested that high physical fitness levels, even in overweight individuals, are protective in terms of all-cause mortality (2,16,17), and low fitness, but not an elevated BMI ($\geq$27 kg·m^{-2}), is associated with an increased risk of death from CVD disease (10). Unfortunately, most studies of the effects of fitness and fatness on mortality or risk of CHD have relied on proxy measures of body fatness or fitness such as body mass index or predicted maximal oxygen consumption.

The purpose of the study was to examine the influences of body fatness and aerobic fitness on risk of future CHD in the HERITAGE Family Study. Percent body fat (%BF) was measured using hydrostatic weighing, whereas maximal oxygen uptake ($\dot{V}O_{2max}$) measured during maximal exercise tests was the indicator of cardiorespiratory, or aerobic, fitness. Risk of future CHD was estimated using the recently published algorithms of the Framingham Heart Study (35). All participants were sedentary for at least 6 months, providing a certain control over physical activity levels that could modify the relationships among fatness, fitness, and CHD risk.

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TABLE 1. Physical characteristics of the sample.

	Black		White	
	Mean	SD	Mean	SD
Men				
N	83		207	
Age (yr)	35.5	11.0	39.4	14.1*
Stature (cm)	175.8	6.5	177.5	6.2*
Body mass (kg)	85.5	15.2	85.6	16.1
BMI ($kg \cdot m^{-2}$)	27.6	4.5	27.2	4.9
Body fat (%)	23.8	6.9	24.0	8.0
$\dot{V}O_{2max}$ ($L \cdot min^{-1}$)	2.7	0.5	3.0	0.6*
Smoking (%)	12.0		17.9	
Leisure Time Activity Index (1 to 4)	1.9	0.5	2.2	0.5
CHD Risk Index	1.5	2.8	2.3	3.3*
Women				
N	129		204	
Age (yr)	33.6	10.3	37.4	13.1*
Stature (cm)	162.4	6.6†	164.0	6.5*†
Body mass (kg)	74.9	17.3†	67.7	13.5*†
BMI ($kg \cdot m^{-2}$)	28.4	6.2	25.2	4.8*†
Body Fat (%)	36.4	8.4†	30.8	9.8*†
$\dot{V}O_{2max}$ ($L \cdot min^{-1}$)	1.8	0.4†	1.9	0.3*†
Smoking (%)	17.1		15.7	
Leisure Time Activity Index (1 to 4)	2.0	0.6	2.3	0.4
CHD Risk Index	−4.6	6.9†	−4.0	7.7†

* $P < 0.05$ between races, within sex.
† $P < 0.05$ between male and female subjects, within race.

METHODS

Sample

The HERITAGE Family Study was designed to investigate the genetics of cardiovascular, metabolic, and hormonal responses to aerobic exercise training and the contribution of regular exercise to changes in risk factors for cardiovascular disease and type II diabetes. The participating research centers consisted of four clinical centers: Indiana University, Laval University, University of Minnesota, University of Texas, and a data coordinating center at Washington University (St. Louis). Recruitment of participants was based on extensive publicity and advertisements at the clinical centers. The essential criteria for participation in the HERITAGE Family Study included being between the ages of 17 and 65 yr, healthy but sedentary (no regular physical activity over the previous 6 months), body mass index (BMI) under 40 $kg \cdot m^{-2}$, and systolic/diastolic blood pressures less than 159/99 mm Hg. Further, individuals with confirmed or possible CHD, chronic or recurrent respiratory problems, and uncontrolled endocrine and metabolic disorders (including diabetes and the use of lipid-lowering drugs) were also excluded from the study. The sample considered here includes 212 black and 411 white participants who were 20 yr of age and older for whom the appropriate measures were available. Sample sizes by sex and race are provided in Table 1.

Measures

The study personnel were centrally trained on all aspects of recruitment and measurement protocols by using a specially prepared manual of procedures. Data quality was assured through an extensive quality control program (11).

Aerobic Fitness

Two progressive maximal exercise tests were conducted on separate days on an Ergometrics 800S cycle ergometer from SensorMedics (Yorba Linda, CA) connected to a SensorMedics 2900 metabolic cart. Heart rate was monitored using an electrocardiogram. Gas exchange parameters ($\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}E$, and RER) were recorded as a rolling average of 20-s intervals. In the first test, participants exercised at a power output of 50 W for 3 min, followed by increases of 25 W each 2 min until they reached volitional fatigue. For older, smaller, or less fit individuals, the test was started at 40 W, with increases of 10–20 W each 2 min thereafter. For the second test, participants exercised for 10–12 min at a power output of 50 W and at a relative power output of 60% $\dot{V}O_{2max}$ for 10–12 min, followed by 3 min at a relative power output of 80% $\dot{V}O_{2max}$. Resistance was increased to the highest power output attained in the first test, and if the participant was able to pedal after 2 min, power output was increased each 2 min thereafter until volitional exhaustion. The criteria for $\dot{V}O_{2max}$ were a RER > 1.1, plateau of $\dot{V}O_2$ (change <100 $mL \cdot min^{-1}$ in the last three 20-s intervals), and a heart rate within 10 $beats \cdot min^{-1}$ of predicted maximal heart rate. All participants achieved $\dot{V}O_{2max}$ by one of these criteria on at least one of the two tests. The average $\dot{V}O_{2max}$ from the two tests was taken as $\dot{V}O_{2max}$ for each participant if the two values were within 5% of one another. If they differed by more than 5%, the higher value was used. Reproducibility of $\dot{V}O_{2max}$ in these participants is quite high, with an intraclass correlation of 0.97 for repeated measures and a coefficient of variation of 5% (30).

Body Fatness

Stature and body mass were measured to the nearest mm and 0.1 kg, respectively, using a standing balance beam scale and a stadiometer. The BMI ($kg \cdot m^{-2}$) was derived. Percent body fat (%BF) was determined from measurements of body density from underwater weighing, with a correction made for residual lung volume by the oxygen dilution technique (34) at three of the clinical centers, or the helium dilution technique (21) at the fourth clinical center (Laval University Clinical Center). Relative body fat was estimated from body density using the equations of Siri (29) for Caucasian men, Lohman (19) for Caucasian women, Schutte et al. (27) for black men, and Ortiz et al. (23) for black women.

CHD Risk

Resting systolic and diastolic blood pressures were measured twice on separate days in the morning (before 11:00 a.m.) in the postabsorptive state. Measurements were made in a quiet room with the participant reclined at a 45° angle, with legs elevated. Blood pressure was determined after a 5-min rest period using a Colin STBP-780 automated unit (San Antonio, TX) while the technician wore ear phones to confirm the values.

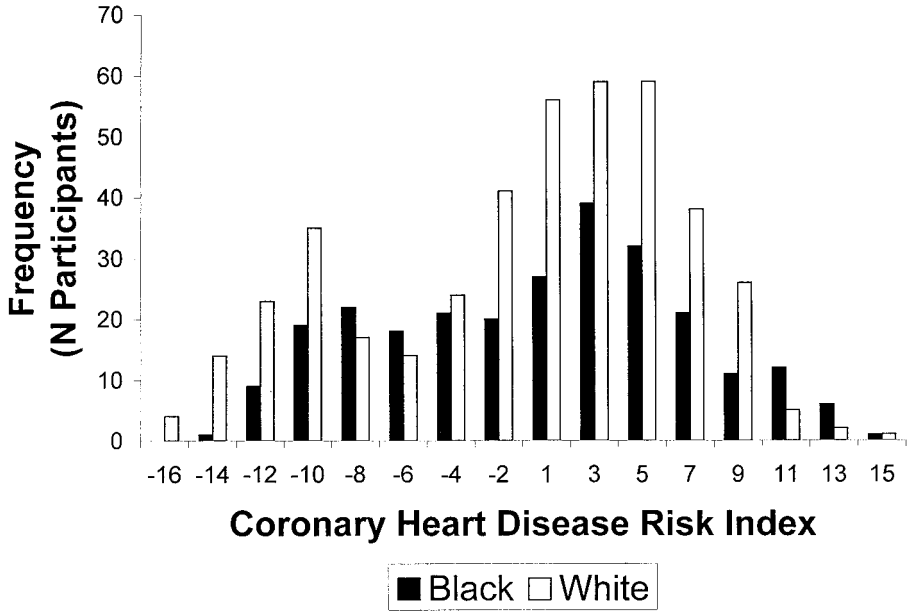

FIGURE 1—Frequency distribution of the CHD risk index (CHDRI) in adults (≥20 yr) of the HERITAGE Family Study.

Fasting (12 h) blood samples were obtained from an antecubital vein and collected into Vacutainer tubes containing EDTA. For women, samples were obtained in the early follicular phase of the menstrual cycle. Plasma was ultracentrifuged and the top fraction containing VLDL was quantitatively recovered. The low density lipoprotein (LDL) in the ultracentrifuged bottom fraction was precipitated with heparin and $MgCl_2$ (7,20), and the high density lipoprotein (HDL) was obtained in the supernatant. The concentrations of cholesterol in the lipoprotein fractions were measured by autoanalyzer (Technicon RA-500, Bayer, Tarrytown, NY). All assays were conducted in the Lipid Core Laboratory at Laval University (11), and the repeatability of repeat assays based on split samples was quite high, with intraclass correlations exceeding 0.95 for both HDL-C and LDL-C (24).

A CHD risk index (CHDRI) was computed using the recently modified algorithms derived from Framingham Heart Study follow-up data (35). The algorithm estimates CHD risk from age, plasma levels of LDL-C, HDL-C, blood pressure, presence of absence of diabetes, and smoking status by using separate prediction equations for male and female subjects. The algorithm was developed from 12-yr follow-up data on 2489 men and 2856 women (Caucasian), 30–74 yr of age, in the Framingham Heart Study and utilizes the fifth Joint National Committee (JNC) blood pressure and National Cholesterol Education Program (NCEP) cholesterol categories. Participants were assigned a score for each of age, LDL-C, HDL-C, blood pressure, diabetes status, and smoking status. One of the exclusion criteria for the HERITAGE Family Study was diabetes requiring medication for blood glucose control, so all participants were assigned a zero score for this variable. Although developed on adults 30–74 yr of age, the algorithm was applied to all adults over the age of 20 yr in the present study, and 20- to 29-yr-olds were assigned the same age score as 30- to 34-yr-olds. The validity of coding 20- to 29-yr-olds as having the same age-associated risk as 30- to 34-yr-olds is unknown; however, this seemed the most logical approach to take. The CHDRI ranges from −17 to +14 in the HERITAGE cohort with a bimodal distribution (Fig. 1). In male subjects, those with a CHDRI of less than −3 have a 1% 10-yr risk of CHD, whereas someone with a score of 14 and above has a greater than 56% 10-yr CHD risk. In female subjects, someone with a CHDRI of less than minus 2 has a 1% 10-yr risk of CHD, whereas someone with a CHDRI above 17 has a greater than 32% 10-yr risk of CHD (35).

Covariates

Several covariates were obtained on the participants. Smoking status was assessed as part of a personal history questionnaire, whereas menopausal and hormone replacement therapy status were obtained for all women using a menstrual history questionnaire. To be eligible for participation in the HERITAGE Family Study, participants had to be sedentary (physically inactive) for at least 6 months before the study. However, the ARIC-BAECKE questionnaire (1, 25) was used to estimate habitual leisure time physical activity levels within the sedentary range of activity.

Statistical Analyses

%BF and $\dot{V}O_{2max}$ were adjusted for the effects of sex, age, and smoking status (0 = no, 1 = yes) by using regression procedures, whereas $\dot{V}O_{2max}$ was further adjusted for body mass. Briefly, sex-specific forward stepwise regressions, retaining terms significant at the 5% level, were used. Up to a cubic polynomial in age was allowed (and in body mass in the case of $\dot{V}O_{2max}$), and the standardized (zero mean and unit variance) residuals were retained for further analysis. Briefly, in male subjects, a full cubic polynomial in age explained 25% of the variance in %BF, whereas age, age^2, mass and mass^2 explained 44% of the variance in

$\dot{V}O_{2max}$. In female subjects, age explained 18% of the variance in %BF, while age^2 and mass accounted for 34% of the variance in $\dot{V}O_{2max}$. Smoking status did not enter as a significant predictor in any of the regressions.

The CHDRI was divided into two groups using the median as the cut-off. The probability of the upper group (high risk) was modeled from body fatness and aerobic fitness using logistic regression. %BF and $\dot{V}O_{2max}$ were divided into tertiles (low, moderate, and high), and odds ratios were computed from the parameters of the logistic regression models for the moderate and high tertiles of body fatness, setting the low category as the reference. Similarly, odds ratios for moderate and low aerobic fitness were calculated after setting the high category as the reference. The total sample was analyzed together, with race (0 = black, 1 = white) and leisure time physical activity (2 = low, 1 = moderate, 0 = high) as covariates. Given that age, sex, and smoking status are factored into the CHDRI, these covariates were not included in the final logistic regression models; rather %BF, and $\dot{V}O_{2max}$ were adjusted for the covariates beforehand using regression procedures as described above. Sex-specific analyses were conducted with menopausal (0 = premenopausal, 1 = menopausal, 2 = postmenopausal) and hormone replacement therapy (0 = no, 1 = yes) status included in the model for female subjects.

To examine the contribution of aerobic fitness and body fatness to the explanation of CHD risk, a series of general and reduced (constrained) models were compared using the likelihood ratio test. General models that included both body fatness and aerobic fitness were developed, and these models were constrained by removing either the indicator of body fatness or the indicator of aerobic fitness. The difference between the -2 ln L of the two models (general and constrained) is distributed asymptotically as a χ^2 statistic with degrees of freedom equal to the number of parameters constrained. All analyses were performed using SAS procedures.

RESULTS

Descriptive statistics, along with significant sex and race differences, are provided in Table 1. The white sample was older, taller, and had a higher mean $\dot{V}O_{2max}$ than the black sample. Further, white women had a lower body mass, BMI, and %BF than black women, and white men had higher CHDRIs than black men. Black women were significantly shorter and had a lower mean body mass, $\dot{V}O_{2max}$, and CHDRI than black men; however, the women had higher %BF. Among whites, women differed from men in almost every variable, with the exception of age, smoking prevalence, and leisure time physical activity.

Body fatness and aerobic fitness were significant contributors to predictions of risk for future CHD (Table 2). The odds ratios for indicators of fatness increased from the low to the high tertiles, with an odds of 1.70 for the high tertile, respectively. The odds ratios for $\dot{V}O_{2max}$ also were significant, within odds ratio of 1.62 for the low tertile compared with the high tertile. The odds ratio for race was also significant (2.22), indicating increased risk to white participants. The odds for leisure time activity also was significant, with a risk ratio of 1.31, indicating that higher levels of physical activity reduce risk of future CHD, based on the CHDRI.

TABLE 2. Odds ratios from the multiple logistic regression models predictiing risk for future CHD from indicators of body fatness and aerobic fitness.

	Odds Ratio	95% CI
Percent body fat		
Low	1.00	
Moderate	1.83	(1.23–2.73)
High	1.70	(1.13–2.58)
$\dot{V}_{2max}$		
High	1.00	
Moderate	1.29	(0.86–1.94)
Low	1.62	(1.05–2.52)
Race	2.22	(1.52–3.27)
Leisure Time Index	1.31	(1.05–1.64)

Categories of Race: 0 = black, 1 = white.
Categories of the Leisure Time Index: 0 = high, 1 = moderate, 2 = low.

The relative strength of the contributions of fatness and fitness to the explanation of CHD risk was examined using maximum likelihood. A general model which included both fatness and $\dot{V}O_{2max}$ was compared with reduced models that contained only the indicator of fatness, or only $\dot{V}O_{2max}$. Based on the χ^2 statistic, removing fatness from the model (aerobic fitness only) significantly changed the fit of the model ($\chi^2 = 10.38$, $P < 0.01$). However, removing $\dot{V}O_{2max}$ from the model did not produce a significant effect ($\chi^2 = 4.78$, NS).

The results of the sex-specific regressions are provided in Table 3. The models for women included menopausal and hormone replacement therapy status as covariates. In general, the results for men and women parallel the results for the combined sample. In both men and women, the odds ratios for %BF increased from the low to the moderate and high categories, whereas the odds ratios for $\dot{V}O_{2max}$ in the sex-specific analyses increased from the high to low categories (Table 3).

DISCUSSION

Typically, studies of the relationship between fatness, fitness, and CHD risk have relied on the BMI as the index of adiposity and an estimate of maximal oxygen consumption, usually derived from a submaximal exercise test. Strengths of the present study include the use of directly

TABLE 3. Odds ratios for prediction of risk of future CHD from indicators of body fatness and aerobic fitness in men and women.

	Men[a] (N = 290)	Women[b] (N = 333)
Percent body fat		
Low	1.00	1.00
Moderate	2.47 (1.27–4.93)	1.67 (0.80–3.52)
High	3.27 (1.52–7.48)	1.86 (0.89–3.97)
$\dot{V}_{2max}$		
High	1.00	1.00
Moderate	1.27 (0.63–3.09)	1.25 (0.59–2.65)
Low	1.39 (0.63–3.09)	1.99 (0.94–4.35)

[a] Odds ratios adjusted for race and leisure time physical activity level.
[b] Odds ratios adjusted for race, leisure time physical activity level, menopausal, and hormone replacement therapy status.

measured maximal oxygen consumption and body fatness measured using underwater weighing as indices of fitness and fatness, respectively. Further, physical activity levels were controlled for at the outset of the study by recruiting only sedentary participants.

The results indicate that both fatness and aerobic fitness are important determinants of risk for future CHD. The odds ratios for %BF and $\dot{V}O_{2max}$ are similar and appear to be equally good predictors of CHD risk, based on the traditional comparison of odds ratios. The use of maximum likelihood methods indicated that the removal of $\dot{V}O_{2max}$ from a model containing %BF and $\dot{V}O_{2max}$ did not appreciably alter the fit of the model to the data; however, removing %BF from the model changed it significantly (Table 2). In other words, the inclusion of fatness significantly improved upon a model that contained only fitness, whereas fitness did not improve the prediction once fatness was accounted for.

The results emphasize the importance of including information about both physical fitness and body fatness in the assessment of CHD risk. Being physically fit reduces the risk of all-cause mortality, even in the face of overweight, based on categories of BMI (3,18). Further, based on measurements of body fatness from underwater weighing, one recent study has demonstrated that the health benefits of leanness are limited to fit men, as all-cause and CVD mortality risks were lower in obese fit men than in lean unfit men (16).

The purpose of this study was not to compare physical activity and physical fitness in terms of CHD risk as others have done (13,31) because participants in the HERITAGE Family study were sedentary by design. This provided a certain control over leisure time physical activity levels in the study of relationships between fitness, fatness, and CHD risk but could underestimate the effects of physical activity in defining risk. However, within the range of sedentary activity levels, the leisure time physical activity index remained a significant predictor of CHD risk, with an odds ratio of 1.31 (Table 2). The odds ratios for physical activity; however, should not be compared with those for fitness or fatness due to the selection criteria of the study; physical activity should be regarded as a covariate only.

White men had a significantly higher CHDRI than black men; means of 2.3 versus 1.5, respectively (Table 1). The CHDRI was also higher in white women (−4.0) than in black women (−4.6), but the difference is not significant. The odds ratio for race was significant at 2.22 (Table 2), indicating that white participants are at increased CHD risk over black participants, after adjustment for fitness, fatness, and leisure time physical activity. These estimates are based on conventional risk factors for CHD, and the CHDRI was developed using a sample of white men and women (35). Rates of CHD mortality are generally lower in black than white men in the United States (14) and, except for cholesterol levels, which were a significant predictor in white men, risk factors for CHD mortality were similar in black and white men (14). In the present study, white participants had more than twice the risk of black participants of having a CHDRI in the upper half of the distribution, after adjustment for fitness, fatness, and physical activity. The relationship between the CHDRI and future CHD risk has not been established in the North American black population; thus, it is difficult to generalize the findings of the present study to this ethnic group. It is also difficult to speculate about the significant race effect observed in the CHDRI and racial differences in the future incidence of CHD without further study of the CHDRI in samples of black participants followed prospectively for CHD incidence.

The present study estimated the contribution of indicators of fitness and fatness to the prediction of future CHD risk, based on an algorithm of risk factor categories (35). This, of course, is not the same as predicting hard endpoints such as acute myocardial infarction or death from CHD. However, receiver operating curve analyses indicated that the risk factor category model effectively predicted CHD in the Framingham cohort (35), and previous CHD risk prediction models from the Framingham Heart study have been shown to be accurate in a U.S. national cohort (15) and the Western Collaborative Group Study (6).

In summary, both body fatness and aerobic fitness were found to be important determinants of a CHD risk index derived from established risk factors. Further work is required to elucidate these relationships by using direct measures of body fatness and aerobic fitness in large population based samples.

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