Targeting the Metabolic Syndrome with Exercise: Evidence from the HERITAGE Family Study

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ABSTRACT

KATZMARZYK, P. T., A. S. LEON, J. H. WILMORE, J. S. SKINNER, D. C. RAO, T. RANKINEN, and C. BOUCHARD. Targeting the Metabolic Syndrome with Exercise: Evidence from the HERITAGE Family Study. *Med. Sci. Sports Exerc.*, Vol. 35, No. 10, pp. 1703–1709, 2003. **Purpose:** To determine the efficacy of exercise training in treating the metabolic syndrome. **Methods:** The sample included 621 black and white participants from the HERITAGE Family Study, identified as sedentary and apparently healthy (no chronic disease or injury). The metabolic syndrome was defined as having three or more risk factors according to the guidelines of the National Cholesterol Education Program, including elevated waist circumference, blood pressure, triglycerides, blood glucose, and low HDL cholesterol. The presence of the metabolic syndrome and component risk factors were determined before and after 20 wk of supervised aerobic exercise training. **Results:** The prevalence of the metabolic syndrome was 16.9% in this sample (105/621) of apparently healthy participants. Of the 105 participants with the metabolic syndrome at baseline, 30.5% (32 participants) were no longer classified as having the metabolic syndrome after the exercise training. Among the 32 participants who improved their metabolic profile, 43% decreased triglycerides, 16% improved HDL cholesterol, 38% decreased blood pressure, 9% improved fasting plasma glucose, and 28% decreased their waist circumference. There were no sex or race differences in the efficacy of exercise in treating the metabolic syndrome: 32.7% of men, 28.0% of women, 29.7% of black, and 30.9% of white participants with the metabolic syndrome were no longer classified as having the syndrome after training. **Conclusion:** Aerobic exercise training in patients with the metabolic syndrome can be useful as a treatment strategy and provides support for a role for physical activity in the prevention of chronic disease.

Key Words: PHYSICAL ACTIVITY, AEROBIC TRAINING, CHOLESTEROL, BLOOD PRESSURE, WAIST CIRCUMFERENCE

A major new feature of the U.S. National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) recommendations for the reduction of high blood cholesterol is the emphasis on aggressively targeting individuals with multiple risk factors for treatment due to their substantially increased risk for coronary artery disease (27). Indeed, results from the Multiple Risk Factor Intervention Trial (MRFIT) indicate that the risk of cardiovascular disease mortality increases with the number of risk factors that a person has (1). The metabolic syndrome is a constellation of multiple hypertension, dyslipidemia, and diabetes risk factors that cluster together and increase the risk of Type 2 diabetes, coronary artery disease, and premature mortality. According to the operational definition provided by the NCEP ATP III, an individual has the metabolic syndrome if three or more of high blood pressure, high blood glucose, high plasma triglycerides, low HDL cholesterol, and high waist circumference are present (27). The metabolic syndrome is a prevalent condition in North America, as recent estimates indicate that 24% and 23% of U.S. men and women, respectively (8), and 17% and 13% of Canadian men and women, respectively (2), have the metabolic syndrome as recently defined by the NCEP ATP III (27). Thus, there is a need to develop efficacious and effective lifestyle strategies to combat the metabolic syndrome and its associated health risks.

Current recommendations for the treatment of the metabolic syndrome and the primary prevention of cardiovascular diseases encourage the use of therapeutic lifestyle changes such as increasing physical activity and reducing the dietary intake of saturated fat and cholesterol (21,27). Physical activity interventions, in the form of exercise training programs, have been shown to reduce individual heart disease risk factors such as high blood pressure (7), high plasma triglycerides (6), high blood glucose (14), and low

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HDL cholesterol (6,19). However, little is known about the effects of exercise training on the reduction of several risk factors simultaneously in individuals already at a high risk for metabolic diseases. Thus, the purpose of this study was to determine the efficacy of aerobic exercise training for treating the metabolic syndrome in participants in the HERITAGE Family Study.

METHODS

Sample. The HERITAGE Family Study was designed to investigate the contribution of regular exercise to changes in risk factors for cardiovascular disease and Type 2 diabetes, and the genetics of cardiovascular, metabolic, and hormonal responses to exercise training (3). The participating research centers included four clinical centers: Arizona State University (now Indiana University), Laval University (now Pennington Biomedical Research Center), University of Minnesota, University of Texas at Austin (now Texas A&M University), and a data coordinating center at Washington University in St. Louis. The inclusion criteria for participation included being between the ages of 17 and 65 yr, healthy but sedentary (no regular physical activity over the previous 6 months), and systolic/diastolic blood pressures less than 160/100 mm Hg; therefore, stage 1 hypertension was acceptable for enrollment. The exclusion criteria included having confirmed or possible coronary artery disease, hypertension (stage 2 or greater), chronic or recurrent respiratory problems, diabetes, the use of lipid-lowering drugs, and a BMI exceeding 40 $kg \cdot m^{-2}$. The later criterion was omitted by the examining physician in a few instances because of an absence of other exclusionary criteria and a demonstrated ability to perform the prescribed exercise during the baseline evaluation. The recruitment of participants was based on extensive publicity and advertisements at the clinical centers. Written informed consent was obtained from all participants, and all procedures were approved by the ethics review boards at each of the clinical centers. The sample considered here consists of 288 men (74 black, 214 white) and 333 women (118 black, 215 white) who had measures available to identify the metabolic syndrome before and after the training program.

Measures. The measurements required for the definition of the metabolic syndrome were obtained at baseline and after the 20-wk aerobic exercise training program. All study personnel were centrally trained on all aspects of recruitment and measurement protocols using a specially prepared manual of procedures. Data quality was assured through an extensive quality control program (10). Blood pressures and plasma concentrations of HDL cholesterol (HDL-C) and triglycerides (TG) were measured after a 12-h fast on two separate days at baseline and 24 and 72 h after the last exercise training session. Given that there were minimal differences in the 24- and 72-h posttraining plasma lipid measurements (18), the values reported in this article are the averages for the two pretraining and two posttraining measurements.

Systolic (SBP) and diastolic blood pressure (DBP) 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 a technician wore earphones to confirm the values. The first measurements were discarded and three valid measurements were made on each day (26).

Blood samples were obtained from an antecubital vein and collected into Vacutainer tubes containing EDTA. For women, samples were collected in the early follicular phase of the menstrual cycle both pretraining and 24 h posttraining, when blood serum cholesterol alterations are reportedly minimal (22). Plasma was ultracentrifuged, and the top fraction containing VLDL was quantitatively recovered. The LDL in the ultracentrifuged bottom fraction was precipitated with heparin and $MgCl_2$ (4), and the HDL was obtained in the supernatant. The concentrations of cholesterol in the HDL fraction and total TG (9) were measured by autoanalyzer (Technicon RA-500). To adjust for potential plasma volume changes accompanying the exercise training, plasma total proteins were analyzed using the biuret method (Roche Molecular Biochemicals, Dallas, TX) on the baseline and posttraining specimens (18). Posttraining values were corrected based on the correlation of pretraining to posttraining plasma total protein levels.

Waist circumference (WC) and fasting plasma glucose were measured once before and once after the exercise training program. Plasma glucose was enzymatically determined using a reagent kit distributed by Diagnostic Chemicals Ltd. (Oxford, Connecticut). WC was measured at the point of noticeable waist narrowing following the procedures recommended by Callaway et al. (5).

The classification of the metabolic syndrome was based on the NCEP ATP III guidelines (27) and is defined as the presence of any three of the following: central obesity (men: WC $>$ 102 cm; women: WC $>$ 88 cm); high TG ($\geq$ 1.69 $mmol \cdot L^{-1}$); low HDL-C (men: $<$1.04 $mmol \cdot L^{-1}$; women: $<$1.29 $mmol \cdot L^{-1}$); high blood pressure (SBP $\geq$ 130 or DBP $\geq$ 85 mm Hg), and high blood glucose ($\geq$ 6.1 $mmol \cdot L^{-1}$). Participants were not aware of their metabolic syndrome classification at any point in the study.

Exercise training program. Each participant completed a 20-wk standardized aerobic exercise training program. The aerobic fitness training response was assessed by two progressive maximal exercise tests conducted on separate days before as well as after training on an Ergometrics 800S cycle ergometer from SensorMedics (Yorba Linda, CA) connected to a SensorMedics 2900 metabolic cart. The protocol for the determination of $\dot{V}O_{2max}$ has been described in detail elsewhere (24). Briefly, 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 before and after training. The average $\dot{V}O_{2max}$ from the two tests before as well as after training was taken as $\dot{V}O_{2max}$ for each participant if the two

TABLE 1. Frequency distribution (%) for number of risk factors for the metabolic syndrome in 621 participants in the HERITAGE Family Study at baseline.

Number of Risk Factors	0	1	2	3	4	5	≥3
Black men ($N = 74$)	20.3	35.1	25.7	10.8	6.8	1.4	18.9
White men ($N = 214$)	21.0	36.0	23.8	14.0	3.3	1.9	19.2
Black women ($N = 118$)	11.0	44.1	25.4	11.9	5.9	1.7	19.5
White women ($N = 215$)	16.3	44.7	26.5	10.2	1.9	0.5	12.6

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% (24).

The exercise training program involved three sessions per week of supervised exercise on a cycle ergometer (Universal Aerocycle, Cedar Rapids, MI). Participants started at 55% of their baseline $\dot{V}O_{2max}$ for 30 min per session and progressed in intensity or duration every 2 wk after a standardized protocol until they were working at 75% $\dot{V}O_{2max}$ for 50 min per session for the final 6 wk. Participants were counseled at baseline and midway (10 wk) through the exercise training program not to alter their usual health and lifestyle habits outside of the study, including diet and physical activity levels. More details about the exercise training program have been provided elsewhere (25).

Compliance with training. From a total of 855 eligible participants in the HERITAGE Family Study who completed baseline measurements, 751 had the required measurements for the classification of the metabolic syndrome. Of these, 621 completed the exercise-training program and provided the required posttraining measurements. These 621 participants finished ≥ 95% of the training sessions and form the sample for the present study. The completion rates were virtually identical among those classified with the metabolic syndrome at baseline and those who were not. A total of 105 of 126 participants with the metabolic syndrome at baseline (83%) and 516 of 625 participants without the metabolic syndrome at baseline (83%) completed the training program.

Analytical approach. The analyses in this paper are largely descriptive rather than inferential, and the clinical rather than statistical significance of the results is emphasized throughout the paper. The prevalence of the metabolic syndrome was determined in the participants in the HERITAGE Family Study at baseline (pretraining). The effects of the aerobic exercise training program were then examined in those participants who were identified as having the metabolic syndrome. Significant differences in the prevalences of the metabolic syndrome and individual risk factors before and after training were tested using chi-squared analyses and an alpha of $P < 0.05$.

RESULTS

Table 1 provides the frequency distribution of risk factors for the metabolic syndrome in the HERITAGE Family Study participants at baseline ($N = 621$). The prevalence of the metabolic syndrome (≥ three risk factors) was 16.9% for the entire sample. The prevalence was similar among black men (18.9%), white men (19.2%), and black women (19.5%) but lower for white women (12.6%). Table 2 provides the descriptive characteristics of the sample of 105 participants who were classified as having the metabolic syndrome. Although there were no differences between white and black men, white women had significantly higher plasma TG and lower resting SBP and DBP than black women.

The prevalence of the individual risk factors in the participants with the metabolic syndrome is shown in Figure 1 for the combined sample and in Table 3 for the separate

TABLE 2. Descriptive characteristics of 105 participants in the HERITAGE Family Study classified as having the metabolic syndrome at baseline.

	Black		White	
	Mean	SD	Mean	SD
Men				
N	14		41	
Age (yr)	42.2	13.1	46.9	14.0
Body mass index (kg·m^{-2})	30.9	4.9	31.8	3.5
Waist circumference (cm)	104.3	12.9	109.2	8.0
Triglycerides (mmol·L^{-1})	2.51	0.92	2.47	1.23
HDL cholesterol (mmol·L^{-1})	0.76	0.11	0.80	0.12
Systolic blood pressure (mm Hg)	131.1	8.4	126.3	13.1
Diastolic blood pressure (mm Hg)	77.7	4.3	74.9	9.4
Fasting glucose (mmol·L^{-1})	5.79	0.67	5.61	1.00
Women				
N	23		27	
Age (yr)	40.9	10.3	45.8	13.9
Body mass index (kg·m^{-2})	34.4	5.0	31.7	5.1
Waist circumference (cm)	106.0	12.1	106.4	13.2
Triglycerides (mmol·L^{-1})	1.27	0.58	2.03	0.68*
HDL cholesterol (mmol·L^{-1})	0.94	0.17	0.95	0.14
Systolic blood pressure (mm Hg)	135.8	13.1	119.7	12.2*
Diastolic blood pressure (mm Hg)	80.1	7.7	67.5	7.4*
Fasting glucose (mmol·L^{-1})	5.70	1.00	5.56	1.37

* $P < 0.05$ between races, within sex.

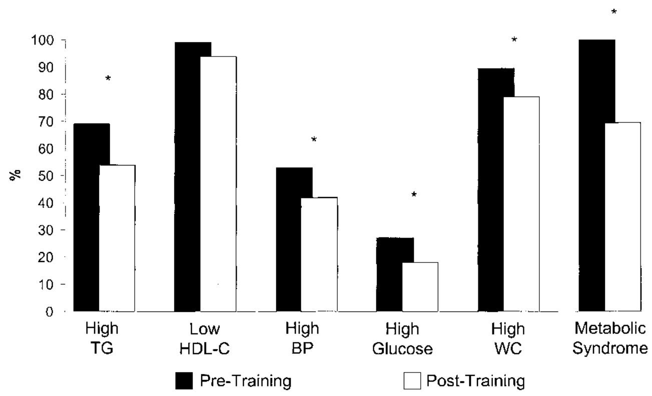

FIGURE 1—Prevalence of individual risk factors before and after 20 wk of aerobic exercise training in the HERITAGE Family Study among 105 participants with the metabolic syndrome at baseline. *P < 0.05 pre- versus posttraining.

sex-by-race groups. In general, the percentage of participants with each risk factor decreased consequent to the exercise training, with the exception of high blood glucose in white women. Of the 105 participants with the metabolic syndrome at baseline, 32 people (30.5%) were no longer classified as having the syndrome after exercise training. There were no significant differences between the 32 people who were no longer classified as having the metabolic syndrome and the other 73 participants in terms of age, baseline maximal oxygen consumption ($\dot{V}O_{2max}$), or the increase in $\dot{V}O_{2max}$ with training (Table 4; $P > 0.05$).

Of the participants who no longer were classified as having the metabolic syndrome after training, 43% reduced their TG, 16% increased their HDL-C, 38% reduced their blood pressure, 9% reduced their blood glucose, and 28% reduced their WC below the threshold values used to diagnose the metabolic syndrome. The shift to the left in the distribution of the number of risk factors in the participants with the metabolic syndrome consequent to the exercise training is displayed in Figure 2A. Figure 2B presents the corresponding distribution of the number of risk factors in participants without the metabolic syndrome at baseline.

The overall prevalence of the metabolic syndrome in the HERITAGE sample decreased from 16.9% before training to 11.8% after training. As noted above, 30.5% of those with the metabolic syndrome before training were no longer classified as having the syndrome after training. On the other hand, only 4% ($N = 22$) of the 516 participants who were not classified as having the metabolic syndrome before training were classified as having the syndrome after the training program. The training effect (increase in maximal oxygen consumption [$\dot{V}O_{2max}$]) observed in the group of participants with the metabolic syndrome (16.3%) was quite similar to that of the entire sample (17.6%) (results not shown).

TABLE 3. Prevalence (%) of risk factors pre- and posttraining among 105 participants in the HERITAGE Family Study classified as having the metabolic syndrome at baseline.

	High TG	Low HDL	High BP	High Glucose	High WC
Black men					
Pre	93	100	71	43	43
Post	79	100	43	29	43
White men					
Pre	76	98	46	24	93
Post	63	93	42	7	76
Black women					
Pre	26	100	87	35	100
Post	13	96	65	30	91
White women					
Pre	81	100	26	15	100
Post	62	93	22	19	93

DISCUSSION

There is good evidence that aerobic exercise training has a beneficial effect on individual cardiovascular disease risk factors such as high blood pressure, dyslipidemia (particularly low HDL and high TG), and glucose intolerance. Indeed, these issues have already been addressed using data from the HERITAGE Family Study (13,17,18,28,29). However, this is the first study to our knowledge that has examined the utility of physical activity in improving a "cluster" of risk factors simultaneously. The results of this study provide compelling evidence of the efficacy of physical activity in treating individuals with multiple cardiovascular disease risk factors such as those with the metabolic syndrome. Thus, the NCEP ATP III recommendations (27) that target individuals with multiple risk factors with intensive therapeutic lifestyle changes (including physical activity) are strongly supported by the findings of this study. In a more general sense, the use of physical activity promotion strategies in the primary prevention of cardiovascular diseases has the potential to have a great public health impact given the high prevalence of physical inactivity in both the United States and Canada.

The finding that exercise training resulted in improvements in the metabolic profile of the participants in the HERITAGE Family Study is encouraging, as the exclusion criteria precluded individuals with overt signs of disease from participating, i.e., those with hypertension, coronary artery disease, chronic or recurrent respiratory problems, or uncontrolled endocrine and metabolic disorders such as diabetes. Thus, the effects of exercise training observed in this study represent an important aspect of the primary prevention of chronic disease because the participants with the metabolic syndrome were at high risk of future disease due to the presence of multiple risk factors.

The results of this intervention study are supported by studies that have examined the cross-sectional relationship between physical activity and the metabolic syndrome. In a sample of white, African-American and Native-American women, leisure-time physical activity levels assessed by questionnaire were inversely associated with the prevalence of the metabolic syndrome, as defined by NCEP ATP III criteria (12). The odds ratio for the metabolic syndrome, adjusted for a number of covariates, was 0.18 (95% confidence interval: 0.33–0.90) for women in the highest category of physical activity compared with women in the lowest category. Similarly, the risk of having ≥ three risk factors (≥75th percentile of

TABLE 4. Age, maximal oxygen consumption, and change in maximal oxygen consumption with training in participants classified with the metabolic syndrome at baseline who were or were not classified as having the metabolic syndrome following exercise training.

	With Metabolic Syndrome			Without Metabolic Syndrome			
	N	Mean	SD	*N*	Mean	SD	*P**
Black men							
Age (yr)	9	46.0	14.6	5	35.2	6.1	0.14
$\dot{V}O_{2max}$ (mL·kg^{-1}·min^{-1})	9	26.7	5.1	5	31.4	2.1	0.09
$\Delta\dot{V}O_{2max}$ (mL)	9	284	205	5	297	101	0.87
White men							
Age (yr)	28	48.0	13.8	13	44.4	14.7	0.45
$\dot{V}O_{2max}$ (mL·kg^{-1}·min^{-1})	28	27.9	4.2	13	30.1	4.8	0.14
$\Delta\dot{V}O_{2max}$ (mL)	28	409	247	13	481	258	0.40
Black women							
Age (yr)	17	41.2	9.4	6	40.2	13.5	0.85
$\dot{V}O_{2max}$ (mL·kg^{-1}·min^{-1})	17	20.1	3.4	6	22.0	2.6	0.23
$\Delta\dot{V}O_{2max}$ (mL)	17	319	148	6	278	158	0.58
White women							
Age (yr)	19	48.3	13.5	8	39.8	13.8	0.15
$\dot{V}O_{2max}$ (mL·kg^{-1}·min^{-1})	19	21.3	5.1	8	24.1	6.3	0.24
$\Delta\dot{V}O_{2max}$ (mL)	19	313	163	8	373	99.4	0.35

* *P* value from independent samples *t*-test comparing those that still were classified with the metabolic syndrome and those that were not following exercise training.

WC, blood pressure, total-to-HDL-C ratio, and insulin resistance index) in a sample of African-American and white young adults from the Bogalusa Heart study was significantly less in those who were moderately-to-very active by comparison with physically inactive participants (relative risk = 0.41 [95% confidence interval: 0.24–0.71]) (11). Taken together, the results of these studies and those from the present study reinforce the

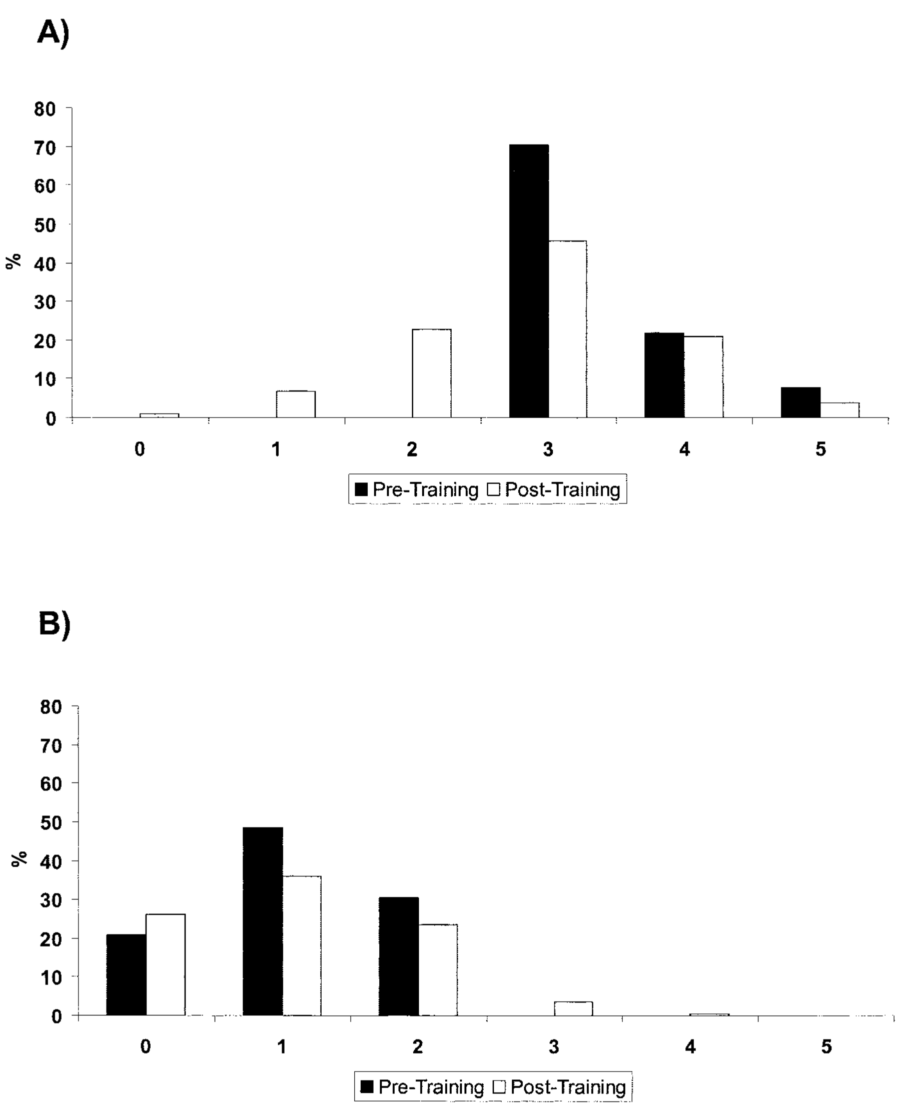

FIGURE 2—Frequency distribution of the number of risk factors present before and after 20 wk of aerobic exercise training in the HERITAGE Family Study among (A) 105 participants with the metabolic syndrome and (B) 516 participants without the metabolic syndrome at baseline.

notion that physical activity is an important correlate of and treatment option for the metabolic syndrome.

An alternative way of expressing the efficacy of this trial is to calculate the "Number Needed to Treat" (NNT), which is the inverse of the absolute risk reduction (i.e., NNT = 1/ARR) (16). Given that 30.5% of the participants with the metabolic syndrome at baseline (of 100%) were no longer classified with the syndrome after training, this translates into a NNT of 3.3 people. In other words, 3.3 people would need to be treated with exercise in order to have one successful outcome. Although it is difficult to establish the clinical significance of this finding, the NNT in the recently reported Diabetes Prevention Program trial was 6.9 for lifestyle change and 13.9 for Metformin drug therapy (15). Thus, aerobic exercise training appears to be a useful strategy to treat the metabolic syndrome.

The current recommendations for physical activity and health in the United States are that all adults should accumulate at least 30 min of moderate-intensity physical activity on most, preferably all, days of the week (20). The protocol of the HERITAGE Family Study included a 20-wk standardized exercise program in which participants increased their physical activity levels from sedentary levels to exercising for 45 min a day, $3\times$ wk^{-1} at 75% of their initial maximal aerobic capacity for the last 6 wk of the program. This protocol is not directly comparable to the current physical activity guidelines. More research should be devoted to understanding the effects of meeting the physical activity guidelines on the treatment of the metabolic syndrome.

The major strengths of this study include the large biracial sample, which allowed the examination of potential race and sex effects, and a rigorously standardized supervised exercise program that limited problems with adherence (only those who attended at least 95% of the exercise training sessions were included) (23). On the other hand, a limitation of this study is the reliance on participants to act as their own controls. In other words, we relied on the changes from baseline to define the treatment effects. Although the inclusion of a control group in the design of the HERITAGE Family Study would have been preferred, it was not feasible due to the prohibitive costs involved. Given the powerful observations observed in this study, the lack of a control group does not change the interpretation of the results. However, further studies using randomized controlled trial designs should be undertaken to confirm the results presented here. This study can be considered to be an *efficacy* trial in which the benefits of supervised aerobic training on multiple risk factors were examined. Clinical trials using intent-to-treat analyses that determine the *effectiveness* or *efficiency* of physical activity in treating the metabolic syndrome are also warranted.

In summary, the results of this study indicate that physical activity is useful for treating the metabolic syndrome. The results were similar in men and women, and in black and white participants, suggesting that the effects of exercise training may be generalizable to a large segment of the North American population. The use of exercise as a component of therapeutic lifestyle change programs in people with multiple risk factors is encouraged.

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