ABSTRACT

Title of Thesis: AEROBIC FITNESS AND PREVALENCE OF THE METABOLIC SYNDROME IN NON-AFRICAN AMERICANS AND AFRICAN AMERICANS IN PREMIER: A RANDOMIZED CONTROLLED TRIAL

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Background: The Metabolic Syndrome is the clustering of several cardiovascular risk factors for coronary heart disease and Type 2 Diabetes Mellitus. This syndrome is of public health importance due to its high prevalence and high correlation to all-cause, CHD, and CVD mortality. The purpose of the current study was to determine if a change in aerobic fitness in the treatment group significantly decreased the odds of Metabolic Syndrome at 6 and 18 months.

Methods: There were 810 adult participants in this trial with above-optimal blood pressure and up to stage I hypertension. Participants were part of an advice-only control group or a treatment group where physical activity increases were the main component.

Results: A change in aerobic fitness, independent of treatment status, was significantly associated with a decrease in prevalent Metabolic Syndrome at both 6 and 18 months (OR: 0.96, CI: 0.94 – 0.98 & OR: 0.96; CI: 0.94 – 0.98, respectively).

AEROBIC FITNESS AND PREVALENCE OF THE METABOLIC SYNDROME IN NON-AFRICAN AMERICANS AND AFRICAN AMERICANS IN PREMIER: A RANDOMIZED CONTROLLED TRIAL

By

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Introduction

The Metabolic Syndrome is the clustering of several cardiovascular risk factors for coronary heart disease (CHD) and Type 2 Diabetes Mellitus (DM) (Eckel,Grundy, and Zimmet, 2005). Instead of one definite definition, there are three commonly used definitions of this syndrome. All three include the presence of at least three cardiovascular risk factors; however, all of the definitions differ in the specific risk factors that are necessary to be present in order to be classified as having the Metabolic Syndrome. The first definition to be utilized was created by the World Health Organization (WHO), followed by the National Cholesterol Education Program (NCEP), and finally the International Diabetes Federation (IDF) (Eckel et al, 2005). Table 1 provides a breakdown of all three definitions.

Table 1 Definitions of the Metabolic Syndrome

WHO 1999	**NCEP 2001**	**IDF**
Diabetes or impaired glucose tolerance or insulin resistance* PLUS 2 or more of the following:	Three or more of the following: Central obesity: waist circumference > 102 cm (M), > 88 cm (F)	Central obesity: waist circumference, ethnicity specific; for Europeans and Africans, >93 cm (M), >79 cm (F) PLUS 2 or more of the following:
Obesity: BMI>30kg/m^2 or WHR > 0.9 (M) > 0.85 (F)	Hypertriglyceridaemia: Triglycerides > 149 mg/dl	Raised triglycerides: >149 mg/dl
Dyslipidemia: Triglycerides > 149 mg/dl or HDL-C < 35 mg/dl (M), < 39 mg/dl (F)	Low HDL-C: < 40 mg/dl (M), < 50 mg/dl (F)	Reduced HDL-cholesterol: <40 mg/dl (M), <50 mg/dl (F)
Hypertension: Blood pressure >139/89 mmHg or medication	Hypertension: Blood pressure > 129/84 mmHg or medication	Raised Blood pressure: systolic>129 mmHg or Diastolic> 84mmHg or treatment
Microalbuminuria: Albumin excretion > 19 ug/min or albumin:creatinine ratio > 29 mg/g	Fasting glucose > 109 mg/dl	Raised fasting plasma glucose: Fasting plasma glucose >99mg/dl or type 2 diabetes

*defined as the top quartile of fasting insulin in the non-diabetic population.
Table adapted from Zimmet et al, 2005.

According to the most recent data from the Third National Health and Nutrition Examination Survey (NHANES III), the unadjusted prevalence of the metabolic syndrome in the US is approximately 35% using the NCEP definition and 39% using the IDF definition (Ford, 2005). This slight discrepancy can be explained by the variations in the definitions. (See table 1 for details). Prevalence of the Metabolic Syndrome is especially high among African Americans (Carnethon, Catherine, Hill, Sidney, Savage, and Liu, 2004; Eckel et al, 2005). Although it is difficult to compare studies with so many definitions in use (Zimmet et al, 2004; Eckel et al, 2005), the Metabolic Syndrome has recently become of importance to epidemiologists due to its high prevalence (Zimmet et al, 2004; Ford, 2005; Grundy, 2005; Ford et al, 2006) and high correlation to all-cause, coronary heart disease (CHD) and cardiovascular disease (CVD) mortality, regardless of the definition used (Isommaa, Almgren, Tuomi, Forsen, Lahti, Nissen, Taskinen, and Groop, 2001; Malik et al., 2004; Lakka, Laaksonen, Lakka, Niskanen, Kumpusalo, Tuomilehto, and Salonen, 2004; Hu, Qiao, Tuomilehto, Balkau, Borch-Johnsen, and Pyorala, 2004). Table 2 provides a breakdown of the odds ratios of mortality from Metabolic Syndrome by definition.

Table 2

CHD, CVD, and All-Cause Mortality Odds Ratios with Metabolic Syndrome				
Author	**Definition Used**	**CHD Mortality**	**CVD Mortality**	**All-Cause Mortality**
Issomma et al., 2001	WHO	3.0	2.0	
Malik et al., 2004	NCEP	2.0		
Lakka et al., 2002	WHO		2.6 – 3.0	2.0
Hu et al., 2004	WHO		Women 2.3 Men 2.8	1.4

Hypertension plays an important role in the Metabolic Syndrome. Hypertension and obesity are the two most common risk factors found in those with the Metabolic Syndrome (Isommaa et al, 2001). Patients with hypertension have greater than a two-fold increase in the prevalence of the Metabolic Syndrome than those without (Ford, 2005). This could be due to the correlation of insulin resistance with the Metabolic Syndrome (Zimmet et al., 2004). There is some evidence that hypertension itself is an insulin resistant state (Ferrannini, Buzzigoli, Bonadnna, Giorico, Oleggini, Graziadei, Pedrinelli, Brandi, and Bevilacqua, 1987). Hypertensive subjects show significantly greater insulin resistance. Furthermore, it is suggested that hyperinsulinemia functions as a compensatory mechanism for insulin resistance in persons with hypertension (Ferrannini et al, 1987). These two mechanisms show the correlation of hypertension and insulin resistance, linking hypertension with the Metabolic Syndrome.

The prevalence of the Metabolic Syndrome is greater among African Americans. Importantly, it is also well documented that the prevalence of hypertension (Thomas, Semenya, Thomas, Thomas, Neser, Pearson, and Gillum, 1987; Jamerson, 1993; Burt, Whelton, Roccella, Brown, Cutler, Higgins, Horan, and Labarthe, 1995; Branson, Davis, and Butler, 2005), as well as insulin resistance (Reiner, Carison, Ziv, Iribarren, Jaquish, and Nerickerson, 2007), is also greater among African Americans. While it was once thought that cultural differences were the sole reason for the discrepancy in the racial prevalence of these cardiovascular risk factors, there is now some research that suggests that physiological differences between African Americans and non-African Americans may make African Americans more prone to certain diseases or risk factors (Thomas et

al, 1987; Jamerson, 1993; Cardillo, Kilcoyne, Cannon, and Panza, 1998; Mall, Wagoner, Levin, Kardia, and Liggett, 2002; Branson et al, 2005).

It is well documented in cross sectional studies that physical activity (Rennie, McCarthy, Yazdgerdi, Marmot, and Brunner, 2003; Franks, Ekelund, Brage, Wong, and Wareham, 2004; Ford, Kohl, Mokdad, Ajani, 2005) and increased physical fitness have a preventive or protective effect on the Metabolic Syndrome (Kullo, Hensrud, and Allison, 2002; Farrell, Cheng, and Blair, 2004; Lee, Kuk, Katzmarzyk, Blair, Church, and Ross, 2005). It is also documented in some cross sectional studies that both physical activity and aerobic fitness have an inverse relationship to the Metabolic Syndrome independent of one another (Wareham, Hennings, Byrne, Hales, Prentice, and Day, 1998; Carroll, Cooke, and Butterly, 2000; Irwin, Ainsworth, Mayer-Davis, Addy, Pate, and Durstine, 2002). However, these studies are limited by their cross sectional nature, small sample sizes, and/or lack of an African American sample.

There are six longitudinal studies showing the preventive effect of fitness on the Metabolic Syndrome (Laaksonen, Lakka, Salonen, Niskanen, Rauramaa, and Lakka, 2002; Carnethon, Gidding, Nehgme, Sidney, Jacobs, and Liu, 2003; Palaniappan, Carnethon, Wang, Hanley, Fortmann, Haffner, and Wagenknecht, 2004; Ekelund, Brage, Franks, Hennings, Emms, and Wareham, 2005; LaMonte, Barlow, Jurca, R., Kampert, Church, and Blair, 2005). However, these studies are limited by homogeneous samples that were either all middle aged non-African American men or non-African American men and women. Only one of these studies included African Americans in the sample (Palaniappan et al, 2004). Five of the six studies agree that there is a protective value of physical activity and/or aerobic fitness (Laaksonen et al, 2002; Carnethon et al, 2003;

Ekelund et al, 2005; LaMonet et al, 2005). The last study found no relationship between physical activity and the incidence of the Metabolic Syndrome (Palaniappan et al, 2004). Interestingly, this was the only study including African Americans. In one study of physical activity and aerobic fitness, those who were the least fit and the most sedentary had a seven fold risk increase of developing the Metabolic Syndrome over a four year follow up (Laaksonen et al, 2002). These cross sectional and longitudinal results give rise to the plausibility that an aerobic fitness intervention should have a protective effect on those subjects without baseline Metabolic Syndrome and a therapeutic effect on those with the Metabolic Syndrome at baseline.

The results from several exercise intervention studies agree with the positive results found in the cross sectional and longitudinal studies. These results all show that with an increase in exercise, some subjects with baseline Metabolic Syndrome can improve their health significantly enough that they are no longer classified as having the Metabolic Syndrome at follow up (Milani and Lavie, 2003; Katzmarzyk, Leon, Wilmore, Skinner, Rao, Rankiknen, and Bouchard, 2003; Shubair, Kdis, McKelvie, Arthur, and Sharma, 2004; Stewart, Bacher, Turner, Lim, Hees, Shapiro, Tayback, and Ouyang, 2005). Although the results of these studies are encouraging, only one of the interventions was a randomized controlled trial (Stewart et al, 2005). Unfortunately, this study was limited to 115 total subjects, only 1% being African American. As previously mentioned, it is important to include African Americans in research because they may differ physiologically and culturally from non-African Americans. Subjects in this study increased their fitness, measured by VO_2max, by 16% compared to controls. There was a trend toward a reduction in Metabolic Syndrome for the exercisers, however, it did not

reach statistical significance (P<.06) (Stewart et al., 2005). Other intervention studies had significantly more subjects, but lacked a control group. In the HERITAGE family study, there were 621 subjects, of which 192 were African American (Katzmarzyk et al., 2003). At baseline, 16.9% of the participants had the Metabolic Syndrome. After a 20 week aerobic exercise program, only 11.8% of those subjects maintained prevalence, which was a statistically significant reduction. Unfortunately, there was no control group for comparison (Katzmarzyk et al., 2003). The last two intervention studies were both performed with cardiac rehabilitation patients, and thus already had known Coronary Heart Disease (CHD). Although both studies did show a significant reduction in the prevalence of Metabolic Syndrome after an exercise intervention, one did not have a control group (Shubair et al, 2004) and the other had a control group that consisted of participants who had agreed to be a control after dropping out of the intervention group (Milani et al, 2003). Because both studies were done on cardiac rehabilitation patients, the results are limited in their generalizability.

As previously mentioned, there is some research suggesting that the differences in African Americans and non-African Americans make it important to over sample for African Americans, as they may have both physiological and cultural differences than non-African Americans. There is a different pattern of hemodynamic reactivity in African Americans and Non-African Americans; African Americans have higher peripheral resistance and a lower cardiac output than their non-African American counterparts (Cardillo et al, 1998). They also have greater circulatory hyperactivity, which can be defined as higher systolic and diastolic blood pressures, as well as heart rate, during both rest and exercise. The exercise blood pressure response remains

significantly greater even when resting blood pressure is accounted for (Thomas et al, 1987).

Although the previously mentioned studies show the physiological reasons for the increase in hypertension in African Americans, there is also data that show the difference may be cultural. In the Coronary Artery Risk Development in Young Adults (CARDIA) study, it was shown that there were no significant genetic differences between African Americans and Non-African Americans, suggesting that the differences may be cultural (Reiner et al, 2007). In the CARDIA study, higher education level, used as a proxy for social economic status (SES), was associated with increased risk factors of the Metabolic Syndrome, specifically, increased waist circumference, hypertension, and risk of pre-diabetes in African Americans. These risks were independent of genetic ancestry. Because there are data implicating both cultural and physiological differences in African Americans and non-African Americans contributing to the increased risk in African Americans for Metabolic Syndrome, it is important not to rule out any possible differences, and treat African Americans as their own sub-population.

Not only are African Americans more prone to cardiovascular risk factors, they also may respond differently than do whites to treatments for these risk factors (Jamerson, 1993; Sacks, Svetkey, Vollmer, Lawrence, Appel, Bray, Harsha, Obarzanek, Conlin, Miller, Simons-Morton, Karanja, and Pao-Hwa, 2001; Branson et al, 2005; Rao, Manjula, and Mayo, 2007). During a dietary intervention using the DASH diet, African Americans responded more positively to sodium reduction as both treatment and prevention of hypertension than did whites (Sacks et al, 2001). Although there is the possibility of poor treatment retention with African Americans when compared with non-

African Americans, it is doubtful that the underlying root of these differences is due to retention issues because in some of the treatments, such as sodium reduction, the African American participants have a more positive treatment effect than the non-African American participants (Sacks et al, 2001). Because African Americans may have a different disease etiology than non-African Americans, and they also may respond differently to dietary treatments, it is logical to question if they will respond differently to physical activity and increased fitness as a treatment for hypertension and insulin resistance, and subsequently, the Metabolic Syndrome. Whether the differences are cultural or physiological, using a randomized controlled trial including a high percentage of African Americans, such as the PREMIER trial, for a secondary analysis on the Metabolic Syndrome will be an important contribution to the literature as well as to public health.

According to a recent review conducted by Ford and Li (2006), there are no rigorous randomized controlled trials examining the effect of physical activity and increasing physical fitness on the Metabolic Syndrome with sufficient sample size and generalizability to the larger population. According to another review by Branson et al (2005), under-representation of African Americans is a common problem that jeopardizes the generalizability of results to the entire population. It is further stated that the health of African Americans as a population depends upon this under-representation being recognized, and that specific interventions be planned and implemented. Therefore, the purpose of the present study was to test the significance of the change in aerobic fitness from the subjects of the PREMIER study as it relates to a change in the Metabolic Syndrome at a 6 month and 18 month follow-up. The current study was an important

addition to the literature on the Metabolic Syndrome because it addresses both of the issues in the two review articles discussed above. One third of the study participants in this data set are African American. Additionally, PREMIER is a randomized controlled trial (RCT). Randomized Controlled Trials are currently the 'gold standard' in research. In brief, participants were randomly recruited from four different locations and grouped into cohorts. They underwent one of three conditions, established guidelines, established guidelines plus the DASH diet, or an advice-only control condition. Briefly, the established guidelines group attended group and individual intervention sessions with goals to increase physical activity and follow dietary guidelines set forth by JNC V. The established guidelines plus DASH diet group attended intervention sessions with the same physical activity guidelines, but also had information about the DASH diet. The participants in the advice-only control group attended only 2 intervention sessions, and were told to increase physical activity and follow the food guide pyramid, but were not given any specific guidelines for either element. (See Table 6 for the specific details of the intervention groups). Measurements of all Metabolic Syndrome criteria were taken at baseline, a 6 month follow-up, and an 18 month follow-up (Funk, Elmer, Stevens, Harsha, Craddick, Lin, Young, Champagne, Brantley, McCarron, Simons-Morton, and Appel, 2006). For further detail on this procedure, refer to the Methods section. For this paper, the NCEP definition of the Metabolic Syndrome will be analyzed so that the results may be compared to the most recent past studies as well as to any future studies being conducted. For the secondary analysis, we specifically examined any possible race differences.

Hypotheses

1. Change in fitness from the two intervention groups (combined for this paper), will be associated with reduced prevalence of Metabolic Syndrome compared with the advice only group. This difference is expected to be the most pronounced from baseline to the 6 month follow up. The difference between baseline and the 18 month follow up is expected to be significant, but to a lesser degree than the 6 month difference due to slightly poorer adherence to the intervention between 6 and 18 months.
2. The change in fitness in African Americans will be associated with a lesser, albeit still significant, reduction in Metabolic Syndrome when compared to their non-African American counterparts at both follow-up time points.

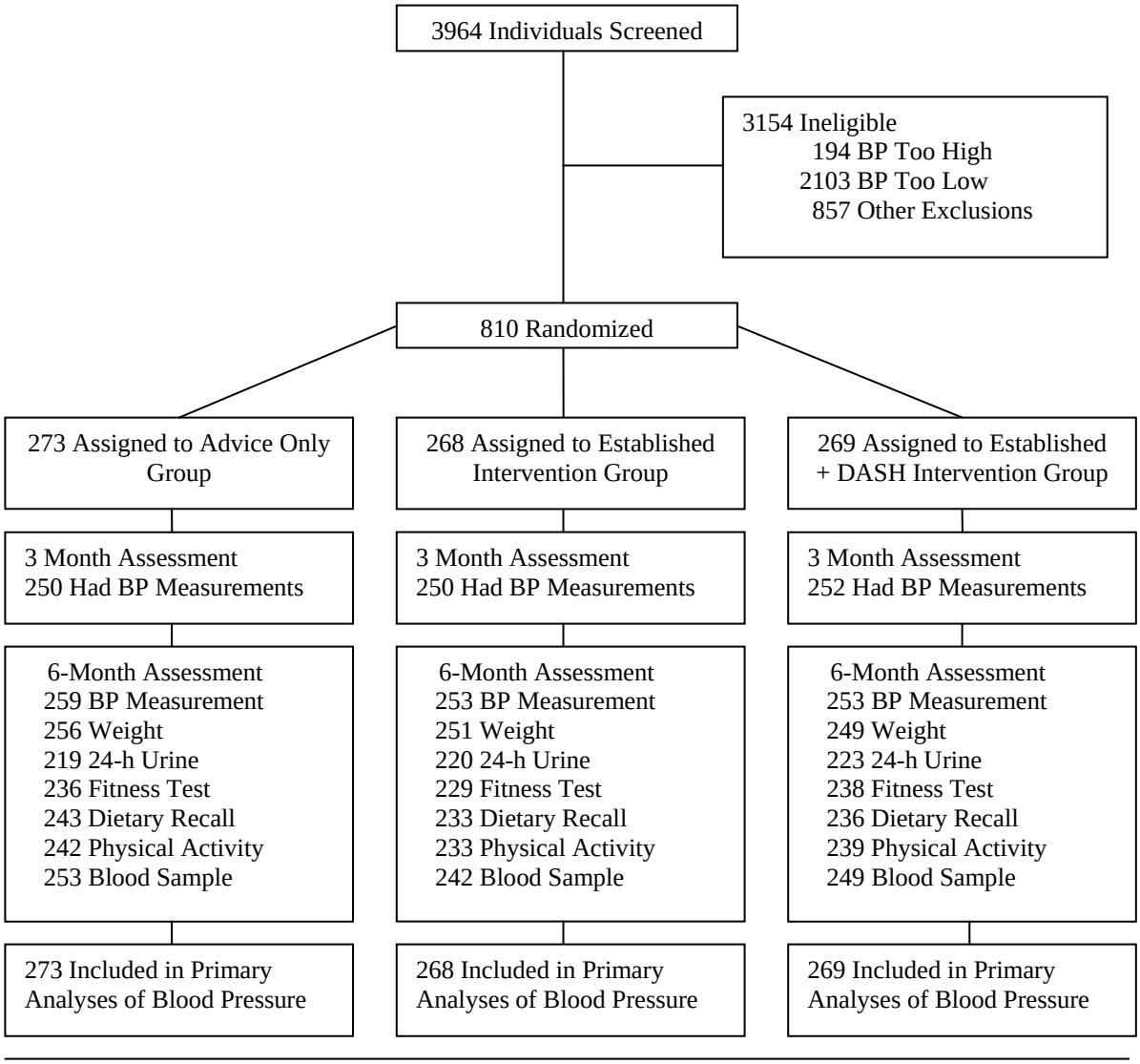
Methods

Participants

All participants are from the PREMIER trial. All were recruited by mass mailings, advertisements, and news stories. African Americans were over-recruited (Funk et al., 2006). There were originally 3964 individuals who came to three screenings. Of these 3964, 3154 were ineligible due to blood pressure being too low (2103), blood pressure being too high (194), or other exclusions as described below (857) (Writing Group of PREMIER, 2003). The final cohort consisted of 810 adults who were at least 25 years of age. The participants are 62% women and 34% African Americans. See figure 1 for a complete participant flow chart. See table 3 for a complete list of baseline characteristics.

Participants are from one of four participating clinical settings including Johns Hopkins University, Baltimore, MD; Pennington Biomedical Research Center, Baton Rouge, La; Duke University Medical Center, Durham, NC; and Kaiser Permanente Center for Health Research, Portland, Ore (Writing Group of PREMIER, 2003). In order to be included in the study, all inclusion and exclusion criteria had to be met. The major components of these criteria are as follows: All participants are at least 25 years of age. All participants have above optimal blood pressure, including anyone with up to stage 1 hypertension according to JNC VI (Writing Group of PREMIER, 2003). All participants have a body mass index (BMI) ranging from 18.5 -45 kg/m^2. Other inclusion criteria were to be willing and able to participate in all aspects of the intervention, provide informed consent, and access to a telephone. Major exclusion criterion were for medications, medical history, pregnancy, psychiatric disabilities, and major body weight changes in the 3 months prior to screening (Svetkey, Harsha, Vollmer, Stevens, Obarzanek, Elmer, Pao-Hwa, Champagne, Simons-Morton, Aickin, Proschan, and Appel, 2003). For complete inclusion/exclusion criteria, see table 4.

Figure 1. Breakdown of Randomization



BP Indicates blood pressure; DASH, Dietary Approaches to Stop Hypertension.
*Figure adapted from JAMA April 23/30, 2003 – Vol 289, No. 16

Table 3

Baseline Characteristics by Randomized Group[1]			
Characteristic	**Advice only (n = 273)**	**Established (n = 268)**	**Established + DASH (n = 269)**
Age, mean (SD), y	49.5 (8.8)	50.2 (8.6)	50.2 (9.3)
Female	172 (63.0)	174 (64.9)	154 (57.2)
Race or ethnicity			
African American	100 (36.6)	100 (37.3)	79 (29.4)
Non-Hispanic white	167 (61.2)	163 (60.8)	181 (67.3)
All others	6 (2.2)	5 (1.9)	9 (3.3)
BMI, mean (SD)[2]	32.9 (5.6)	33.0 (5.5)	33.3 (6.3
Weight classification			
Non-overweight (BMI, ,25)	15 (5.5)	13 (4.9)	16 (6.0)
Overweight (BMI, 25-29.9)	76 (27.8)	80 (29.9)	82 (30.5)
Obese (BMI, ≥30)	182 (66.7)	217 (81.0)	224 (83.6)
Alcohol, mean (SD), drinks/d	0.21 (0.41)	0.24 (0.47)	0.29 (0.52)
Sedentary (kcal/kg/d ≤35)	223 (81.7)	217 (81.0)	224 (83.6)
Annual household income			
<$30,000	31 (11.4)	26 (9.7)	27 (10.0)
$30,000-$60,000	91 (33.3)	83 (31.0)	82 (30.5)
> $60,000	142 (52.0)	151 (56.3)	148 (55.0)
Unknown (no answer)	9 (3.3)	8 (3.0)	12 (4.5)
Education			
High school or less	21 (7.7)	20 (7.5)	33 (12.3)
Some college	175 (64.1)	157 (58.6)	144 (53.5)
Some graduate school	77 (28.2)	91 (34.0)	92 (34.2)
Current cigarette smokers	14 (5.1)	18 (6.7)	7 (2.6)
Dyslipidemia[3]	59 (21.6)	68 (25.4)	64 (23.8)
Blood pressure, mean (SD), mm Hg			
Systolic	134.2 (10.1)	135.5 (9.2)	134.9 (9.4)
Diastolic	84.8 (4.3)	85.0 (4.1)	84.6 (4.0)
Hypertensive	104 (38.1)	100 (37.3)	100 (37.2)
Total Participants (n)			
Metabolic Syndrome	399		
No Metabolic Syndrome	397		

Abbreviations: BMI, body mass index; DASH, Dietary Approaches to Stop Hypertension.
[1] Data are presented as No. (%) unless otherwise indicated
[2] Body mass index is calculated as weight in kilograms divided by the square of the height in meters.
[3] Total cholesterol >240 mg/dL (6.21 mmol/L) and/or use of lipid-lowering medication.

*Table adapted from JAMA April 23/30, 2003 – Vol 289, No. 16 and Lien et al, 2007

Table 4

Eligibility Criteria
Inclusion Criteria
Baseline SBP 120-159 mmHg and DBP 80-95 mmHg
Age 25 or older
BMI 18.5-45 kg/m^2
Willing and able to participate fully in all aspects of the intervention
Informed consent
Access to telephone
Medication Exclusions
Regular use of anti-hypertensive drugs or other drugs that raise or lower BP
Current use of insulin or oral hypoglycemic agents
Current use of medications for treatment of psychosis or manic-depressive illness
Use of weight-loss medications in the three months prior to first screening visit
Medical History Exclusions
Cardiovascular event
Congestive heart failure
Current symptoms of angina or peripheral vascular disease
Cancer diagnosis (except for non-melanoma skin cancer) or treatment in past two years
Renal insufficiency (GFR < 60 ml/min as estimated using Crokroft-Gault formula)
Random glucose $\geq$ 160 mg/dL or Fasting Blood Sugar $\geq$ 126 mg/dL
Psychiatric hospitalization within the last two years
Other Exclusions
Inability to provide acceptable BP measurements
Consumption of more than 21 alcoholic drinks per week or binge drinking
Planning to leave the area prior to the anticipated end of participation
Body weight change > 15 pounds in the three months prior to first screening visit
Pregnant, breast feeding, or planning pregnancy prior to the end of participation
Current participation in another clinical trial
Investigator discretion for safety or adherence reasons
Household member of another PREMIER participant or of a PREMIER staff member
* Table adapted from Svetkey et al, 2003

Study Design

All participants were randomly assigned by a computer program. Assignments were stratified by clinic and hypertension status; randomization block size was 24 (Writing Group of PREMIER, 2003). Participants were randomly assigned to one of three groups: Advice only control group, a comprehensive lifestyle intervention group,

termed the Established Diet Group, or a comprehensive intervention plus DASH diet group, termed the Established Group plus DASH Diet (Funk et al, 2006). The control group participants followed recommendations set forth by the National High Blood Pressure Education Program (NHBPEP) for patients with above optimal blood pressure and stage 1 hypertension (Funk et al, 2006). The recommendations include weight loss if overweight, limiting alcohol and dietary sodium intake, regular physical activity, and eating a healthful diet. Written materials were provided at a baseline visit and again at the six-month follow up visit. No behavioral counseling was provided (Funk et al, 2006).

The comprehensive lifestyle intervention and the comprehensive lifestyle plus DASH diet groups received a multi-component lifestyle intervention program based on the most current clinical practice guidelines for blood pressure control and cardiovascular health (Svetkey et al, 2003). The specific guidelines were as follows: (1) weight loss of at least 15lbs (6.8 kg) at six months for those with a BMI of at least 25, (2) at least 180 minutes per week of moderate intensity physical activity, (3) daily intake of no more than 100 mEq of dietary sodium, and (4) daily intake of 1 oz or less of alcohol (Writing Group of PREMIER, 2003). See table 6 for full detail of the intervention groups. The comprehensive lifestyle plus DASH diet group was instructed on how to properly eat according to the DASH diet. The most emphasized aspects of the DASH diet in the PREMIER trial were eating 9 to 12 servings of fruits and vegetables and 2 to 3 servings of low-fat dairy products per day while limiting fat intake to less than 25% of total kcals. Saturated fat was also to be reduced to less than 10% (Funk et al, 2006). For original DASH diet requirements, see table 5. Although the dietary component for the two intervention groups differed, the two groups had identical intervention goals and

schedules regarding physical activity, sodium intake, and weight loss. Therefore, for the purpose of this paper, the two intervention groups were combined into one intervention group. The follow-up values of each individual part of the DASH diet were co-varied for in a logistic regression in order to isolate the effects of the change in aerobic fitness within the combined treatment group. Refer to the statistical analysis for details.

The intervention schedules for the two intervention groups were identical (Funk et al, 2006). During the initial six months, there were 18 face to face intervention contacts, (14 were group meetings and 4 were individual). Group sessions were approximately 1.5 to 2 hours in duration. They were interactive and dealt mostly with problem solving, support, and program ownership. They included four components, (1) taste it!, (2) progress check, (3) try it!, and (4) next steps. The taste it! section allowed participants to be introduced to new foods, recipes, and products that met the study dietary targets. The progress check was a discussion aiming to encourage exploration of supportive behavioral strategies. The goal of try it! was to allow for small-group activities that reinforced social support and physical activity. Finally, the next steps portion was used as a time for participants to draft plans and goals for the upcoming weeks. Physical activity diaries were kept and used as feedback at these sessions (Funk et al, 2006).

The main outcome results were published in 2003. The investigators found that lifestyle changes can significantly reduce blood pressure and risk of cardiovascular disease in persons with above optimal blood pressure (Writing Group of PREMIER, 2003). The reduced blood pressure and cardiovascular disease risk were significant in African Americans and non-African Americans. However, the lifestyle changes had a smaller positive effect on the African American participants (Svetkey, 2003). Recently

investigators studied the effects of the individual intervention components and SBP for participants having or not having Metabolic Syndrome. They found that presence of Metabolic Syndrome attenuated the SBP reduction in the established group, but that the attenuation was overcome in the Established plus DASH diet group (Lien, F. L., Brown, A. J., Ard, J. D, Loria, C., Erlinger, T. P., Feldstein, A. C, Lin, P., Champagne, C. M., King, A. C., McGuire, H. L., Stevens, V. J., Brantley, P. J., Harsha, D. W., McBurnie, M. A., Appel, L. J., and Svetkey, L. P., 2007).

Table 5

Original DASH Dietary Pattern Targets for Nutrient Amounts and Servings From Food Groups (at the 2100 kcal level: Appel et al., 1997)	
Nutrients	*Nutrient Amount*
Total fat. % kcal	27
Saturated fat. % kcal	6
Protein. % kcal	18
Carbohydrate. % kcal	55
Fiber. g	31
Potassium. mg	4700
Magnesium. mg	500
Calcium. mg	1240
Food Groups	*Servings/Day*
Vegetables	4 to 5
Fruit	4 to 5
Low-fat or fat-free dairy foods	2 to 3
Lean meats, poultry, and fish	$\leq$ 2
Grains, and grain products	7 to 8
Nuts, seeds, and dry beans	4 to 5/week
Fats and oils[a]	2 to 3
Sweets (added sugars)[b]	5/week
NOTE: DASH = Dietary Approaches to Stop Hypertension (Appel et al., 1997). [a]. Margarine, low-fat mayonnaise, or salad dressing, vegetable oils. [b]. Sugar, jelly, jam, syrups, sorbets, ices. * Table adapted from Funk et al., 2006	

Table 6

Intervention Lifestyle Targets and Delivery Approaches for PREMIER Treatment Groups			
	Established Guidelines (EG)	EG + DASH	Advice Only Comparison
Lifestyle Targets		Goals	
Physical Activity/week	180 min.	180 min.	Increase
Weight loss[a]	$\geq$ 15 lb	$\geq$ 15 lb	As needed
Total calories/day	Individual target[b]	Individual target[b]	No target
Sodium/day	$\leq$ 2400 mg	$\leq$ 2400 mg	Reduce
Alcohol/day	$\leq$ 1 oz. Men. $\leq$ .5 oz. Women.	$\leq$ 1 oz. Men. $\leq$ .5 oz. Women.	$\leq$ 1 oz. Men. $\leq$ .5 oz. Women.
Dietary focus	JNC V	DASH	FGP
% kcal fat	$\leq$ 30%	$\leq$ 25%	FGP
% kcal saturated fat	$\leq$ 10%	$\leq$ 7%	FGP
F&V servings	Not emphasized	9 to 12 servings[c]	FGP
Low-fat dairy servings	Not emphasized	2 to 3 servings[c]	FGP
Recommended Self-Monitoring	*Yes*	*Yes*	*None*
# of days/week	$\geq$ 3	$\geq$ 3	None
Lifestyle targets monitored	Calories, Na, PA	Calories, Na, PA, Fat, F&V, Dairy	None
Intervention delivery approach	*Description*		
Approach	Intensive behavioral program with extensive self-monitoring and ME	Intensive behavioral program with extensive self-monitoring and ME	Advice only
Total # of sessions			
Individual	7	7	2
Group	26	26	0

NOTE: JNC V = The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (National Institutes of Health. 1992): DASH = Dietary Approaches to Stop Hypertension (Appel et al., 1997): FGP = Food Guide Pyramid (U.S. Department of Health and Human Services & U.S. Department of Agriculture. 2000): Na = Sodium: PA = Physical Activity: F&V = fruits & vegetables: ME = motivational enhancement

a. Weight loss for those with body mass index $\leq$ 25.

b. Individual target set for caloric intake to achieve weight loss.

c. Servings are adjusted based on caloric intake.

* Table adapted from Funk et al., 2006

Variables

The main independent variable of interest was intervention status. From the intervention status, change in fitness was isolated from the dietary component of the intervention in a logistical regression. The two intervention groups, one with a dietary component and one without, were combined because the physical activity and weight loss goals were the same. Although there was a dietary component to the intervention, it was held constant in a logistical regression analysis. See statistical analysis section for details. Physical activity was used as a means to increase aerobic fitness in this study. However, the change in fitness was chosen as the only independent variable because there were intervention related changes in fitness but not for physical activity. The investigators believe that this was due to sub-optimal measures for physical activity in this population (Writing Group of PREMIER, 2003).

The main outcome, or dependent variable, is the presence of the Metabolic Syndrome as defined by the NCEP at the 6 month and/or the 18 month follow up. Metabolic Syndrome is defined by the NCEP as having three or more of the following criteria: central obesity, hypertriglyceridaemia, low HDL-C, hypertension, or an elevated fasting glucose (Zimmet et al, 2005). For a complete list of the specifications, refer to Table 1. Six months was chosen as the initial follow up because some of the participants had been diagnosed with stage 1 hypertension at baseline. After 6 months, it is recommended that individuals with persistent blood pressure of 140/90 or higher be referred for medication if a lifestyle intervention was not sufficient (JNC VI, 1997).

Instrumentation/measurement technique

Aerobic fitness was assessed using a sub-maximal treadmill exercise test developed specifically for the PREMIER trial (Writing Group of PREMIER, 2003). The test was designed to achieve an age and sex specific moderate intensity (approximately 60% of maximal METS). The protocol lasted a total of ten minutes (Writing Group of PREMIER, 2003) with two, three minute stages along with warm up and cool down stages (Young et al, 2005). The first stage achieved a light intensity effort, (approximately 40% of maximal METs), and the second stage achieved a moderate intensity effort, (approximately 60% of estimated METs) (Writing Group of PREMIER, 2003). Heart rate was taken at the end of each minute. The test was over when either the participant reached 85% of his/her age-predicted maximal heart rate (220-age), or when the protocol was completed (Young et al, 2005). The main outcome was heart rate at the end of stage two, or the last available stage for participants who stopped early because of heart rate (Writing Group of PREMIER, 2003). For this paper, the primary outcome is a change in aerobic fitness as defined by a change in stage 2 heart rate. The baseline stage 2 heart rate was subtracted from the stage 2 heart rate at each respective follow-up visit to get a change in heart rate (or fitness) variable. Heart rate was chosen because it has been shown to have a relatively linear relationship to VO_2. The correlation between heart rate and VO_2 is >0.90 (ACSM, 2006). Therefore, the change in stage 2 heart rate was used as a continuous variable to establish a change in fitness. A lower heart rate at the end of stage two implies an improvement in fitness. Participants without a baseline or follow-up fitness test will be excluded from the main analysis.

Blood Pressure measurements were taken by trained individuals with a random zero sphygmomanometer (Writing Group of PREMIER, 2003). In a study done by

Labarthe et al (1973), the Random Zero sphygmomanometer means for both systolic and diastolic blood pressure did not significantly differ from the respective blood pressure means of 6 other blood pressure instruments, showing concurrent validity (Labarthe, Hawkins, and Remington, 1973). This instrument is often referred to as the "gold standard" of blood pressure measurements in epidemiological studies because it attenuates the zero digit preference (Gillman and Cook, 1995). Blood pressure measurements were obtained after the participant sat quietly for at least 5 minutes. Two measurements were taken at each visit (baseline, 3 months, 6 months, and 18 months), all on the right arm with an appropriate sized cuff. There was at least a 30 second interval between each measurement. Four sets of blood pressure measurements were taken over three months and averaged to determine baseline blood pressure. The same protocol was used for the 6 and 18 month follow-ups (Young et al, 2005).

Triglycerides and HDL cholesterol were measured from a blood sample obtained after a 12 hour fast (Writing Group of PREMIER, 2003). Analyses were performed at the Core Laboratory for Clinical Studies at Washington University, St. Louis, MO (Svetkey et al, 2003).

Serum glucose levels were assessed using the intravenous glucose tolerance test with minimal model analysis after a 12 hour fast (Ard, Grambow, Liu, Slentz, Kraus, and Svetkey, 2004). Serum glucose levels were measured on the Roche Cobas Mira Plus using the Hexokinase/G-6-PD methodology (Ard et al, 2004). When this assay was compared to two others, the "r" correlations were greater than 0.95, showing concurrent validity (Sasieta and Jimeno, 1996).

Waist circumference was measured by trained staff using anthropometric measuring tape at baseline, 6 months, and 18 months (Ard et al, 2004). Waist circumference has been found to be better correlated with cardiovascular disease risk factors such as glucose, high blood pressure, and a negative lipid profile than body mass index (BMI) (Zhu, Wang, Heshka, Heo, Faith, and Heymsfield, 2002). Waist circumference is also highly correlated to BMI at 0.891 and 0.880 in men and women, respectively (Zhu et al, 2002). When the intraclass reliability of waist circumference was measured in 4 slightly different sites on the waist in both men and women, the reliability coefficients of all sites were above 0.99 (Wang, Thornton, Bari, Williamson, Gallagher, Heymsfield, Horlick, Kotler, Laferrère, Mayer, Pi-Sunyer, and Pierson, 2003).

All measurements were taken at baseline, six months, and 18 months. Six months was chosen as the primary follow up point for three reasons: (1) those with stage one hypertension need to begin medication after 6 months; (2) 6 months gives maximum blood pressure data for analysis; and (3) adherence to lifestyle changes peaks at 6 months (Svetkey et al, 2003). Although 6 months was the primary outcome, it was the 18 month follow up data that gives the PREMIER study its public health importance. Previous studies have shown that health benefits persist up to 6 months, but it is important to see if it is possible for these benefits to persist over time (Svetkey et al, 2003).

Statistical Analysis

Participants were classified as having the Metabolic Syndrome according the NCEP definition. Briefly, they had to have three or more of the following, above normal waist circumference, elevated triglycerides, low HDL, hypertension, or an elevated

fasting glucose. Refer to table 1 for the specific criteria for this classification. At baseline, there were no significant differences among the participants in any of the three intervention groups (Writing Group of PREMIER, 2003). See table 3 for complete baseline characteristics. For participants with missing data the following adjustments will be applied: if only 1 criterion was missing, but the participant still had 3 or more of the risk factors associated with the syndrome, that participant was classified as having the Metabolic Syndrome. However, if one or more criterion was missing and the participant did not have three or more of the risk factors, that participant was eliminated from the analysis (Lien et al, 2007).

For the purpose of this paper, the two intervention treatment groups were combined into one to isolate the effects of the change in fitness on the Metabolic Syndrome relative to the advice-only control group. To test for that effect, a logistic regression analysis model was used. The main independent variable was intervention status. To isolate the change in fitness from other aspects of the intervention, the dietary component of the intervention was adjusted for in the model along with other possible confounding factors such as race, gender, age, trial site, and cohort. The specific dietary components that were adjusted for are as follows: total calories per day, sodium intake per day, alcohol consumption per day, percentage of kilocalories from fat and saturated fat per day, the fruit and vegetable servings, and the low fat dairy servings. For the above-stated variables, the average respective follow-up values were co-varied for in the model. Analyses were run with and without weight status to determine if possible effects of fitness change on Metabolic Syndrome are independent of or mediated by change in weight. If race is significant in the logistic regression, a stratified logistic regression will

be done by race to further test for the effect of race on Metabolic Syndrome prevalence in response to treatment status. For all analyses, a P value of 0.05 will be needed to reach significance.

Results

Baseline Characteristics

Of the 810 participants randomized, 6 did not have sufficient data to be classified as having or not having Metabolic Syndrome and were excluded. Therefore, 804 participants were included in the present analysis. The 804 participants analyzed for the current analysis were divided into two treatment groups, advice-only (control) group (n=271) and a combined treatment group (n=533). The latter group consisted of the established guidelines group and the established guidelines plus DASH diet group from the original PREMIER study design. See figure 1 for details.

Table 7 displays baseline characteristics of the 804 included participants by their respective randomized treatment groups. The mean age in both groups was approximately 50 years. In the advice-only group, 63.5% were female and 36.9% were African American. In the combined lifestyle treatment group, 61.5% were female and 33.0% were African American. Most participants had at least some college education, did not currently smoke cigarettes, and were overweight or obese. The average stage 2 heart rate was approximately 130 beats per minute (bpm) in both groups. Approximately half of the participants in each group had Metabolic Syndrome at baseline. The prevalence was 47.2% and 49.9% in the advice-only and combined treatment groups, respectively. The prevalence of Metabolic Syndrome in African Americans (42.8%) was slightly less than the prevalence in non-African Americans (47.7%).

Table 7. Baseline Characteristics by Randomized Treatment Group

Characteristic	Advice Only (n = 271)	Combined Treatment Groups* (n = 533)
Age, mean (SD) y	49.5 (8.9)	50.2 (8.9)
Female	63.5%	61.5%
Race or ethnicity		
African American	36.9%	33.0%
Non-African American	63.1%	70.0%
Annual Household Income		
<$30,000	14.0%	8.4%
$30,000 - $60,000	30.3%	32.3%
>$60,000	51.7%	55.9%
Unknown (no answer)	4.1%	3.4%
Education		
High school or less	10.7%	8.4%
Some college	60.5%	58.2%
Some graduate school	28.8%	33.4%
Current Cigarette Smokers	5%	5%
BMI, mean (SD)	32.9 (5.58)	33.2 (5.9)
Weight Classification		
Non-overweight (BMI < 25)	4.8%	4.5%
Overweight (BMI 25-29.9)	27.7%	29.8%
Obese (BMI >30)	66.8%	64.7%
Stage 2 Heart Rate, mean bpm**	130.2 (14.5)	130.1 (14.4)
Current Metabolic Syndrome	47.2%	49.9%
Metabolic Syndrome Risk Factors***		
Central waist obesity	79.3%	80.5%
Hypertriglyceridaemia	31.7%	34.3%
Low HDL-C	43.5%	49.0%
Elevated blood pressure	74.5%	77.9%
Fasting glucose > 109 mg/dl	9.6%	14.1%

*Combination of the Established Guidelines group and the Established Guidelines plus DASH diet group form original PREMIER study

**The mean stage 2 heart rate, measured in beats per minute (bpm), as determined from the VO_2 max treadmill test to determine fitness level.

***Metabolic Syndrome as classified by NCEP guidelines

- Central waist obesity (F): >88cm; (M): >102cm
- Hypertriglyceridaemia: triglycerides > 149 mg/dl
- HDL-C: (F): < 50 mg/dl; (M): < 40 mg/dl
- Elevated blood pressure: blood pressure > 129/84 OR medication
- Fasting glucose > 109 mg/dl

Relationship of Treatment, Fitness and Metabolic Syndrome

At the six month follow-up, treatment group assignment (advice-only control versus the combined lifestyle intervention groups) was significantly related to an increase in aerobic fitness (F=0.008). However, this relationship was no longer significant at the 18 month follow-up (F=0.85). Figure 2 shows the unadjusted percentages of participants, by treatment group assignment, with Metabolic Syndrome at baseline, 6 month follow-up, and 18 month follow-up. At baseline and both the 6 and 18 month follow-up visits, fitness was significantly related to the presence of Metabolic Syndrome. Lower fitness levels was associated with higher prevalence of Metabolic Syndrome ($P<0.02$; $P<0.0001$; and $P<0.0001$ for each time point, respectively). This significant relationship remains after adjusting for age, sex, BMI, race, and baseline fitness levels ($P<0.004$; $P<0.0001$; and $P<0.0001$ for each time point, respectively). Figure 3 shows the change in stage 2 heart rate, representing aerobic fitness, of the participants by Metabolic Syndrome Status at each respective time point. From baseline to 6 months as well as from baseline to 18 months, the fitness level of participants in both randomized treatment groups increased. Importantly, fitness level increased at 6 months and 18 months, regardless of race, although African Americans had a slightly more modest increase than non-African Americans at both time points ($P=0.03$ and $P<0.0001$, respectively).

Figure 2

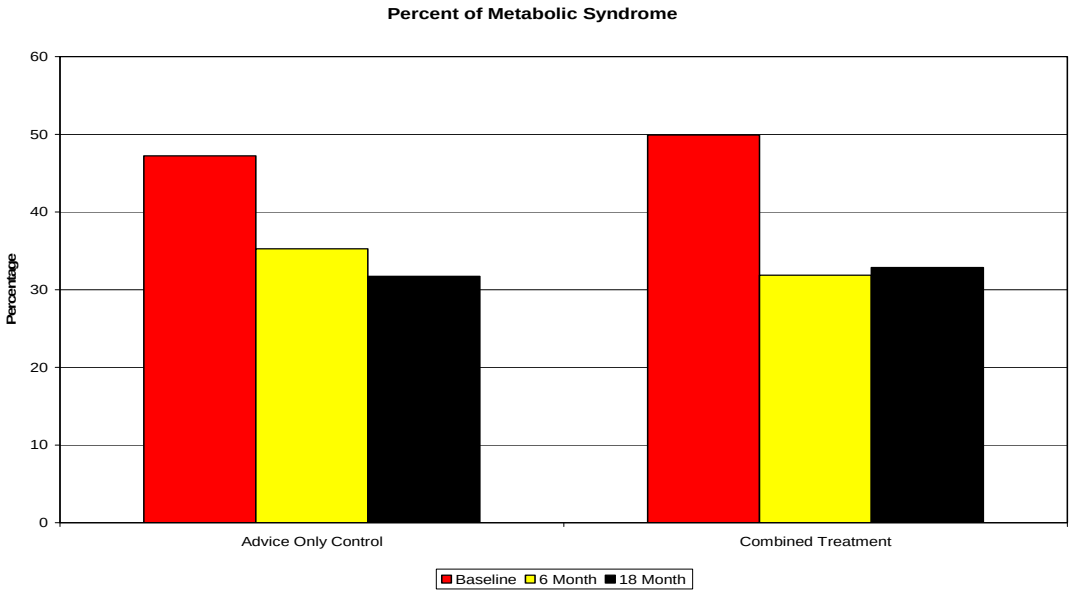
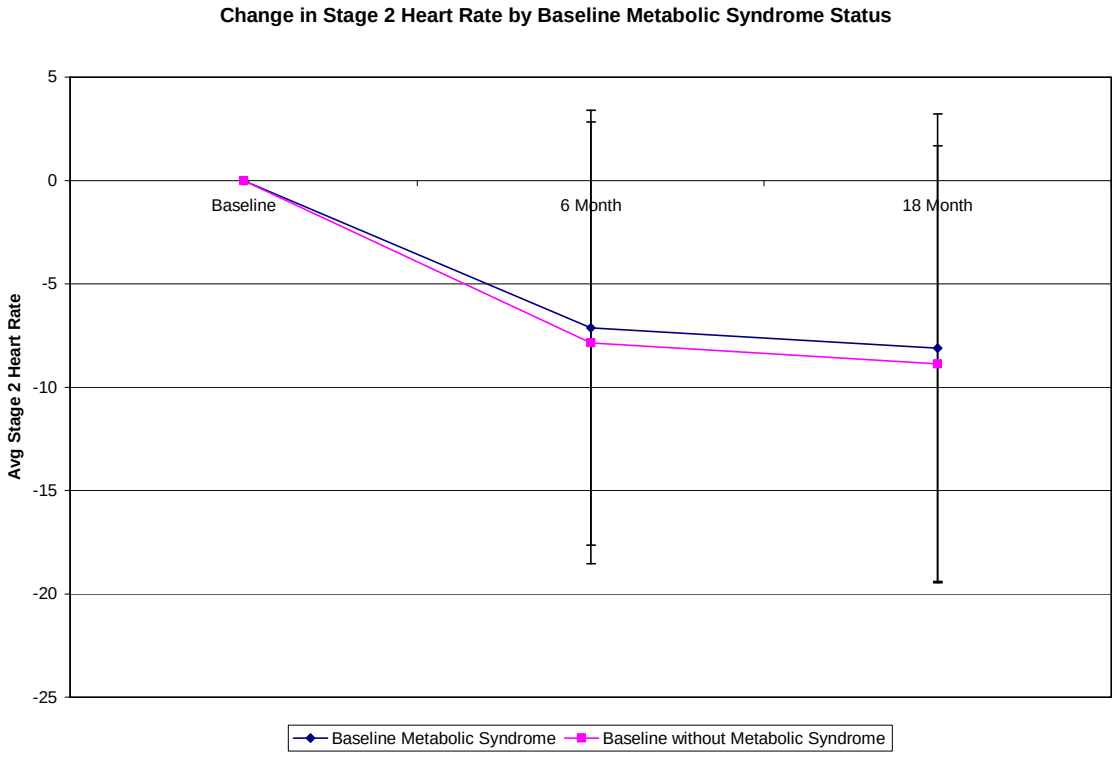


Figure 3



Primary Outcome: Predictors of Metabolic Syndrome at 6 and 18 month follow-ups

The main results for the change in aerobic fitness and prevalence of Metabolic Syndrome at 6 months are presented in Table 8. All data examining the change in aerobic fitness has only 665 participants at the 6 month follow up and 656 participants at the 18 month follow up due to missing fitness data. The assigned treatment group had no effect on prevalence of Metabolic Syndrome at the 6 month follow-up (P=0.17). However, all participants increased their fitness, by lowering their stage 2 heart rate, regardless of treatment status (Figure 4). Importantly, a positive change in aerobic fitness significantly impacted the odds of having Metabolic Syndrome at the 6 month follow-up (P=0.0003). At six months, a one beat per minute reduction in stage 2 heart rate was associated with a 4% reduction in the odds of prevalent metabolic syndrome (OR: 0.96, CI: 0.94 – 0.98).

The 18 month results are presented in table 9. At 18 months, the assigned treatment group still had no significant effects. Importantly, the decreased odds for the prevalence of Metabolic Syndrome due to an increase in aerobic fitness remained the same at 18 months as it was for the 6 month follow-up (OR: 0.96; CI: 0.94 – 0.98). The odds for having Metabolic Syndrome were still 4% less for every one beat per minute reduction in stage 2 heart rate (P<0.0005). Interestingly, race had no significant effect on the prevalence of Metabolic Syndrome at either time point.

Table 8. Change in Aerobic Fitness and Prevalence of Metabolic Syndrome at 6 Months*

	Odds Ratio	P value	95%Confidence Interval
Treatment **	0.71	0.17	0.44 – 1.15
1 beat change in HR	**0.96**	**.0003**	**0.94 – 0.98**
Race (non-AA vs. AA)	0.71	0.21	0.41 – 1.21

*Models for treatment and change in fitness variables were separate. Both controlled for site, cohort, age, sex, race, BMI, baseline fitness, baseline Metabolic Syndrome, and dietary variables (daily alcohol intake, dairy consumption, fruit and vegetable intake, total fat intake, sodium consumption, and fat servings per day)

**Advice-only versus combined treatment group

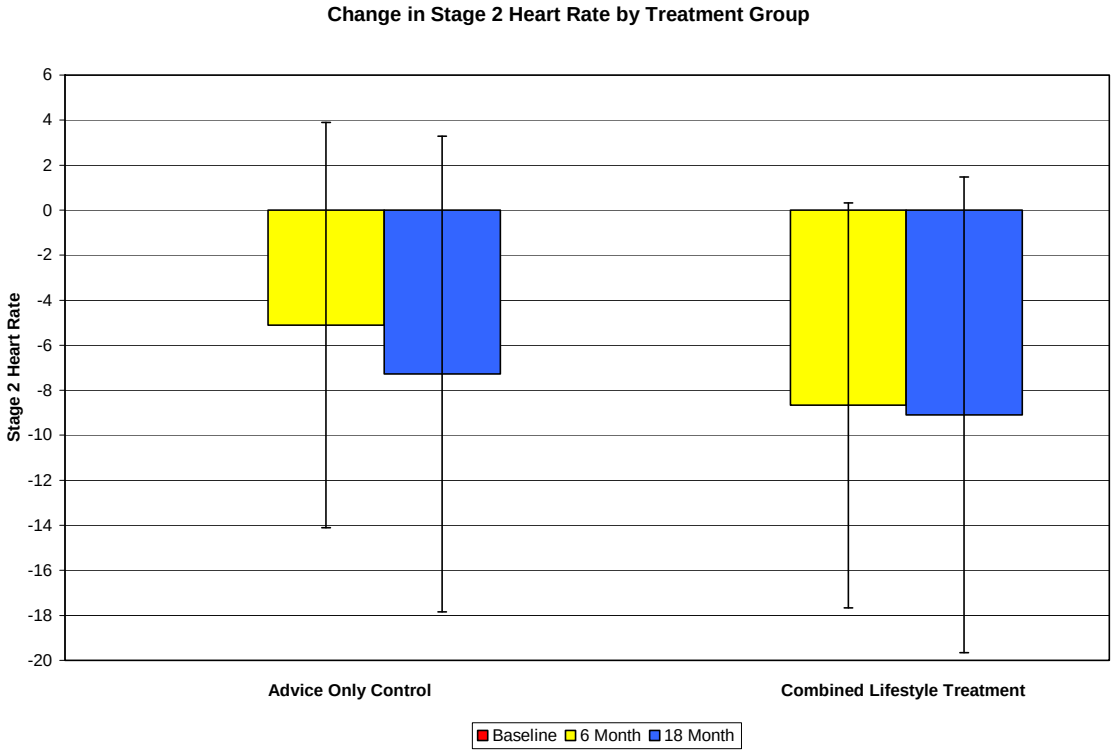
Table 9. Change in Aerobic Fitness and Prevalence of Metabolic Syndrome at 18 months*

	Odds Ratio	P value	95%Confidence Interval
Treatment***	1.00	1.00	0.63 – 1.58
1 beat change in HR	**0.96**	**0.0005**	**0.94 – 0.98**
Race (non-AA vs. AA)	0.70	0.19	0.41 – 1.19

*Models for treatment and change in fitness variables were separate. Both adjusted for site, cohort, age, sex, race, BMI, baseline fitness, baseline Metabolic Syndrome, and dietary variables (daily alcohol intake, dairy consumption, fruit and vegetable intake, total fat intake, sodium consumption, and fat servings per day)

** Advice-only versus combined treatment group

Figure 4



Predictors of Metabolic Syndrome at 6 months stratified by presence of Metabolic Syndrome at baseline

Presence of Metabolic Syndrome at baseline was a significant predictor of having Metabolic Syndrome at the 6 month follow-up. Therefore, we stratified the analysis by presence of Metabolic Syndrome at baseline. Race was not reported for this analysis because it was not a significant predictor of Metabolic Syndrome prevalence at 6 months. Table 10 displays the results for those with and without Metabolic Syndrome at baseline. Of the 323 participants who had Metabolic Syndrome at baseline, only 184 still had it at 6 months. Of the 338 participants who were free of Metabolic Syndrome at baseline 26 participants had it at six months. Only 11 of these participants were in the advice-only control group and 15 were in the combined lifestyle treatment group.

The treatment status had no effect on participants with or without Metabolic Syndrome at baseline. For individuals with baseline Metabolic Syndrome, the odds of no longer having Metabolic Syndrome at the 6 month follow-up are significantly increased with increasing aerobic fitness (P<0.0001). For every one beat per minute reduction in stage 2 heart rate the odds of still having it at baseline are decreased by 5% (OR:0.95, CI: 0.92 – 0.97). However, for those who did not have Metabolic Syndrome at baseline, a change in aerobic fitness had no significant impact on the incidence of Metabolic Syndrome at the 6 month follow-up.

Table 10. Change in Aerobic Fitness on Prevalence of Metabolic Syndrome at 6 months stratified by baseline Metabolic Syndrome status*

	N	Odds Ratio	P value	95% Confidence Interval
Treatment**				
Baseline MS				
Yes	323	0.65	0.14	0.36 – 1.15
No	338	0.70	0.46	0.27 – 1.81
Change in Aerobic Fitness				
Baseline MS				
Yes	317	**0.95**	**<0.0001**	**0.92 – 0.97**
No	338	1.00	0.81	0.95 – 1.04

*Models for treatment and change in fitness variables were separate. Both controlled for site, cohort, age, sex, race, BMI, baseline fitness, baseline Metabolic Syndrome, and dietary variables (daily alcohol intake, dairy consumption, fruit and vegetable intake, total fat intake, sodium consumption, and fat servings per day)
**Advice-only versus combined treatment group

Predictors of Metabolic Syndrome at 18 months stratified by presence of Metabolic Syndrome at Baseline

Table 11 displays the results for the participants with and without Metabolic Syndrome at the 18 month follow-up. Treatment group was not a significant predictor of follow-up Metabolic Syndrome for participants with or without Metabolic Syndrome at baseline. For participants with Metabolic Syndrome at baseline, increasing aerobic

fitness by one beat per minute reduced the odds for having Metabolic Syndrome at 18 months by 6% (OR: 0.94, CI: 0.92 -0.97). Of the 323 participants who had Metabolic Syndrome at baseline, only 116 still had it at the 18 month follow-up. Of the 338 participants who were Metabolic Syndrome-free at baseline, 11 participants from the advice-only control group and 22 participants from the combined lifestyle group got Metabolic Syndrome at 18 months. For participants who did not have Metabolic Syndrome at baseline, an increase in fitness is not a significant predictor of Metabolic Syndrome at 18 months.

Table 11. Change in Aerobic Fitness on Prevalence of Metabolic Syndrome at 18 months stratified by baseline Metabolic Syndrome status*

	N	Odds Ratio	P value	95% Confidence Interval
Treatment**				
Baseline MS				
Yes		0.95	.86	0.55 – 1.64
No		1.03	.96	0.39 – 2.69
Change in Aerobic Fitness				
Baseline MS				
Yes		**0.94**	**<.0001**	**0.92 – 0.97**
No		0.99	.62	0.95 – 1.03

*Models for treatment and change in fitness variables were separate. Both controlled for site, cohort, age, sex, race, BMI, baseline fitness, baseline Metabolic Syndrome, and dietary variables (daily alcohol intake, dairy consumption, fruit and vegetable intake, total fat intake, sodium consumption, and fat servings per day)

** Advice-only versus combined treatment group

Predictors of Metabolic Syndrome at 6 months stratified by weight loss

Baseline BMI was a significant predictor of prevalence of Metabolic Syndrome at the 6 month and 18 month follow-up (OR: 0.92, CI: 0.88 – 0.96; and OR: 0.91, 0.87 – 0.95, respectively). Therefore, we ran a second stratified analysis by weight loss. Because race was not a significant predictor of Metabolic Syndrome prevalence at either follow-up, results for race are not shown in this analysis. Further, there was not a significant difference in weight loss between the two races at either 6 or 18 months

(P=0.45 and P=0.88, respectively) (results not shown). Participants were divided into 2 groups; the first were those who lost at least 4kg of body weight (n=397) and the second were those who lost less than 4kg of body weight (n=248). For those who lost at least 4kg, the average weight loss was 10.0kg (+/-15.2kg) at 6 months. (Figure 5) The results for this analysis are presented in table 12. Treatment group assignment had no significant effect on either weight group. An increase in aerobic fitness was only a significant predictor of Metabolic Syndrome for the participants who lost greater than 4 kg of body weight (OR: 0.97; CI: 0.94 - 0.99). For each beat per minute reduction in stage 2 heart rate, the odds of having Metabolic Syndrome at the 6 month follow-up were 3% less (P=0.01). For those who did not lose at least 4kg of body weight, an increase in aerobic fitness was not a significant predictor of Metabolic Syndrome at the 6 month follow-up (P=0.59).

Figure 5

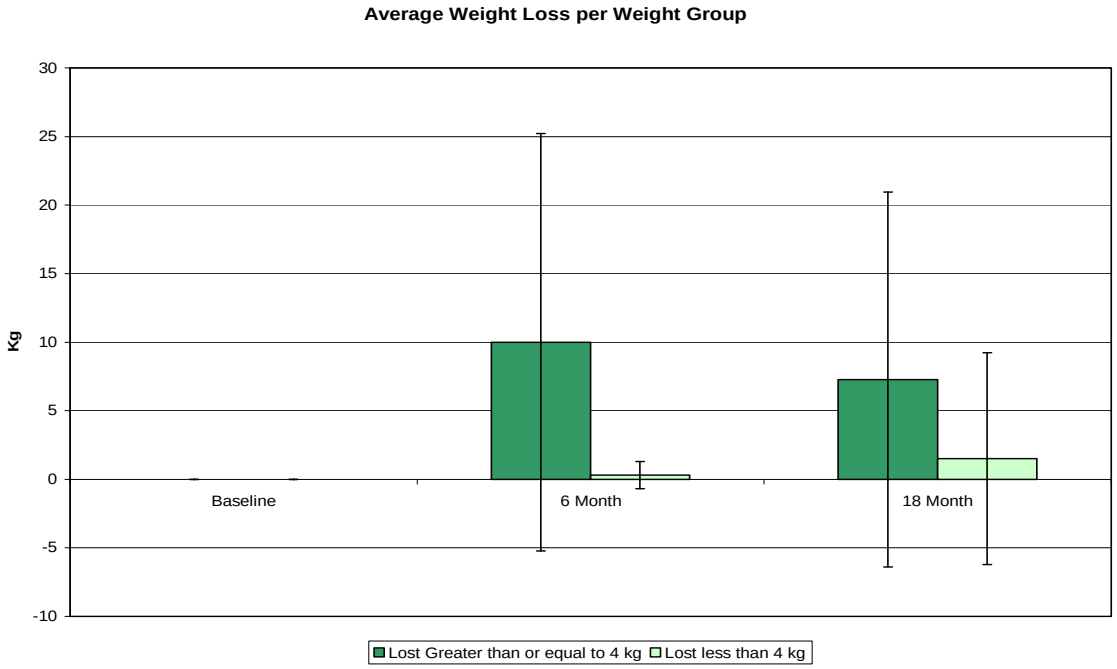


Table 12. Change in Aerobic Fitness on Prevalence of Metabolic Syndrome at 6 months stratified by weight loss status*

	N	Odds Ratio	P value	95% Confidence Interval
Treatment**				
Weight Group				
Lost >4 kg	397	0.74	0.45	0.34 – 1.61
Lost <3.99 kg	248	1.83	0.13	0.84 – 3.97
1 beat change in stage 2 HR				
Weight Group				
Lost >4 kg	397	**0.97**	**0.01**	**0.94 – 0.99**
Lost <3.99 kg	248	0.99	0.59	0.94 – 1.03

*Models for treatment and change in aerobic fitness are separate. Both are adjusted for site, cohort, age, sex, race, baseline body weight, baseline fitness, baseline Metabolic Syndrome, and dietary variables (daily alcohol intake, dairy consumption, fruit and vegetable intake, total fat intake, sodium consumption, and fat servings per day)
**Advice-only versus combined treatment group

Predictors of Metabolic Syndrome at 18 months stratified by weight loss

As previously mentioned, BMI was a significant predictor of the prevalence of Metabolic Syndrome at 18 months (OR: 0.91, 0.87 – 0.95). Table 13 displays the 18 month follow-up results of Metabolic Syndrome stratified by weight group. Treatment group remained insignificant for the 18 month prevalence of Metabolic Syndrome. For the participants who lost at least 4 kg of body weight, an increase in aerobic fitness was a significant predictor of Metabolic Syndrome at 18 months (OR: 0.97; CI: 0.94 -1.00). For participants in the weight loss group, the odds of having Metabolic Syndrome at the 18 month follow-up are decreased by 3% for every one beat per minute reduction in stage 2 heart rate (P=0.03). For those who did not lose at least 4kg of body weight at 18 months, an increase in fitness was not a significant predictor of Metabolic Syndrome for that time frame. However, there was a trend toward significance (P=0.07), showing that an increase in aerobic fitness may be a more significant predictor of Metabolic Syndrome long term, regardless of weight loss.

Table 13. Change in Aerobic Fitness on Prevalence of Metabolic Syndrome at 18 months stratified by weight loss status *

	N	Odds Ratio*	P value	95% Confidence Interval
Treatment**				
Weight Group				
Lost >4 kg		1.33	.44	0.65 – 2.73
Lost <3.99 kg		1.41	.34	0.70 – 2.85
1 beat change in stage 2 HR				
Weight Group				
Lost >4 kg		**0.97**	**.03**	**0.94 – 1.00**
Lost <3.99 kg		0.96	.07	0.93 – 1.00

*Models for treatment and change in aerobic fitness are separate. Both are adjusted for site, cohort, age, sex, race, baseline body weight, baseline fitness, baseline Metabolic Syndrome, and dietary variables (daily alcohol intake, dairy consumption, fruit and vegetable intake, total fat intake, sodium consumption, and fat servings per day)
**Advice-only control versus treatment group

Secondary Outcome: Predictors of individual risk factors for Metabolic Syndrome at 6 months

The combined lifestyle treatment group had no significant effects on the prevalence of Metabolic Syndrome at either follow-up. However, we ran a series of models predicting each respective risk factor in order to determine if any individual risk factors of the Metabolic Syndrome were being impacted by the combined lifestyle treatment group. Because aerobic fitness was a significant indicator of follow-up Metabolic Syndrome, we were interested in precisely which risk factors it had the largest impact on. Table 14 displays the predictors for these individual risk factors at the 6 month follow-up. Of the five risk factors included in the Metabolic Syndrome definition (elevated blood pressure, elevated triglycerides, high waist circumference, low HDL and high fasting glucose), treatment group was a significant predictor of elevated blood pressure (OR: 0.54; CI: 0.36 – 0.82) and high waist circumference (OR: 0.42 CI: 0.19 – 0.95), but not for any of the other Metabolic Syndrome risk factors. Participants in the combined treatment group were 48% and 59% less likely to have elevated blood pressure

(P<0.002) or a high waist circumference (P<0.02), respectively, at 6 months compared to the advice-only control. An increase in aerobic fitness had a larger impact on the individual risk factors or Metabolic Syndrome. All risk factors except for low HDL are significantly impacted by an increase in aerobic fitness. For elevated blood pressure and elevated triglycerides, the odds of having Metabolic Syndrome at 6 months are 2% and 3% less, respectively, with each beat per minute decrease in stage 2 heart rate (OR: 0.98; CI: 0.96 – 1.00; and OR: 0.97; CI: 0.94 – 0.99). For both high waist circumference and high fasting glucose, the odds of having Metabolic Syndrome at 6 months are 7% less for each beat per minute decrease in stage 2 heart rate (OR: 0.93; CI: 0.90 – 0.97; OR: 0.93; CI: 0.90 – 0.97).

Secondary Outcome: Predictors of individual risk factors for Metabolic Syndrome at 18 months

Table 15 displays the predictors for the individual Metabolic Syndrome risk factors at 18 months. The treatment group remained a significant predictor of high waist circumference (OR: 0.34; CI: 0.16 – 0.70) but not elevated blood pressure at 18 months. Participants in the combined lifestyle treatment group were 66% less likely to experience high waist circumference measurements than those in the advice-only control group (P=0.003). An increase in aerobic fitness remained a significant predictor of elevated blood pressure, high waist circumference, and high fasting glucose (OR: 0.97; CI: 0.95 – 0.99; OR: 0.95; CI: 0.92 – 0.98; OR: 0.95; CI: 0.92-0.99). An increase in aerobic fitness did not remain a significant predictor for high fasting glucose at the 18 month follow-up.

Table 14. Change in Aerobic Fitness and Prevalence of Individual Risk Factors for Metabolic Syndrome at 6 Months*

	Treatment			1 beat change in HR		
	OR**	CI (95%)	P	OR	CI(95%)	P
Elevated Blood Pressure	**0.52**	**0.34 – 0.79**	**.002**	**0.98**	**0.96 – 1.00**	**.02**
Elevated Triglycerides	0.76	0.46 – 1.26	.29	**0.97**	**0.94 – 0.99**	**.005**
High Waist Circumference	**0.39**	**0.18 – 0.87**	**.02**	**0.93**	**0.90 – 0.97**	**.0001**
Low HDL	1.23	0.74 – 2.06	.43	1.01	0.99 – 1.03	.45
High Fasting Glucose	0.68	0.33 – 1.40	.30	**0.93**	**0.90 – 0.97**	**.0003**

* Separate models were adopted for the treatment and change in fitness variables. Both adjusted for site, cohort, age, sex, race, BMI, baseline fitness, baseline status of each respective risk factor, and dietary variables (daily alcohol intake, dairy consumption, fruit and vegetable intake, total fat intake, sodium consumption, and fat servings per day)
**Advice-only versus combined treatment group
Referent is absence of risk factor

Table 15. Change in Aerobic Fitness and Prevalence of Individual Risk Factors for Metabolic Syndrome at 18 Months*

	Treatment			1 beat change in HR		
	OR**	CI(95%)	P	OR	CI(95%)	P
Elevated Blood Pressure	0.93	0.62 – 1.36	.67	**0.97**	**0.95 – 0.99**	**.0008**
Elevated Triglycerides	0.68	0.40 – 1.16	.16	0.99	0.96 – 1.01	.34
High Waist Circumference	**0.34**	**0.16 – 0.70**	**.003**	**0.95**	**0.92 – 0.98**	**.003**
Low HDL	0.94	0.60 – 1.49	.80	0.99	0.97 – 1.01	.25
High Fasting Glucose	1.12	0.55 – 2.31	.76	**0.95**	**0.92 – 0.99**	**.009**

*Separate models were adopted for the treatment and change in fitness variables. Both adjusted for site, cohort, age, sex, race, BMI, baseline fitness, baseline status of each respective risk factor, and dietary variables (daily alcohol intake, dairy consumption, fruit and vegetable intake, total fat intake, sodium consumption, and fat servings per day)
**advice-only versus combined treatment group
Referent is absence of risk factor

Discussion

In our study population, the prevalence of Metabolic Syndrome at baseline was approximately 50%. Although this is much higher than the 35% prevalence of Metabolic Syndrome in the overall population as reported by the most recent NHANES data, our sample consisted of only individuals with above optimal blood pressure. Ford (2005) reported that individuals with hypertension have greater than a 2 fold increase in risk for having the Metabolic Syndrome when compared to individuals with normal blood pressure (Ford, 2005). Therefore, it was to be expected that the prevalence of Metabolic Syndrome in the current sample would be higher than the national average.

The prevalence of Metabolic Syndrome decreased from baseline to 6 months by 12% and from baseline to 18 months by 16% in the advice-only control group. In the treatment group, the prevalence of Metabolic Syndrome decreased by 18% and 17% at 6 and 18 months, respectively. These prevalence decreases appear reasonable as they compare with prevalence decreases reported by Stewart and colleagues (2005) in the analysis of the Senior Hypertension and Physical Exercise trial. Stewart et al reported that in men and women aged 55-75 years, after a 6 month exercise trial, the prevalence of Metabolic Syndrome decreased by 17.7% in the exercise group and 8.2% in the control group (Stewart et al, 2005). Although in the present analysis the control group and the treatment group showed similar decreases, this can be explained because the control group also changed their fitness and lost weight.

We hypothesized that the treatment status would cause an increase in aerobic fitness for the combined lifestyle treatment group, and that this treatment group would

have significantly less prevalence of Metabolic Syndrome at both follow-up time points. Our results did not fully support this hypothesis. Treatment status had no significant effects on Metabolic Syndrome prevalence at either the 6 or 18 month follow-up. However, an increase in aerobic fitness was significantly related to treatment status (P=0.008) at 6 months only. At 18 months, the fitness levels between the two intervention groups were not significantly different, which could explain the loss of significance between aerobic fitness and treatment status. At both 6 and 18 months, aerobic fitness was a significant predictor of Metabolic Syndrome prevalence independent of treatment status. Therefore, aerobic fitness is a mediator between treatment status and follow-up prevalence of Metabolic Syndrome at 6 months.

At 18 months increasing aerobic fitness no longer explains the lack of significance for treatment status. In addition to the similarities between the fitness levels of participants in both intervention groups, it is plausible that other mediators, such as weight loss, were contributing to the decreased Metabolic Syndrome status. When the main results for PREMIER were published, it was reported that participants in the control group from this study lost weight (Writing Group of PREMIER, 2003). We found that weight loss was a significant contributor to decreased Metabolic Syndrome prevalence at 6 and 18 months. Thus, it is plausible that weight loss was the mediator between treatment status and Metabolic Syndrome prevalence at 18 months.

There was an inverse relationship between increasing aerobic fitness and prevalence of Metabolic Syndrome in our sample. This relationship was to be expected as it agrees with previous cross sectional (Kullo et al, 2002; Farrell, et al, 2004; Lee, Kuk et al, 2005) and longitudinal studies (Laaksonen et al, 2002; Carnethon et al, 2003;

Palaniappan et al, 2004; Ekelund et al, 2005). Two studies of adults (Mathieu, Brochu, and Beliveau, 2008; & Carnethon et al, 2003) show support for our results. Mathieu et al (2008) found that increasing aerobic capacity had a 0.28 effect size in decreasing the prevalence of Metabolic Syndrome by 25%. However, that study included only 29 participants. Our results have greater public health impact due to our large and racially diverse sample. In the CARDIA study, a sub-set of participants with an average age of 25 at baseline, took a treadmill duration fitness test at baseline and at a 7 year follow-up. After adjusting for covariables, improving aerobic fitness was associated with approximately a 50% reduction in for developing Metabolic Syndrome after 7 years, showing a protective benefit of cardiovascular fitness. However, there is no evidence from this study of fitness being used as a treatment for the Metabolic Syndrome. In contrast, Thompson et al found that in Native American women, aerobic fitness was not significantly associated with Metabolic Syndrome after adjusting for age and BMI. However, the sample was not racially diverse and included only women. The mean age was also 20 years younger than the age of participants in our sample. Therefore, it appears that higher aerobic fitness levels have a protective effect against prevalence of Metabolic Syndrome in middle-aged adults.

Further analysis revealed that for the participants who had Metabolic Syndrome at baseline, the prevalence of Metabolic Syndrome at 6 and 18 months decreased by approximately 36% and 49%, respectively, in response to an increase in aerobic fitness. These results are consistent with other studies showing that Metabolic Syndrome is reversible by improving aerobic fitness (Anderssen, Carroll, Urdal, and Holme, 2006; Maxwell, Goslin, Gellish, Hightower, Olson, Moudgil, and Russi, 2008). Anderssen et al

(2006) found that for every one mL/kg/min unit increase in aerobic fitness, there is a 32% increase in the likelihood that Metabolic Syndrome (using the IDF definition) will be reversed after one year. Although it was a randomized controlled trial, only 188 men were included in the analyses. Maxwell et al (2008) found that after a three-year period, all participants who reversed their Metabolic Syndrome also improved their aerobic fitness. Participants who were Metabolic Syndrome-free at baseline, but had Metabolic Syndrome after 3 years, decreased their fitness. However, the magnitude of the impact of aerobic fitness on Metabolic Syndrome was not reported. Although both aerobic fitness and Metabolic Syndrome changes were statistically tested, the relationship between them was not. It is interesting to note that the reversal of Metabolic Syndrome due to increased aerobic fitness stays stable or improves over time. Changing aerobic fitness may be one important aspect of improving long-term health effects.

It was hypothesized that race would be a significant predictor of follow-up prevalence of Metabolic Syndrome. It was expected that the African American subgroup would see a lesser change than the non-African American participants. However, race was not a significant indicator of Metabolic Syndrome at either follow-up. It has been previously reported that there are physiological and cultural differences between African Americans and non-African Americans that make African Americans more prone to certain cardiovascular risk factors, specifically, hypertension (Thomas et al, 1987 & Reiner et al, 2007). In a review article, Jamerson (1993) reported that African Americans also respond differently to treatment than non-African Americans (Jamerson, 1993). However, in the current study, all participants lost weight and improved their fitness, resulting in lower prevalence of Metabolic Syndrome, regardless of race. Our data show

that improving fitness and losing weight should be the primary treatment targets for Metabolic Syndrome in African Americans and non-African Americans. For interventions aiming to reduce the prevalence of Metabolic Syndrome through an improvement in aerobic fitness, it does not appear to be necessary to provide separate interventions for these two races.

In our sample, BMI was one of the predictors of Metabolic Syndrome at both 6 (OR: 0.92, CI: 0.88 – 0.96) and 18 (OR: 0.91, 0.87 – 0.95) months. This relationship has been shown in many previous studies examining predictors of Metabolic Syndrome (Mathieu et al, 2008; Okura et al, 2007, Thompson, Herman, Helitzer, Wilson, Whyte,, Perez, & Wolfe, 2007; Ribisl, Lang, Jaramillo, jakicic, Stewart, Bahnson, Bright, Curtis, Crow, & Soberman, 2007; Eisenmann, Wlek, Wickel, & Blair, 2006; and Carnethon et al, 2004). Although our primary analysis indicated that aerobic fitness was significantly related to prevalence of Metabolic Syndrome even after adjusting for BMI, the 4 kg weight loss stratification results suggests that body weight is an important mediator between aerobic fitness and prevalence of Metabolic Syndrome at 6 and 18 months. Importantly, our results are consistent with previous research showing the link between weight loss and cardiovascular disease risk factors associated with Metabolic Syndrome. Carnethon et al (2004) found that for every 4.5kg of body weight gained, risk for Metabolic Syndrome increases 23%. Krebs et al reported that that a sustained loss of 10% body weight is needed for long term health benefits (Krebs, Evans, Conney, Mishra, Fruhbeck, Finer, & Jebb, 2002).

It is apparent from our results that in a racially diverse sample of middle aged men and women, an increase in aerobic fitness reduces the prevalence of Metabolic

Syndrome after 6 and 18 months. However, this increase in fitness is more strongly associated with certain risk factors that constitute Metabolic Syndrome than it is with others. Of the five risk factors included in the Metabolic Syndrome definition (elevated blood pressure, elevated triglycerides, high waist circumference, low HDL and high fasting glucose), all except for low HDL are significantly impacted by an increase in aerobic fitness after 6 months. These results are in agreement with Mathieu et al (2008), who reported that a physical activity and aerobic fitness intervention significantly improved blood pressure, waist circumference, and HDL cholesterol. Although there were some discrepancies in the risk factors, they can be explained by the many differences in the two study designs. In the Mathieu study, the effects of increased aerobic fitness were not separated from the effects of the physical activity for the individual risk factor analyses. This study also had fewer participants (n=29) and more normal weight than overweight participants (15:14) (Mathieu et al, 2008). The strong differences in the sample population between our study and this one could explain the slight differences in the results.

At the 18-month follow-up, triglycerides were no longer significantly impacted by an increase in aerobic fitness, and HDL cholesterol still showed no significant changes due to aerobic fitness increases. These results do not compare to the changes reported by Maxwell et al (2008) after a retrospective analysis on Metabolic Syndrome risk factor changes with fitness level changes. Maxwell and colleagues found that all of the Metabolic Syndrome risk factors measured were positively reduced due to an increase in fitness level after 3 years. Waist circumference was the only risk factor not measured in this analysis (Maxwell et al, 2008). However, the relationship between aerobic fitness

and Metabolic Syndrome risk factors was not statistically tested. It is only known that fitness increased and the risk factors decreased. Similarly, Hightower et al (2007) reported that after 2 years, participants of a health and fitness assessment center study reduced all risk factors of the Metabolic Syndrome except for waist circumference (not calculated). Interestingly, in this study, the most dramatic difference between participants who reversed their Metabolic Syndrome and those who did not was the triglyceride level and HDL cholesterol (Hightower et al, 2007). The previously mentioned results are in direct contrast with the results found in the current analysis, as we found that after 18 months, triglyceride level and HDL cholesterol were no longer impacted by an increase in aerobic fitness. However, in the Hightower study, fitness changes were not reported and all results were due to the combined aspects of the intervention. It is plausible that one of the other aspects of the health and fitness intervention was responsible for the large changes in triglycerides and HDL cholesterol. Overall, our results show that all risk factors of the Metabolic Syndrome except for triglycerides and HDL cholesterol can improve and be maintained long-term by increasing aerobic fitness. However, due to previously published results, it is possible that aerobic fitness may have an impact on all five risk factors and is an important intervention tool to decrease Metabolic Syndrome and all of the risk factors it entails.

Our study is not without limitations. As previously mentioned, there may not have been sufficient distinction between the control group and the treatment group. All participants in the trial were highly motivated individuals who were willing to participate in all aspects of the intervention, as they did not know which group they would be randomized into. The advice-only group, which served as the control, got two individual

sessions with an interventionist. During these sessions they received information about physical activity, weight loss, and dietary changes. This group increased their fitness even though they did not receive any additional pieces of the intervention. Importantly, the advice-only control group also lost weight. Because increasing aerobic fitness was an important mediator between treatment status and follow-up Metabolic Syndrome, and weight loss was an important mediator between aerobic fitness and follow-up Metabolic Syndrome, it is reasonable that the treatment status had no significant impact on Metabolic Syndrome prevalence at either follow-up. Further, our measurement of variables may have introduced some error. The zero sphygmomanometer, while being the current "gold standard" in blood pressure measurement, has been shown to give a lower reading of 1 to 3 mmHg of both systolic and diastolic blood pressure when compared with the mercury sphygmomanometer (Gillman and Cook, 1995). Due to randomization, any error introduced by this instrument should have been equally distributed among participants. Stage 2 heart rate was used as a predictor of fitness. Although heart rate and VO_2max are highly correlated (r=0.90) (ACSM, 2006), a maximal VO_2 test was not conducted. We also lost 146 participants due to missing follow-up fitness tests, which may have biased the results.

Our findings have great public health importance as they show that Metabolic Syndrome can be prevented and reversed in males and females as well as African Americans and non-African Americans by improving aerobic fitness. Importantly, these results can be maintained long-term as long as aerobic fitness levels remain elevated above baseline levels. The prevalence decreased from well above the national average of 35% at approximately 50% to below the national average at approximately 32% after 18

months. In conclusion, it is crucial to implement health promotions aimed at improving aerobic fitness in order to reduce the prevalence of Metabolic Syndrome, especially in a population with elevated blood pressure.

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