Effects of PREMIER Lifestyle Modifications on Participants With and Without the Metabolic Syndrome


Abstract—Lifestyle modification can reduce blood pressure and lower cardiovascular risk. Established recommendations include weight loss, sodium reduction, and increased physical activity. PREMIER studied the effects of lifestyle interventions based on established recommendations alone and with the addition of the Dietary Approaches to Stop Hypertension (DASH) dietary pattern. This analysis aimed to assess the interventions’ impact on cardiometabolic variables in participants with, compared with those without, metabolic syndrome. The primary outcome was 6-month change in systolic blood pressure. Participants with prehypertension or stage-1 hypertension were randomly assigned to an advice only control group, a 6-month intensive behavioral intervention group of established recommendations (EST), or an established recommendations plus DASH group (EST+DASH). Metabolic syndrome was defined per National Cholesterol and Education Program Adult Treatment Panel III. We used general linear models to test intervention effects on change in blood pressure, lipids, and insulin resistance (homeostasis model assessment), in subgroups defined by the presence or absence of metabolic syndrome. Of 796 participants, 399 had metabolic syndrome. Both EST and EST+DASH reduced the primary outcome variable, systolic blood pressure. Within the EST+DASH group, those with and without metabolic syndrome responded similarly (P=0.231). However, within EST, those with metabolic syndrome had a poorer response, with a decrease in systolic blood pressure of 8.4 mm Hg versus 12.0 mm Hg in those without metabolic syndrome (P=0.002). Thus, metabolic syndrome attenuated the systolic blood pressure reduction of EST, but this attenuation was overcome in EST+DASH. Finally, diastolic blood pressure, lipids, and homeostasis model assessment responded similarly to both interventions regardless of metabolic syndrome status. Our data suggest that strategies for lowering BP in individuals with metabolic syndrome may be enhanced by recommendations to adopt the DASH dietary pattern. (Hypertension. 2007;50:609-616.)

Key Words: hypertension ■ metabolic syndrome ■ insulin resistance ■ lifestyle modification ■ DASH

Lifestyle modification has great potential to reduce blood pressure (BP) and cardiovascular disease risk. National recommendations emphasize weight loss in those who are overweight/obese, sodium reduction, increased physical activity, limited alcohol intake, and the Dietary Approaches to Stop Hypertension (DASH) dietary pattern for preventing and treating high BP.1–4 DASH emphasizes fruits, vegetables, and low-fat dairy products while reducing total and saturated fat.4,5 The PREMIER Trial studied effects on BP of 2 multicomponent lifestyle interventions compared with advice only.6 The effectiveness of PREMIER interventions in proving BP and insulin resistance has been published.7–9 However, the impact of these interventions on patients at higher risk for cardiovascular disease, such as those with the metabolic syndrome (MetSyn), deserves attention.

MetSyn was described by Reaven10 in 1988 and has become a major focus of study. Estimated to affect >20% of US adults,11,12 MetSyn refers to a grouping of cardiovascular risk factors including hypertension, insulin resistance, dyslipidemia, and abdominal obesity.13–18 Recently, MetSyn has gained renewed attention and controversy,19 because some have questioned its predictive use,20,21 whereas others believe

Received February 17, 2007; first decision March 5, 2007; revision accepted July 25, 2007.

From the Division of Endocrinology, Metabolism, and Nutrition (L.F.L., A.J.B.) and Duke Hypertension Center and the Division of Nephrology (P.-H.L., H.L.M., L.P.S.), Department of Medicine, and Sarah W. Stedman Nutrition and Metabolism Center (L.F.L., P.-H.L., L.P.S.), Duke University Medical Center, Durham, NC; Department of Nutrition Sciences (J.D.A.), University of Alabama at Birmingham; National Heart, Lung, and Blood Institute (C.L.), National Institutes of Health, Bethesda, Md; University of Texas Medical Branch (T.P.E.), Austin; Kaiser Permanente Center for Health Research (A.C.F., V.J.S., M.A.M.), Portland, Ore; Pennington Biomedical Research Center (C.M.C., P.J.B., D.W.H.), Baton Rouge, La; Stanford University Medical Center (A.C.K.), Stanford, Calif; and Bloomberg School of Public Health (L.J.A.), Johns Hopkins Medical Institutions, Baltimore, Md.

This work was presented at the American Heart Association Council on High Blood Pressure Research Annual Fall Conference, Chicago, Ill, October 11, 2004, and published in abstract form (Hypertension. 2004;44:50–51).

Correspondence to Lillian Frances Lien, Division of Endocrinology, Metabolism, and Nutrition, DUMC 2956, Duke University Medical Center, Durham, NC 27710, E-mail lien0002@mc.duke.edu

© 2007 American Heart Association, Inc.

Hypertension is available at http://hyper.ahajournals.org

DOI: 10.1161/HYPERTENSIONAHA.107.089458
that it identifies high-risk individuals who would not have been detected if only conventional risk factors were considered.\textsuperscript{22,23} Evidence for the clinical relevance of MetSyn includes data showing that it is a strong predictor of vascular risk, independent of insulin resistance,\textsuperscript{24} and is a risk factor for stroke, independent of type 2 diabetes.\textsuperscript{25}

The role of nutrition in the pathogenesis of MetSyn, and, conversely, the therapeutic impact of dietary change, are complex issues. In the Diabetes Prevention Program, participants randomly assigned to an intensive lifestyle intervention (including a low-calorie, low-fat diet and weight loss) showed a lower 3-year cumulative incidence of MetSyn when compared with those who received metformin or placebo.\textsuperscript{26} In a randomized trial of patients with MetSyn, the DASH dietary pattern has been shown to be more effective than a “control diet” (50% to 60% carbohydrate, 15% to 20% protein, and <30% fat) in lowering SBP and DBP.\textsuperscript{27} Given the importance of lifestyle modification in addressing cardiovascular risk, this article describes the impact of PREMIER behavioral interventions on BP, lipids, and insulin resistance in subgroups defined by the presence or absence of MetSyn. Given the excess risk associated with the MetSyn, this evaluation for a differential response to lifestyle treatment has important public health implications.

Methods

The rationale, design, main results, and subgroup findings for PREMIER have been published.\textsuperscript{5,7,9} The protocol was reviewed by an external protocol review committee and the National Heart, Lung, and Blood Institute at the National Institutes of Health and was approved by the institutional review board at each of the 4 clinical centers (Duke University Medical Center, Johns Hopkins Medical Institutes, Pennington Biomedical Research Center, and Kaiser Permanente Center for Health Research) and at the coordinating center (also at Kaiser Permanente Center for Health Research in Portland). Each participant provided written informed consent.

PREMIER Participants

The population consisted of generally healthy adults with above-optimal BP (120 to 139 mm Hg systolic and/or 80 to 89 mm Hg diastolic) and individuals with stage-1 hypertension (140 to 159 mm Hg systolic and/or 90 to 95 mm Hg diastolic) who met national criteria for a 6-month trial of nonpharmacological therapy.\textsuperscript{2} These groups correspond with prehypertension and stage-1 hypertension by Joint National Committee criteria (which were published after the study was completed).\textsuperscript{2} Persons were eligible if they fit the above systolic BP (SBP) and diastolic BP (DBP) criteria and were not taking antihypertensive medication. Other inclusion criteria were age >25 years and body mass index 18.5 to 45.0 kg/m\textsuperscript{2}. Major exclusion criteria were regular use of drugs affecting BP, history of target organ damage and/or diabetes,\textsuperscript{2} use of weight-loss medications, previous cardiovascular event, heart failure, and angina.\textsuperscript{9,10}

Intervention

Eligible study participants were randomly assigned to 1 of 3 intervention groups: (1) an “advice only” control group (advice only); (2) a group that received intensive behavioral intervention based on established lifestyle modifications for lowering BP (EST);\textsuperscript{2} and (3) a group that received the same established intervention plus the DASH dietary pattern (EST+DASH).\textsuperscript{4,5} This analysis reports outcomes at 6 months after randomization (the a priori designated time point of primary outcome [SBP] assessment). Participant goals for both the EST and EST+DASH interventions included weight loss of ≥15 lb (6.8 kg) for those with a body mass index ≥25 kg/m\textsuperscript{2}, ≥180 minutes per week of moderate-intensity physical activity, ≤100 mmol/d of dietary sodium, and ≤1 oz/d of alcohol (men) or 0.5 oz/d (women). Individuals in EST+DASH were additionally instructed to follow the DASH dietary pattern by consuming 9 to 12 servings of fruits and vegetables and 2 to 3 servings of low-fat dairy products daily and limiting total and saturated fat to ≤25% and 7% of total calories, respectively.\textsuperscript{3} To achieve weight loss, both interventions emphasized moderate physical activity and reduced total energy intake.

In contrast, the advice only group received a single 30-minute individual advice session, immediately after random assignment, in which participants received instructions describing established recommendations and the DASH dietary pattern. No further contact was provided during the 6-month period.

Individuals assigned to either EST or EST+DASH were scheduled to attend 18 face-to-face intervention contacts. Counseling sessions were conducted by trained interventionists using social cognitive theory.\textsuperscript{9}

Measurements

Measurements were taken at baseline and at the 6-month follow-up visit by staff masked to random assignment. BP was measured by certified individuals using a random-0 sphygmomanometer, as in previous studies.\textsuperscript{4,28,29} After the participant sat quietly for 5 minutes, BP was measured in the right arm with an appropriate size cuff. At each visit, 2 BP measurements separated by ≥30 seconds were obtained. SBP was the appearance of the first Korotkoff sound; DBP was the disappearance of Korotkoff sounds. At each assessment point, BP was the mean of all of the available measurements.\textsuperscript{30,31}

Weight was measured using a calibrated scale; height was measured using a wall-mounted stadiometer. Aerobic fitness was defined as heart rate at a fixed workload (stage 2 or last available heart rate from stage 1) during a submaximal treadmill stress test.\textsuperscript{32,33} Other measurements included waist circumference, fasting blood glucose, insulin, and lipids.\textsuperscript{9}

Intake of nutrients and food groups was assessed from 2 unannounced 24-hour dietary recalls conducted by telephone.\textsuperscript{9} Self-reported dietary intake was corroborated using 24-hour urine collections for sodium (for salt intake), potassium (for fruit and vegetable intake), phosphorus (for dairy intake), and urea nitrogen (for protein intake). Lipids, fasting glucose, and fasting insulin levels were measured at a central laboratory (Washington University). For logistical purposes, participants were randomly assigned in 4 cohorts over time. Assays were run in batches by cohort: all of the samples from each cohort were run together, with no distinction by treatment group or subgroup.

Insulin resistance was estimated using the homeostasis model assessment (HOMA-index) formula (fasting insulin [microunits per milliliter]×fasting glucose[millimoles per liter])/22.5, with higher HOMA values indicating greater insulin resistance.\textsuperscript{31}

Analysis

Participants were determined to have MetSyn as per the National Cholesterol and Education Program Adult Treatment Panel III criteria, which required ≥3 of the following: waist circumference >102 cm (men) or >88 cm (women); triglycerides ≥150 mg/dL; high-density lipoprotein (HDL) <40 mg/dL (men) or <50 mg/dL (women); BP ≥130/≥85 mm Hg; and fasting glucose ≥110 mg/dL.\textsuperscript{12,34} For participants with data missing, the following applied: if 1 criterion was missing and ≥3 of the remaining criteria were met, the person was categorized as having MetSyn. If 1 criterion was missing and only 2 were met, the participant was eliminated from the analysis. Participants on lipid-lowering medications with HDL cholesterol less than the cutoff or triglycerides greater than the cutoff were censored as having met the lipid criteria; otherwise, the lipid criteria were deemed not met and were censored.

We used general linear models to test the effects of the interventions on change in BP, lipids, and HOMA, adjusting for potential confounding factors (ie, race, gender, and age), the baseline measure of interest, site, and cohort. For the MetSyn subgroup variable, we included subgroup main effect and interaction terms.
Analyses were conducted using the general linear models procedure and the logistic regression procedure in SAS (version 8.2). For measures of interest with skewed distributions (ie, triglycerides, HOMA, glucose, and insulin), the logarithmic-normal transformation was applied. Results for these measures were also back transformed to geometric means to facilitate interpretation. A $P/11021_0.05$ was used to define statistical significance; however, caution must be used in interpreting the results reported here, because the study was not powered to evaluate treatment-by-MetSyn status interactions in the measures evaluated, and no adjustment was made for multiple comparisons, as consistent with other secondary analyses in the PREMIER Study.

Results

Baseline Characteristics

Of the 810 randomly assigned participants, 14 did not have sufficient data to determine the presence or absence of MetSyn and were excluded. Therefore, 796 participants were included, of whom 399 had MetSyn at baseline, and 397 did not.

Table 1 shows baseline characteristics of those with MetSyn and without MetSyn (no MetSyn). In the MetSyn subgroup, 29.8% were black, and 58.1% were women. In the no MetSyn subgroup, 39.0% were black, and 65.5% were women. (Participants were black or white; there were no Asian or Indian participants). Mean age was $50$ years in both subgroups. As expected, cardiovascular risk factors were more prevalent in the MetSyn subgroup. Participants who had MetSyn weighed more than those who did not: women had mean weights of 96.0 and 86.9 kg (with and without MetSyn, respectively), and men had mean weights of 107.9 and 96.1 kg, respectively. Also, participants with MetSyn had larger baseline waist circumference, higher baseline SBP and triglyceride levels, and lower HDL cholesterol. The percentage of patients who were sedentary tended to be greater in those

![Image](https://example.com/image.png)

**Figure.** Mean reduction in SBP at 6 months by treatment group and MetSyn subgroup.

Table 1. Baseline Characteristics by MetSyn Subgroup

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MetSyn</th>
<th>No MetSyn</th>
<th>$P$ (t Test or $\chi^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>399</td>
<td>397</td>
<td></td>
</tr>
<tr>
<td>Black, %</td>
<td>29.8</td>
<td>39.0</td>
<td>0.0063</td>
</tr>
<tr>
<td>Female, %</td>
<td>58.1</td>
<td>65.5</td>
<td>0.0331</td>
</tr>
<tr>
<td>Age, y, mean, SD</td>
<td>49.7 (8.6)</td>
<td>49.9 (9.0)</td>
<td>0.6863</td>
</tr>
<tr>
<td>Weight for women, kg, mean, SD*</td>
<td>96.0 (16.8)</td>
<td>86.9 (17.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight for men, kg, mean, SD*</td>
<td>107.9 (17.1)</td>
<td>96.1 (18.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Waist circumference for women, cm, mean, SD*</td>
<td>110.7 (14.2)</td>
<td>101.7 (16.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Waist circumference for men, cm, mean, SD*</td>
<td>114.7 (11.9)</td>
<td>105.6 (14.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BP mm Hg: SBP baseline, mean, SD</td>
<td>136.1 (8.8)</td>
<td>133.7 (10.2)</td>
<td>0.0003</td>
</tr>
<tr>
<td>BP mm Hg: DBP baseline, mean, SD</td>
<td>85.4 (4.0)</td>
<td>84.2 (4.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% with high BP($\geq140/90$ mm Hg at baseline)</td>
<td>41.4</td>
<td>34.0</td>
<td>0.0326</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL, mean, SD*</td>
<td>214.0 (40.8)</td>
<td>209.0 (35.4)</td>
<td>0.0705</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol, mg/dL, mean, SD*</td>
<td>136.3 (34.0)</td>
<td>133.9 (33.9)</td>
<td>0.3157</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol, mg/dL, mean, SD*</td>
<td>41.1 (8.9)</td>
<td>55.5 (12.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides, mg/dL, mean, SD*</td>
<td>187.0 (110.1)</td>
<td>99.5 (60.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lipid medications, %*</td>
<td>3.5</td>
<td>0.8</td>
<td>0.0146</td>
</tr>
<tr>
<td>Physical activity, % sedentary†</td>
<td>84.6</td>
<td>79.6</td>
<td>0.0648</td>
</tr>
<tr>
<td>HOMA index, mean, SD</td>
<td>4.7 (4.1)</td>
<td>2.7 (1.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fasting insulin, micro-IU/mL</td>
<td>17.4 (10.9)</td>
<td>11.6 (7.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>5.7 (1.1)</td>
<td>5.2 (0.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>103.4 (19.1)</td>
<td>94.2 (8.1)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Number vary slightly for each parameter because of variations in completeness of data collection.
†Sedentary defined at physical activity recall $\leq35$ kcal/kg per day.

*By guest on May 2, 2017 http://hyper.ahajournals.org/* Downloaded from
with MetSyn, as were the percentages of patients who had a diagnosis of high BP (≥140/90 mm Hg) or who took lipid-lowering medications. Those with MetSyn had higher mean fasting insulin and glucose and higher HOMA-index levels.

**Primary Outcome Results: Change in SBP**

The Figure presents mean reductions in SBP by treatment group and MetSyn subgroup. Table 2 shows differences between treatment groups for all of the outcomes. Participants experienced significant SBP reductions regardless of treatment group and regardless of their MetSyn status, but the presence or absence of MetSyn modulated this effect. SBP was the only measure for which the treatment-arm-by-MetSyn subgroup interaction term was statistically significant (P=0.032).

In participants without MetSyn, the Figure shows that both EST and EST+DASH interventions equivalently reduced SBP by >11 mm Hg. Table 2 also confirms that, for those without MetSyn, both of these interventions significantly reduced SBP by ≥5.0 mm Hg when net of control was calculated, ie, relative to the advice only control group (P≤0.025).

However, in participants with MetSyn, the effectiveness of the EST and EST+DASH interventions was less comparable. The SBP reduction from EST (1.58 mm Hg when calculated net of control) was less than the SBP reduction from EST+DASH (3.01 mm Hg net of control; Table 2; although the difference between EST and EST+DASH treatment groups was not statistically significant). In those with MetSyn, only the EST+DASH intervention showed a significant reduction in SBP over control (P≤0.025 for [EST+DASH−Advice Only], but P>0.05 for [EST−Advice Only]; Table 2). The Figure also shows that, for those with MetSyn, the SBP reduction from the EST intervention was less than the SBP reduction from EST+DASH.

Furthermore, when comparing between the MetSyn subgroups, EST was not as effective in reducing SBP in those with versus without MetSyn (ie, reductions of 8.4 mm Hg

### Table 2. Change at 6 Months in BP/Lipids/Insulin Resistance by MetSyn Subgroup and by Treatment Group

<table>
<thead>
<tr>
<th>Outcome and Difference (95% CI) Between Treatment Groups</th>
<th>MetSyn</th>
<th></th>
<th>No MetSyn</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EST−Advice Only</td>
<td>EST+DASH−Advice Only</td>
<td>EST−EST</td>
</tr>
<tr>
<td><strong>Change in SBP, mm Hg§</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(−3.78 to 0.63)‡</td>
<td>(−5.26 to −0.76)†</td>
<td>(−3.65 to 0.78)</td>
<td>(−8.04 to −3.56)‡</td>
</tr>
<tr>
<td><strong>Change in DBP, mm Hg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(−2.54 to 0.55)</td>
<td>(−3.12 to 0.02)†</td>
<td>(−2.10 to 0.99)</td>
<td>(−3.93 to −0.80)†</td>
</tr>
<tr>
<td><strong>Change in total cholesterol, mg/dL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(−13.61 to −2.35)‡</td>
<td>(−11.67 to −0.15)†</td>
<td>(−3.55 to 7.71)</td>
<td>(−13.06 to −1.76)‡</td>
</tr>
<tr>
<td><strong>Change in lipoprotein, mg/dL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(−9.69 to 0.43)</td>
<td>(−8.63 to 1.82)</td>
<td>(−3.83 to 6.27)</td>
<td>(−11.84 to −1.95)‡</td>
</tr>
<tr>
<td><strong>Change in HDL, mg/dL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.67</td>
<td>0.09</td>
<td>−0.58</td>
<td>1.42</td>
</tr>
<tr>
<td><strong>Change in triglycerides, mg/dL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(−0.25 to −0.07)‡</td>
<td>(−0.17 to 0.02)</td>
<td>(−0.01 to 0.17)</td>
<td>(−0.19 to −0.01)‡</td>
</tr>
<tr>
<td><strong>Geometric mean change</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0.78 to 0.93)†</td>
<td>(0.84 to 1.02)</td>
<td>(0.99 to 1.19)</td>
<td>(0.82 to 0.99)†</td>
</tr>
<tr>
<td><strong>Change in LN HOMA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−0.24</td>
<td>−0.19</td>
<td>0.06</td>
<td>−0.22</td>
</tr>
<tr>
<td><strong>Geometric mean change</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0.70 to 0.88)†</td>
<td>(0.74 to 0.93)‡</td>
<td>(0.94 to 1.19)</td>
<td>(0.71 to 0.90)†</td>
</tr>
<tr>
<td><strong>Change in LN insulin, uIU/mL¶</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(−0.31 to −0.10)‡</td>
<td>(−0.27 to −0.06)‡</td>
<td>(−0.06 to 0.15)</td>
<td>(−0.31 to −0.10)‡</td>
</tr>
<tr>
<td><strong>Geometric mean change</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0.73 to 0.90)†</td>
<td>(0.76 to 0.94)‡</td>
<td>(0.94 to 1.16)</td>
<td>(0.73 to 0.91)†</td>
</tr>
<tr>
<td><strong>Change in glucose, mmol/L¶</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(−0.06 to −0.01)§</td>
<td>(−0.04 to 0.001)</td>
<td>(−0.01 to 0.03)</td>
<td>(−0.04 to 0.01)</td>
</tr>
<tr>
<td><strong>Geometric mean change</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0.05 to 0.19)§</td>
<td>(0.06 to 0.10)</td>
<td>(0.09 to 0.14)</td>
<td>(0.07 to 0.10)</td>
</tr>
</tbody>
</table>

*Within the subgroup: P≤0.05 for the difference between treatment groups.
†Within the subgroup: P=0.05 for the difference between treatment groups.
‡Between the subgroups: P=0.05 for MetSyn versus no MetSyn.
§Statistical methods: generalized linear models of change in a given measure (eg, SBP) at 6 months, regressed on treatment arm and treatment-by-MetSyn group interactions, adjusted for race (black versus white), gender, age, site, recruitment cohort, and baseline value of the measure. Specified linear contrasts were tested using the F test.
¶Variables that were skewed were natural log (LN) transformed. However, to facilitate interpretation, back transformed (geometric mean change) values are also provided.
¶Plasma insulin and plasma glucose measurements were all performed during fasting.
versus 12.0 mm Hg, respectively; Figure), and this within-
treatment difference between subgroups was significant 
(within EST: MetSyn versus no MetSyn, \( P=0.002; \) Figure).
In contrast, the EST+DASH intervention produced statistically 
similar reductions in SBP, regardless of the presence or 
absence of MetSyn (ie, reductions of 9.8 and 11.2 mm Hg, 
respectively, within EST+DASH: MetSyn versus no 
MetSyn, \( P=0.231; \) Figure). Similarly, when BP changes 
were expressed as the net of control (Table 2), EST led to a 
significant difference between the MetSyn subgroups, but 
EST+DASH led to no statistically significant difference 
between the MetSyn subgroups.

Secondary Outcomes Results

**DBP**

Treatment effects were similar for DBP, but there were no 
significant differences in these effects between the MetSyn 
subgroups.

**Lipids**

Table 2 shows that EST significantly improved total triglyc-
erides as compared with control (EST—advice only compar-
sion), and this was the case within both MetSyn subgroups 
(within subgroup: \( P<0.025 \)). However, EST+DASH did not 
significantly improve triglycerides as compared with control 
(EST+DASH—advice only) within either MetSyn subgroup.

Changes in HDL cholesterol were unremarkable. However, 
the EST and EST+DASH interventions were more effective 
than advice only in reducing total cholesterol in both of 
the MetSyn subgroups (within subgroup \( P\leq 0.05 \)). Although 
changes in low-density lipoprotein cholesterol in those with 
MetSyn did not achieve statistical significance, both EST and 
EST+DASH tended to improve low-density lipoprotein cho-
lesterol, as compared with control, regardless of MetSyn 
status. Thus, overall, both EST and EST+DASH benefited 
from the lipid profile, but the effect on lipids was not 
influenced by MetSyn (Table 2).

**Insulin Resistance**

Both EST and EST+DASH interventions led to greater 
reductions in fasting insulin levels and in the HOMA index 
(ie, greater improvements in insulin resistance) than the 
advice only group (within subgroup \( P\leq 0.025; \) Table 2). 
However, there were no statistically significant differences 
in the HOMA index, fasting insulin, and fasting glucose levels 
to those with and without MetSyn.

**Lifestyle Changes**

Participant attendance at intervention sessions was similar for 
each subgroup. In the EST and EST+DASH groups, particip-
ants attended an average of 14 to 15 of 18 possible 
intervention sessions. Neither the number of sessions at-
tended nor the percentage of participants attending \( \geq 15 \) 
sessions differed significantly between the MetSyn 
subgroups.

Both EST and EST+DASH treatment groups were suc-
cessful in achieving weight loss, regardless of MetSyn status 
at baseline. Those with MetSyn had a mean weight decrease 
of 4.8±5.8 kg in EST and a decrease of 6.0±6.5 kg in 
EST+DASH. Those without MetSyn had a mean weight 
decrease of 4.9±5.2 kg in EST and a decrease of 5.4±4.9 kg 
in EST+DASH. Within each treatment group, there were no 
significant differences in weight change or in change in total 
calorie intake between those with and without MetSyn. 
Within each treatment group, there were also comparable 
improvements in aerobic fitness (heart rate at stage 2 or last 
available heart rate at stage 1) between those with and without 
MetSyn.

The EST+DASH treatment group was more successful 
than the advice only group in increasing fruit and vegetable 
\( (P<0.0001) \) and low-fat dairy \( (P<0.01) \) intake and decreas-
ing saturated fat \( (P<0.0001) \) regardless of MetSyn status. In 
EST+DASH, mean fruit and vegetable intake increased by 
2.8±3.9 servings per day in those with and by 3.2±3.3 
servings per day in those without MetSyn. Participants in 
EST+DASH also increased low-fat dairy intake by 0.4±1.6 
servings per day in those with and by 0.6±1.6 servings per 
day in those without MetSyn and decreased saturated fat intake 
by 3.3±4.2% kcal and by 3.3±3.6% kcal, respectively. Of note, 
there were no significant differences between the MetSyn and no 
MetSyn subgroups for these lifestyle changes within the 
EST+DASH group. All 3 of the treatment groups reduced 
sodium intake, but there was no significant difference in sodium 
reduction between the MetSyn subgroups.

**Discussion**

Our analyses showed that lifestyle changes through both 
PREMIER EST and EST+DASH interventions substantially 
reduced the primary outcome variable, SBP, regardless of 
whether participants had MetSyn or not. Yet, the presence of 
MetSyn at baseline appeared to attenuate the level of effec-
tiveness of the EST intervention in reducing SBP. In contrast, 
this attenuation did not occur for those with MetSyn who 
received the EST+DASH intervention; ie, participants both 
with and without the MetSyn had similar SBP reductions 
in EST+DASH.

In addition to improving SBP, the EST+DASH interven-
tion reduced DBP, total cholesterol, HOMA, and fasting 
insulin among those with and without MetSyn compared with 
the advice only group. However, when comparing partici-
pants between the MetSyn subgroups, there were no signifi-
cant differences in these measures within either the 
EST+DASH or EST treatment groups.

Although some of the observed BP reduction may be 
derived from the change in weight,\(^\text{29,32}\) the data in this study 
indicate that weight change is not the only important factor. 
Indeed, there were no significant differences in weight 
change between the MetSyn subgroups; yet, the EST inter-
vention was apparently less effective in reducing SBP in 
those with versus without MetSyn. Thus, other factors may 
be important to consider, particularly in the presence of MetSyn. 
When weight loss is \(<10\%\), as seen in most short-term (eg, 
6-month) behavioral weight loss interventions, dietary com-
position might be particularly important. In the setting of 
MetSyn, the effectiveness of the EST+DASH intervention in 
SBP reduction is likely related to key differences in dietary 
intakes between the 2 intervention groups.

Possible mechanisms by which DASH may reduce BP 
come from studies of vascular and endothelial function.
DASH encourages lower intake of saturated fat. High fat intake may impair endothelial function; oxidative stress and endothelial dysfunction have been implicated in hypertension. Also, DASH encourages higher intake of fruits, vegetables, and low-fat dairy products, leading to an abundance of potassium, magnesium, and calcium. Potassium may lower BP via endothelium-dependent vascular relaxation, natriuresis, and effects on the renin-angiotensin-aldosterone system. Although the DASH studies were not designed to elucidate mechanism, there is evidence of DASH effects on the renin-angiotensin-aldosterone system via genetic studies: BP reduction with DASH has been associated with the G-6A polymorphism of the angiotensinogen gene. If, in fact, the BP-lowering mechanisms of DASH involve the renin-angiotensin-aldosterone system and endothelial function, this would further support its efficacy in MetSyn, because inhibition of the renin-angiotensin-aldosterone system (ie, with angiotensin II receptor blockers) may have particular use in MetSyn, and endothelial dysfunction is associated with obesity and MetSyn.

As above, our data suggest differential treatment effects on SBP between the MetSyn subgroups. However, our data revealed no statistically significant differences in treatment intervention effects on insulin sensitivity (ie, HOMA or fasting insulin levels) between the MetSyn subgroups (although it is true that PREMIER was not powered for MetSyn subgroups analysis.) This may seem counterintuitive given that the DASH dietary pattern likely results in an increase in nutrients (such as calcium and potassium) noted to be deficient in patients with impaired insulin sensitivity (sometimes considered a pathophysiologic precursor of MetSyn). DASH provides all of these nutrients and also high amounts of fiber. However, our finding of no significant differential effects on insulin sensitivity could result from the inherent heterogeneity of MetSyn: not all individuals with MetSyn are insulin resistant, and not all insulin resistant individuals have MetSyn. As per recent literature, this heterogeneity is one of the challenges in MetSyn research, because a diagnosis of MetSyn does not indicate precisely which risk factors are present.

The EST+DASH intervention had little effect on other components of MetSyn, such as triglycerides. Indeed, the EST intervention significantly improved triglycerides (compared with advice only) in both those with and without MetSyn, but the EST+DASH intervention did not show any significant improvement compared with advice only, (although it did not raise triglycerides either). Perhaps the lack of improvement in triglycerides in EST+DASH is because of the higher carbohydrate content of DASH. Researchers have shown a hypertriglyceridemic effect of higher-carbohydrate diets in patients with type 2 diabetes. The OmniHeart trial also demonstrated that substituting protein or unsaturated fat for carbohydrate results in greater improvements in triglycerides and HDL as part of a dietary pattern similar to DASH. Thus, in our study, the higher carbohydrate content of EST+DASH may have obscured the short-term benefits of weight reduction on triglycerides.

Lipid responsiveness to DASH was also studied in an analysis of the DASH-Sodium Trial. Higher C-reactive protein levels were associated with a lesser reduction in low-density lipoprotein and total cholesterol in response to the DASH dietary pattern, suggesting that inflammation may diminish improvement in lipids. Others have also noted an association between baseline C-reactive protein levels and lipid responsiveness to low-fat diets. Patients with MetSyn have been shown to have higher baseline inflammatory cytokine levels, and inflammatory cytokines have been linked to insulin resistance and atherosclerotic events. The impact of inflammation on responsiveness to lifestyle changes in those with MetSyn requires further study.

**Limitations**

There are several limitations to this study. Our analysis of lifestyle changes revealed that even those participants in the advice only group averaged 1 kg of weight loss at 6 months. This highlights the possibility of selection bias: research participants may be more motivated toward behavior modification than those who do not participate. Therefore, our results may not be generalizable to a less selected population. Still, the randomization process ensures good internal validity when comparing treatment effects. PREMIER also involved interventions in free-living individuals, making it more difficult to determine precise dietary intake; nonetheless, the participation of free-living individuals does enhance generalizability. One caution on results interpretation is that baseline subgroup differences did exist with regard to race, weight, and waist circumference. However, some of this was accounted for in our model, which adjusted for race, gender, age, and baseline measure of interest.

It should further be acknowledged that participants in the EST and EST+DASH groups attended 18 face-to-face sessions, an effective but resource-intensive intervention. Although attendance did not differ between subgroups, this is admittedly a crude comparison, and differences in adherence could not be measured directly. Finally, another variable to consider is the role of physical activity. Although not a perfect correlate, the best assessment available from PREMIER regarding this issue is physical fitness: improvements in aerobic fitness did not differ between MetSyn subgroups in this study.

This study assessed insulin sensitivity using the HOMA index, a nondynamic measure of glucose handling in the fasted state, which differs from other assessments of insulin resistance (such as the dynamic Intravenous Glucose Tolerance Test or the nondynamic but “gold-standard” euglycemic clamp technique). However, there is good correlation between estimates of insulin resistance made using HOMA versus the Intravenous Glucose Tolerance Test and versus the euglycemic clamp. Finally, these results should be interpreted with caution, because the PREMIER study was not powered to evaluate differential treatment effects between those with and without MetSyn. Furthermore, given the number of statistical tests performed, it is important to acknowledge that even statistically significant findings could be because of chance. Nevertheless, these findings contribute unique information regarding the potential impact of diet/lifestyle interventions in those with MetSyn.
Perspectives
In sum, a behavioral intervention to implement recommended lifestyle interventions (EST) appears to be less effective in reducing SBP in the presence of MetSyn, but the addition of the DASH dietary pattern to those recommendations (EST+DASH) appears to be equally effective in those with and without MetSyn. Thus, a multicomponent lifestyle intervention including the DASH dietary pattern may have potential benefits for the reduction of SBP in patients with MetSyn. In addition to improving SBP, the addition of the DASH dietary pattern to recommended lifestyle interventions also reduces DBP, total cholesterol, and insulin resistance among those with (and without) MetSyn.

Our data suggest that behavioral strategies aimed at lowering BP in individuals with MetSyn may be enhanced by recommendations to adopt the DASH dietary pattern. Further research should assist in confirming this assessment.

Acknowledgments
We thank the PREMIER Collaborative Group, including investigators and staff at the National Heart, Lung, and Blood Institute project office, the Coordinating Center (Center for Health Research, Portland, Ore), each of the clinical sites (Duke University Medical Center, Durham, NC; Pennington Biomedical Research Center, Baton Rouge, La; Johns Hopkins Medical Center, Baltimore, Md; and Center for Health Research clinical site, Portland, Ore). We further thank the Data Safety and Monitoring Board and devoted study participants.

Sources of Funding
This work was supported by National Institutes of Health grants UO1 HL60570, UO1 HL60571, UO1 HL60573, UO1 HL60574, and UO1 HL62828.

Disclosures
L.J.A. received research support from King Pharmaceuticals. The remaining authors report no conflicts.

References


Effects of PREMIER Lifestyle Modifications on Participants With and Without the Metabolic Syndrome


Hypertension. 2007;50:609-616; originally published online August 13, 2007; doi: 10.1161/HYPERTENSIONAHA.107.089458

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2007 American Heart Association, Inc. All rights reserved.

Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://hyper.ahajournals.org/content/50/4/609

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/