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Impact of Baseline Physical Activity and Diet Behavior on Metabolic Syndrome in a Pharmaceutical Trial: Results from NAVIGATOR

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Abstract

Objective—The cardiometabolic risk cluster metabolic syndrome (MS) includes 3 of elevated fasting glucose, hypertension, elevated triglycerides, reduced high-density lipoprotein cholesterol (HDL-c), and increased waist circumference. Each can be affected by physical activity and diet. Our objective was to determine whether baseline physical activity and/or diet behavior impact MS in the course of a large pharmaceutical trial.

Materials/Methods—This was an observational study from NAVIGATOR, a double-blind, randomized (nateglinide, valsartan, both, or placebo), controlled trial between 2002 and 2004. We studied data from persons (n=9306) with impaired glucose tolerance and cardiovascular disease (CVD) or CVD risk factors; 7118 with pedometer data were included in this analysis.

Physical activity was assessed with 7-day pedometer records; diet behavior was self-reported on a 6-item survey. An MS score (MSSc) was calculated using the sum of each MS component, centered around the Adult Treatment Panel III threshold, and standardized according to sample standard deviation. Excepting HDL-c, assessed at baseline and year 3, MS components were assessed yearly. Follow-up averaged 6 years.

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Conflicts of Interest

KMH was supported by NIH/NIAMS K23 AR054904. JLS, LT, JJVM, and JT have nothing to disclose.

Author Contributions

KMH, JS, and LT participated in the manuscript's conceptual design, data analyses, data interpretation, and manuscript drafting. CWB, TY, MJD, RRH, JT, SMH, WEK, RMC, RRH, JJVM, and MAB participated in conceptual design, data interpretation, and manuscript editing.

Results—For every 2000-step increase in average daily steps, there was an associated reduction in average MSSc of 0.29 (95% CI −0.33 to −0.25). For each diet behavior endorsed, there was an associated reduction in average MSSc of 0.05 (95% CI −0.08 to −0.01). Accounting for the effects of pedometer steps and diet behavior together had minimal impact on parameter estimates with no significant interaction. Relations were independent of age, sex, race, region, smoking, family history of diabetes, and use of nateglinide, valsartan, aspirin, antihypertensive, and lipid-lowering agent.

Conclusions—Baseline physical activity and diet behavior were associated independently with reductions in MSSc such that increased attention to these lifestyle elements provides cardiometabolic benefits. Thus, given the potential to impact outcomes, assessment of physical activity and diet should be performed in pharmacologic trials targeting cardiometabolic risk.

Keywords

pedometer; clinical trials; diabetes risk; diet surveys; z scores

INTRODUCTION

Metabolic syndrome is the cardiometabolic risk cluster comprised of elevated fasting glucose, hypertension, elevated triglycerides (TGs), reduced high-density lipoprotein cholesterol (HDL-c), and increased waist circumference (WC). While 3 or more of these components defines the presence of the metabolic syndrome, the corresponding continuous measures may be aggregated to create a more refined, quantitative metabolic syndrome score (MSSc). While the elements of MSSc are known to be affected by lifestyle (physical activity and diet), in the context of clinical pharmacologic trials targeting diabetes or cardiovascular disease (CVD), these lifestyle elements are rarely monitored. In the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study, 9306 participants with impaired glucose tolerance and either CVD or CVD risk factors completed baseline assessments of physical activity and diet behaviors and were then assigned, in a double-blind, randomized fashion, to receive nateglinide, valsartan, both, or placebo, in a 2-by-2 factorial design. Also, all participants were provided a lifestyle modification program. We report the effect of baseline physical activity, as measured by 7-day pedometer records and diet behavior as self-reported on a 6-item survey, on overall average MSSc.

In this ancillary investigation of NAVIGATOR, our objectives were to 1) assess the association between physical activity (pedometer steps) at baseline and metabolic syndrome as assessed by MSSc, 2) assess the association between diet behavior at baseline and metabolic syndrome, and 3) evaluate whether diet behavior alters the relation between physical activity and metabolic syndrome and whether physical activity alters the relation between diet behavior and metabolic syndrome. Our hypothesis was that baseline physical activity and diet behavior would each independently associate with reductions in a continuous measure for metabolic syndrome and justify the recommendation that physical activity and diet be assessed in clinical interventions targeting cardiometabolic risk.

METHODS

Study Population

NAVIGATOR was a multicenter, randomized, placebo-controlled trial designed to investigate whether nateglinide or valsartan treatment effectively reduced the risk of cardiovascular events in individuals with impaired glucose tolerance and existing CVD (if 50 years of age or older) or with at least 1 additional cardiovascular risk factor (if 55 years of age or older). Details of the NAVIGATOR rationale, inclusion/exclusion criteria, and primary outcomes have been previously reported [1–3]. Briefly, impaired glucose tolerance was defined as a 2-hour, post-challenge glucose value of at least 140 mg/dL (7.8 mmol/L) and less than 200 mg/dL (11.1 mmol/L); in addition, inclusion criteria required fasting plasma glucose (FPG) in the range of 95 mg/dL (5.3 mmol/L) to less than 126 mg/dL (7.0 mmol/L). Participants were recruited from 806 centers in 40 countries between January 2002 and January 2004. In total, 9306 participants were included in the study and randomized [1:1:1:1] into 1 of the 4 study arms. Participants were followed for an average of 6 years after baseline. In this analysis relating baseline physical activity and diet behaviors to metabolic syndrome in NAVIGATOR, 7118 participants with pedometer data were included.

Clinical Assessment

Each participant underwent a baseline oral glucose tolerance test (fasting and 2-hour post-challenge glucose), electrocardiogram, and fasting blood collection for HbA1c, lipid profile (TG, total, HDL, and low-density lipoprotein cholesterol), and renal function (albumin, creatinine and sodium). Baseline blood pressure, pulse rate, body weight, height, and WC were measured. In addition, a detailed medical history was collected, including previous and existing CVD and concomitant diseases/conditions; smoking status was also collected. All measures were assessed using the same standard operating procedures across sites. Biochemical and anthropometric measures were repeated annually (apart from lipid factors, which were measured at baseline, year 3, and year 6 at study conclusion).

Physical Activity Measurement

Habitual ambulatory activity was assessed objectively using a pedometer. Research-grade pedometers (Accusplit, San Jose, CA, USA) were dispatched to all NAVIGATOR study centers. These pedometers measure purposeful steps taken through a horizontal, spring-suspended lever arm that moves up and down with each step, opening and closing an electric circuit. Two weeks after the initial baseline clinical measurements were performed but prior to randomization, participants were fitted with a pedometer and instructed to wear it during waking hours for 7 consecutive days. Participants were given a log book and instructed to write down their daily step counts at the end of each day. Participants then returned their step logs to the study team. For this study, physical activity was summarized for each participant by the average of 7 consecutive days. Physical activity data were available for 7118 of 9306 participants.

Prudent Diet Behavior Score

At baseline, participants completed a 6-item questionnaire assessing 6 diet behaviors with recognized beneficial consequences. The 6 prudent behaviors regarded limiting total fat, saturated fat, sugar, and salt in the diet; restricting alcohol (to 2 or fewer drinks per day); and including daily fruits and vegetables. Responses were recorded as “yes” or “no,” and a sum of “yes” responses was used as the prudent diet behavior score for each participant such that a higher score indicates more prudent behaviors endorsed.

Metabolic Syndrome Score

Using the formula below, MSSc was calculated as the sum of each continuous component, which was centered around the sex-specific Adult Treatment Panel III (ATP-III) threshold [4] and standardized according to the sex-specific sample standard deviation (SD). Consequently, each variable contributes equally to the score, and this score can be used to compare cardio-metabolic risk regardless of meeting the threshold criteria for metabolic syndrome.

$$z \text{ score}_{\text{women}} = ([50 - \text{HDL-c}]/\text{SD HDL-c}_{\text{women}}) + ([\text{TG} - 150]/\text{SD TG}_{\text{women}}) + ([\text{FPG} - 100]/\text{SD FPG}_{\text{women}}) + ([\text{WC} - 88]/\text{SD WC}_{\text{women}}) + ([\text{MAP} - 100]/\text{SD MAP}_{\text{women}})$$

$$z \text{ score}_{\text{men}} = ([40 - \text{HDL-c}]/\text{SD HDL-c}_{\text{men}}) + ([\text{TG} - 150]/\text{SD TG}_{\text{men}}) + ([\text{FPG} - 100]/\text{SD FPG}_{\text{men}}) + ([\text{WC} - 102]/\text{SD WC}_{\text{men}}) + ([\text{MAP} - 100]/\text{SD MAP}_{\text{men}})$$

Mean arterial pressure (MAP) was calculated as follows: (systolic blood pressure + 2 × diastolic pressure)/3. All components were measured yearly, except TG and HDL-c, which were measured at baseline and 3 years. Yearly MSScs were calculated for baseline through year 5, with missing data and interim values of HDL-c handled by carrying the most recently measured value forward.

Statistical Analyses

Baseline participant characteristics were compared by quartiles of pedometer steps and low (0–3) versus high (4–6) diet scores. Continuous variables were reported as medians and 25th and 75th percentiles and compared using the Kruskal-Wallis test. Categorical variables were reported as frequencies and percentages and compared using the Pearson chi-square or Fisher exact tests. Using linear modeling with repeated measures, relations were assessed for baseline ambulatory activity, baseline diet behavior score, and average concurrent and subsequent MSSc. Models were adjusted for study medications and known prognostic factors, including age, sex, race, geographic region, smoking, family history of diabetes, aspirin use, antihypertensive use, and lipid-lowering agent use.

The first modeling step included pedometer steps and the adjustments; the second modeling step included nutrition score and the adjustments; the third modeling step included pedometer steps, nutrition score, and the adjustment. We also added the interactions between pedometer steps and nutrition score to the third model to see whether the associations changed. Statistical significance was established as $p < 0.05$. The SAS statistical software, version 9.2 (SAS Institute Inc., Cary, NC, USA), was used for all statistical analyses.

RESULTS

Table 1 shows median participant characteristics both overall and by daily pedometer-step quartiles. Table 2 shows median participant characteristics by diet scores (0–3 vs. 4–6). On average, participants were 63 years old (58, 69), 50.6% female, and engaged in a median of 5669 (3456, 8569) steps/day. By quartiles, median (25th, 75th) daily steps were 1960 (624, 2782), 4560 (4004, 5096), 6988 (6256, 7719), and 10,685 (9494, 12,506). For diet behavior scores, 5301/7118 (75%) endorsed 4–6 prudent diet behaviors. When prudent diet behavior scores were evaluated by pedometer quartiles, prudent diet behavior scores increased slightly for each increasing pedometer quartile ($p=0.04$). Similarly, as compared with those reporting fewer (diet behavior score 0–3) prudent diet behaviors, those endorsing diet behavior scores from 4–6 had slightly more daily pedometer steps (5760 [3493, 8654] vs. 5369 [3292, 8288]; $p=0.004$).

At baseline, 5122/7118 (72%) of individuals met criteria for metabolic syndrome. For MSSc, negative values represented lower cardiometabolic risk and positive values represented greater cardiometabolic risk. MSSc ranged from -13.4 to 61.2 with a median of 0.71 . Median (25th, 75th) scores for those with and without metabolic syndrome were 1.8 ($0.5, 3.2$) and -1.4 ($-2.6, -0.2$), respectively.

As shown in Figure 1A, baseline pedometer steps were inversely related to overall average MSSc ($p<0.0001$). Specifically, for every 2000 average daily steps, there was an associated reduction in average MSSc of 0.29 (95% CI -0.33 to -0.25) (Table 3). As displayed in Figure 1B, prudent diet behaviors were inversely related to overall average MSSc ($p<0.0003$) (Table 3). Each diet behavior endorsed was associated with an average MSSc reduction of 0.05 (95% CI -0.08 to -0.01) (Table 3). When accounting for the effects of both daily pedometer steps and diet behavior on MSSc, the inverse association between MSSc and pedometer steps was independent of the effects of prudent diet behavior ($p<0.0001$), while the effect of diet behavior approached the threshold for significance ($p<0.06$) (Table 3). More importantly, when accounting for the effects of both daily pedometer steps and diet behavior, there were minimal changes in parameter estimates ($\beta_{\text{steps}}=-0.29$, 95% CI -0.32 to -0.25 ; $\beta_{\text{diet}}=-0.03$, 95% CI -0.06 to 0.002) (Table 3 and Figure 2). There was no significant interaction between daily pedometer steps and diet behavior ($p=0.41$) (Table 3).

DISCUSSION

In the context of a large, multicenter, randomized, placebo-controlled pharmaceutical trial, small reductions in a continuous MSSc, and, as such, cardiometabolic risk, were related to both increased baseline physical activity and diet behavior. These findings emphasize that cardiometabolic health accrues with increasing judicious lifestyle behaviors, specifically physical activity and diet. Most importantly, given the impact on outcomes, albeit small, clinicians monitoring interventions targeting cardiometabolic risks should carefully monitor physical activity and diet behaviors.

Physical activity has a recognized association with all-cause and cardiovascular mortality [5, 6]. Nonetheless, while age, sex, tobacco use, body mass indices, and other recognized cardiovascular risks are typically monitored during interventions, physical activity is rarely assessed. We believe this is the first large investigation of a pharmaceutical agent or agents designed to improve cardiometabolic risk in which physical activity was objectively assessed. Given the impact of physical activity on cardiometabolic risk, independent of diet behavior, we propose that leaders of large clinical trials targeting cardiometabolic risk should consider including objectively monitored physical activity.

Another important finding is that the inverse relation between cardiometabolic risk and physical activity is linear. In prior investigations, metabolic syndrome presence has been associated with a threshold of daily steps below a range of 3100–6000 per day [7–11]. In contrast, by using a continuous MSSc, it is clear that the relationship between reduced cardiometabolic risk and physical activity is more than a threshold effect. On the other hand, physical activity appears to have a dose-dependent effect. For every 2000-step-per-day increase in physical activity, additional cardiometabolic benefit accrues. Further, these relations are across the range of physical activity, implying that both initiations of and increases in physical activity are associated with reduced cardiometabolic risk.

It is also notable that the effect of physical activity on cardiometabolic risk is independent of other mediators of reduced cardiometabolic risk, specifically diet behavior. The beneficial effects of diet and nutrition on metabolic syndrome are well-documented [12–14]. Interestingly, despite a large degree of statistical power afforded by the number of participants in this clinical trial, there was no significant interaction between daily physical activity and diet behavior for effects on cardiometabolic risk. Such a lack of significant interaction indicates that diet behavior did not alter the relation between physical activity and MSSc. Nonetheless, while the effect of diet behavior on cardiometabolic risk was of lower absolute magnitude than that of physical activity, it is important to note that diet behavior was defined by endorsement of several general, prudent dietary principles and was assessed via self-report. As diet behaviors were self-reported, individuals might have endorsed prudent behaviors that were not performed but were recognized as healthy.

This investigation is not without limitations. It was not designed specifically to address the effects of physical activity or diet behavior on MSSc. However, independent of the effects of numerous pharmacologic agents, there were measureable effects of both physical activity and diet behavior on cardiometabolic risk. Additionally, we are not able to attest to a causal effect of physical activity or diet behavior on cardiometabolic risk with this observational design. Additionally, a quantitative metabolic syndrome measure applies best to individuals not treated for cardiometabolic disease, whereas close to 75% of participants were treated with antihypertensives alone. However, analyses described here have been adjusted for medication use in each of the categories relevant to the metabolic syndrome. Another limitation of this study is that the continuous MSSc has a difficult conceptual interpretation. However, this score allows each risk factor to weigh equally and provides a quantitative rather than qualitative risk measure. Here, this continuous score was of value in demonstrating accrual of cardiometabolic benefit with stepwise increases in physical activity and dietary behaviors.

Thus, in the context of a large randomized, controlled investigation, physical activity and diet behavior were associated independently with reductions in a continuous score for metabolic syndrome. These findings highlight the importance of each of these lifestyle factors on cardiometabolic risk and support that additional benefits are accrued with increasing attention to these risk factors. Finally, this work shows that in large clinical trials targeting cardiometabolic risk, assessments of physical activity and diet behavior should be considered.

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Abbreviations

ATP III	Adult Treatment Panel III
CVD	cardiovascular disease
FPG	fasting plasma glucose
HDL-c	high-density lipoprotein cholesterol
MAP	mean arterial pressure
MSSc	metabolic syndrome score
NAVIGATOR	Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research study
SD	standard deviation
TG	triglyceride
WC	waist circumference

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Figure 1.

A: Box plots for overall MSSc by quartiles of pedometer steps.

B: Box plots for overall MSSc by 2 diet behavior score groups.

At baseline, physical activity was assessed with 7 days of pedometer-measured steps, and diet behavior was assessed with a 6-item questionnaire. Metabolic syndrome components were measured yearly, except HDL-c, which was measured at baseline and year 3. A continuous MSSc was calculated using ATP-III threshold criteria and sample standard deviations for each component of the metabolic syndrome. To improve visibility, 2 outliers were removed from each plot.

Figure 2.

Predicted MSSc by pedometer counts and diet behavior scores. Baseline physical activity, baseline diet behavior score, and average concurrent and subsequent MSSc were related using linear modeling with repeated measures. Model predicted MSScs are depicted. Relations were adjusted for study medications, age, sex, race, geographic region, smoking, family history of diabetes, aspirin use, antihypertensive use, and lipid-lowering agent use. Physical activity and diet behavior were each related to MSSc ($p < 0.001$ for both). Physical activity was related to MSSc independent of diet behavior ($p < 0.0001$). After accounting for the effect of physical activity, the effect of diet behavior approached the threshold for significance ($p < 0.06$). No significant interaction between physical activity and diet behaviors was identified ($p = 0.40$).

Table 1

Baseline characteristics by pedometer quartile.

Characteristic	Total Population (N=7118)	Quartile 1 (N=1779)	Quartile 2 (N=1780)	Quartile 3 (N=1780)	Quartile 4 (N=1779)	P Value
Average daily pedometer steps: month 0.5						
Median (25th, 75th)	5669.1 (3456.4, 8568.9)	1960.3 (623.6, 2781.6)	4560.2 (4003.7, 5095.7)	6987.8 (6255.6, 7719.4)	10,685.1 (9494.4, 12,505.7)	<0.0001
Mean (SD)	6178.4 (3832.5)	1752.8 (1167.8)	4554.1 (640.8)	7013.3 (833.5)	11393.9 (2483.8)	<0.0001
Metabolic syndrome, no. (%)						<0.0001
Yes	5122 (72.0)	1391 (78.2)	1308 (73.5)	1265 (71.1)	1158 (65.1)	
No	1996 (28.0)	388 (21.8)	472 (26.5)	515 (28.9)	621 (34.9)	
Metabolic syndrome score, median (25th, 75th)	1.2 (−0.4, 2.8)	1.7 (0.2, 3.2)	1.3 (−0.2, 2.9)	1.1 (−0.5, 2.5)	0.7 (−0.9, 2.3)	<0.0001
Diet behavior score, ^a no. (%)						
4–6	5301 (75)	1291 (73)	1309 (74)	1345 (76)	1356 (76)	
0–3	1817 (25.5)	488 (27.4)	471 (26.5)	435 (24.4)	423 (23.8)	0.04
Age at screening, median (25th, 75th), y	63.0 (58.0, 69.0)	65.0 (59.0, 71.0)	64.0 (59.0, 69.0)	63.0 (58.0, 68.0)	62.0 (57.0, 66.0)	<0.0001
Female, no. (%)	3605 (50.6)	971 (54.6)	928 (52.1)	920 (51.7)	786 (44.2)	<0.0001
Pooled race group: original, no. (%)						<0.0001
White	5837 (82.0)	1507 (84.7)	1513 (85.0)	1466 (82.4)	1351 (75.9)	
Black	157 (2.2)	64 (3.6)	39 (2.2)	37 (2.1)	17 (1.0)	
Asian	536 (7.5)	64 (3.6)	94 (5.3)	133 (7.5)	245 (13.8)	
Other	588 (8.3)	144 (8.1)	134 (7.5)	144 (8.1)	166 (9.3)	
Current smoker, no. (%)	760 (10.7)	228 (12.8)	190 (10.7)	175 (9.8)	167 (9.4)	0.005
Alcohol (2 drinks/day), no. (%)	6123 (86.0)	1534 (86.2)	1537 (86.3)	1534 (86.2)	1518 (85.3)	0.81
BMI, median (25th, 75th), kg/m ²	29.6 (26.7, 33.2)	31.1 (27.7, 35.4)	30.2 (27.3, 33.9)	29.1 (26.6, 32.4)	28.2 (25.8, 31.6)	<0.0001
Waist circumference, median (25th, 75th), cm	100.0 (92.0, 109.0)	104.0 (96.0, 113.0)	101.0 (94.0, 110.0)	99.0 (91.0, 107.0)	97.0 (89.0, 105.0)	<0.0001
SBP, median (25th, 75th), mmHg	140.0 (128.0, 150.0)	140.0 (129.5, 151.0)	140.0 (129.0, 150.0)	138.0 (127.0, 150.0)	139.0 (127.5, 149.5)	<0.0001
DBP, median (25th, 75th), mm Hg	82.0 (76.0, 90.0)	82.0 (76.0, 90.0)	82.0 (75.5, 90.0)	81.0 (76.0, 90.0)	82.0 (76.0, 90.0)	0.66
MAP, median (25th, 75th), mmHg	101.0 (94.0, 108.7)	101.3 (94.3, 109.0)	101.7 (94.0, 109.0)	100.2 (93.7, 108.3)	101.0 (94.0, 108.3)	0.06
HDL cholesterol, median (25th, 75th), mg/dL	47.8 (39.8, 56.8)	47.2 (39.8, 56.5)	48.0 (40.2, 56.8)	47.6 (39.8, 56.8)	48.0 (39.8, 56.8)	0.30
Triglycerides, median (25th, 75th), mg/dL	150.6 (108.9, 209.9)	155.9 (113.4, 216.1)	154.1 (113.4, 217.0)	151.5 (108.9, 212.1)	139.9 (101.9, 194.9)	<0.0001
Fasting glucose, median (25th, 75th), mg/dL	109.8 (102.6, 115.2)	109.8 (102.6, 115.2)	109.8 (102.6, 115.2)	109.8 (104.4, 117.0)	109.8 (102.6, 117.0)	0.05
Nutrition avoidance score, median (25th, 75th)	5.0 (3.0, 6.0)	5.0 (3.0, 6.0)	5.0 (3.0, 6.0)	5.0 (4.0, 6.0)	5.0 (4.0, 6.0)	<0.0001

Characteristic	Total Population (N=7118)	Quartile 1 (N=1779)	Quartile 2 (N=1780)	Quartile 3 (N=1780)	Quartile 4 (N=1779)	P Value
Medications, no. (%)						
Aspirin	2635 (37.0)	690 (38.8)	703 (39.5)	639 (35.9)	603 (33.9)	0.002
Antihypertensive	5313 (74.6)	1386 (77.9)	1341 (75.3)	1294 (72.7)	1292 (72.6)	0.0005
Alpha blocker	448 (6.3)	117 (6.6)	129 (7.2)	103 (5.8)	99 (5.6)	0.15
ACE inhibitor	480 (6.7)	148 (8.3)	130 (7.3)	106 (6.0)	96 (5.4)	0.002
ARB	25 (0.4)	9 (0.5)	9 (0.5)	6 (0.3)	1 (0.1)	0.08
Calcium channel blockers	2345 (32.9)	613 (34.5)	599 (33.7)	527 (29.6)	606 (34.1)	0.01
Diuretic	2293 (32.2)	659 (37.0)	594 (33.4)	543 (30.5)	497 (27.9)	<0.0001
Lipid-lowering agent	2755 (38.7)	688 (38.7)	725 (40.7)	680 (38.2)	662 (37.2)	0.18
Statins	2417 (34.0)	612 (34.4)	640 (36.0)	597 (33.5)	568 (31.9)	0.08

^aDiet Behavior Score: Indicates the number of prudent dietary behaviors endorsed by participants. The 6 prudent behaviors regarded limiting total fat, saturated fat, sugar, and salt in the diet, restricting alcohol (< 2 drinks/day), and including daily fruits and vegetables.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; MAP, mean arterial pressure; SBP, systolic blood pressure; SD, standard deviation.

The *P* values are for comparisons across quartiles.

Table 2

Baseline characteristics by reported diet behavior score

Characteristic	Total (N=7118)	Diet Behavior Score		P Value
		0-3 (N=1817)	4-6 (N=5301)	
Average daily pedometer steps: month 0.5, median (25th, 75th)	5669.1 (3456.4, 8568.9)	5369.3 (3292.1, 8288.4)	5760.0 (3492.9, 8654.2)	0.004
Metabolic syndrome, no. (%)				0.02
Yes	5122 (72.0)	1347 (74.1)	3775 (71.2)	
No	1996 (28.0)	470 (25.9)	1526 (28.8)	
Metabolic syndrome score, median (25th, 75th)	1.2 (-0.4, 2.8)	1.5 (-0.1, 3.0)	1.1 (-0.4, 2.7)	<0.0001
Age at screening, median (25th, 75th), y	63.0 (58.0, 69.0)	62.0 (57.0, 68.0)	63.0 (58.0, 69.0)	<0.0001
Female, no. (%)	3605 (50.6)	804 (44.2)	2801 (52.8)	<0.0001
Pooled race group: original, no. (%)				0.0001
White	5837 (82.0)	1541 (84.8)	4296 (81.0)	
Black	157 (2.2)	43 (2.4)	114 (2.2)	
Asian	536 (7.5)	95 (5.2)	441 (8.3)	
Other	588 (8.3)	138 (7.6)	450 (8.5)	
Current smoker, no. (%)	760 (10.7)	259 (14.3)	501 (9.5)	<0.0001
Alcohol (2 drinks/day), no. (%)	6123 (86.0)	1171 (64.4)	4952 (93.4)	<0.0001
BMI, median (25th, 75th), kg/m ²	29.6 (26.7, 33.2)	30.4 (27.4, 34.1)	29.3 (26.5, 32.9)	<0.0001
Waist circumference, median (25th, 75th), cm	100.0 (92.0, 109.0)	102.0 (94.0, 111.0)	99.0 (91.0, 108.0)	<0.0001
SBP, median (25th, 75th), mm Hg	140.0 (128.0, 150.0)	139.0 (128.0, 150.5)	140.0 (128.0, 150.0)	0.41
DBP, median (25th, 75th), mm Hg	82.0 (76.0, 90.0)	82.5 (76.5, 90.0)	81.0 (76.0, 90.0)	0.001
MAP, median (25th, 75th), mm Hg	101.0 (94.0, 108.7)	101.7 (94.0, 109.7)	100.8 (94.0, 108.3)	0.01
HDL cholesterol, median (25th, 75th), mg/dL	47.8 (39.83, 56.84)	47.6 (39.83, 56.84)	48.0 (39.83, 56.84)	0.82
Triglycerides, median (25th, 75th), mg/dL	150.6 (108.9, 209.9)	154.1 (110.7, 212.6)	149.7 (108.1, 209.9)	0.08
Fasting glucose, median (25th, 75th), mg/dL	109.8 (102.6, 115.2)	109.8 (102.6, 115.2)	109.8 (102.6, 115.2)	0.33
Medications, no. (%)				
Aspirin	2635 (37.0)	650 (35.8)	1985 (37.4)	0.20
Antihypertensive	5313 (74.6)	1294 (71.2)	4019 (75.8)	0.0001
Alpha blocker	448 (6.3)	108 (5.9)	340 (6.4)	0.48
ACE inhibitor	480 (6.7)	107 (5.9)	373 (7.0)	0.09
ARB	25 (0.4)	7 (0.4)	18 (0.3)	0.78
Calcium channel blockers	2345 (32.9)	543 (29.9)	1802 (34.0)	0.001
Diuretic	2293 (32.2)	553 (30.4)	1740 (32.8)	0.06
Lipid-lowering agent	2755 (38.7)	610 (33.6)	2145 (40.5)	<0.0001
Statins	2417 (34.0)	526 (28.9)	1891 (35.7)	<0.0001

Diet Behavior Score: Indicates the number of prudent dietary behaviors endorsed by participants. The 6 prudent behaviors regarded limiting total fat, saturated fat, sugar, and salt in the diet, restricting alcohol (2 drinks/day), and including daily fruits and vegetables.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; MAP, mean arterial pressure; SBP, systolic blood pressure.

The *P* values are for comparisons between Diet Behavior Score groupings.

Table 3**Modeling**

	Estimate	SE	P Value	95% CI
Average daily pedometer steps (per 2000-step increase)				
Model 1A: Unadjusted	−0.24	0.02	<0.0001	−0.28 to −0.20
Model 2A: Adjusted ^a	−0.30	0.02	<0.0001	−0.33 to −0.26
Model A3: Adjusted ^b	−0.29	0.02	<0.0001	−0.33 to −0.25
Diet behavior score				
Model 1A: Unadjusted	−0.08	0.02	<0.0001	−0.11 to −0.04
Model 2A: Adjusted ^a	−0.05	0.02	0.005	−0.08 to −0.01
Model A3: Adjusted ^b	−0.05	0.02	0.006	−0.08 to −0.01
Model 4: Multivariable adjusted ^b				
Average daily pedometer steps (per 2000 increase)	−0.29	0.02	<0.0001	−0.33 to −0.25
Diet behavior score	−0.03	0.02	0.06	−0.06 to 0.002
Model 5: Multivariable adjusted ^b with interaction				
Model 5A: Interaction for average daily pedometer steps * diet behavior score	--	--	0.22	--
Model 5B: Interaction for average daily pedometer steps * Valsartan	--	--	0.26	--
Model 5C: Interaction for average daily pedometer steps * Nateglinide	--	--	0.97	--
Model 5D: Interaction for diet behavior score * Valsartan	--	--	0.46	--
Model 5E: Interaction for diet behavior score * Nateglinide	--	--	0.77	--

^a Adjusted for age, sex, region, race, smoking, family history of diabetes.

^b Adjusted for age, sex, region, race, smoking, family history of diabetes, and use of valsartan, nateglinide, aspirin, antihypertensive, lipid-lowering agent.

Abbreviations: CI, confidence interval; SE, standard error.