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No association of dietary fiber intake with inflammation or arterial stiffness in youth with type 1 diabetes

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Abstract

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Aim—To examine the association of dietary fiber intake with inflammation and arterial stiffness among youth with type 1 diabetes (T1D) in the US.

Methods—Data are from youth 10 years old with clinically diagnosed T1D for 3 months and 1 positive diabetes autoantibody in the SEARCH for Diabetes in Youth Study. Fiber intake was assessed by food frequency questionnaire with measurement error (ME) accounted for by structural sub-models derived using additional 24-hour dietary recall data in a calibration sample and the respective exposure-disease model covariates. Markers of inflammation, measured at baseline, included IL-6 ($n=1405$), CRP ($n=1387$), and fibrinogen ($n=1340$); markers of arterial stiffness, measured approximately 19 months post-baseline, were available in a subset of participants and included augmentation index ($n=180$), pulse wave velocity ($n=184$), and brachial distensibility ($n=177$).

Results—Mean (SD) T1D duration was 47.9 (43.2) months; 12.5% of participants were obese. Mean (SD) ME-adjusted fiber intake was 15 (2.8) g/day. In multivariable analyses, fiber intake was not associated with inflammation or arterial stiffness.

Conclusion—Among youth with T1D, fiber intake does not meet recommendations and is not associated with measures of systemic inflammation or vascular stiffness. Further research is needed to evaluate whether fiber is associated with these outcomes in older individuals with T1D or among individuals with higher intakes than those observed in the present study.

Keywords

type 1 diabetes; youth; dietary fiber; inflammation; arterial stiffness

Introduction

A high-fiber diet may be protective against inflammation, which plays a key role in the development of atherosclerosis and subsequent vascular disease. Both observational and experimental studies among adults have reported an inverse relationship between dietary fiber and acute-phase inflammatory response markers, including interleukin 6 (IL-6) [1,2] and C-reactive protein (CRP) [2-4], and indicators of an abnormal prothrombotic state, such as fibrinogen [5,6]. Two recent studies among adolescents have also supported an inverse relationship between fiber intake and inflammation [7,8].

A more limited literature exists on the relationship between dietary fiber and measures of subclinical vascular disease. An Australian study among overweight and obese adults showed a decrease in augmentation index (AIx), a measure of central vascular function, after 6 weeks on a fiber supplement relative to placebo [9], and a longitudinal observational study among adolescents and young adults in the Netherlands reported an inverse association between fiber intake and carotid artery distensibility [10].

Patients with type 1 diabetes (T1D) are at increased risk of cardiovascular disease (CVD): coronary heart disease occurs earlier and is associated with higher mortality among these individuals [11]. Indeed, decreased carotid artery distensibility [12,13] and brachial distensibility [14], and increased AIx [15] and carotid artery intima-media thickness [13,16] have been reported in children and adolescents with T1D. While dietary fiber has been

linked to improved postprandial glycemia [17,18] and total cholesterol [19] among individuals with T1D, a potential protective effect of fiber on inflammation and subclinical vascular disease, particularly among youth, has yet to be confirmed. One observational study among adults with T1D reported an inverse association between dietary fiber intake and low-grade inflammation, quantified as an overall z-score of IL-6, CRP, and tumor necrosis factor α levels [20]. To our knowledge, only a single experimental study, conducted in 1981, has explored this relationship in youth with T1D, reporting a decrease in fibrinogen after 4 weeks on a diet supplemented with 0.45 g guar gum/kg body weight/day [21]. If a protective effect of high-fiber diets on inflammation and subclinical vascular disease indeed exists, it would represent an important opportunity for early intervention to reduce CVD risk in this population. To address this gap in scientific knowledge, we evaluated the association of dietary fiber with inflammation and arterial stiffness among youth with T1D.

Methods

Study Population

Data are from SEARCH for Diabetes in Youth [22], which includes a cohort of youth diagnosed with diabetes at < 20 years of age across 5 sites in the U.S. beginning in 2002. In 2001, prevalent cases were also identified. Participants were asked to complete an initial survey and after completion were invited for an initial study visit. Participants in the prevalent 2001 and incident 2002-2005 cohorts who completed the dietary intake assessment (restricted to those ≥ 10 years old) and had ≥ 1 inflammatory marker measured during this initial study visit, had a diabetes duration ≥ 3 months, were positive for ≥ 1 diabetes autoantibody (GAD65 and IA2), and had a complete covariate set were included in this analysis. The final sample size was 1405. Study protocols were approved by Institutional Review Boards at all participating sites, and written informed consent was obtained for all participants ≥ 18 years of age and parent/guardian permission and participant assent for participants < 18 years of age.

Dietary Intake Assessment

A modified version of the Block Kid's Food Frequency Questionnaire (FFQ) was used to assess dietary intake in SEARCH participants ≥ 10 years of age during the initial study visit [23]. The FFQ included approximately 85 food items for which information on consumption in the past week ("yes" or "no") was collected. For participants responding "yes", additional data on how many days in the past week the item was consumed and typical portion size were collected. The nutrient and portion-size databases were established using the Nutrition Data System for Research (Database 3, Version 4.05/33, 2002, Nutrition Coordinating Center, University of Minnesota, Minneapolis, Minnesota) and industry sources.

In order to address measurement error (ME) associated with the FFQ, a Dietary Assessment Calibration Subsample was conducted in the SEARCH Nutrition Ancillary Study that included 172 participants who completed the FFQ and then completed up to three 24-hour dietary recalls over the course of the following 30 days. From these data, models were constructed to predict 24-hour dietary recall intake (assumed to be unbiased) from intake assessed by FFQ and the respective exposure-disease model covariates. The application of

this method has been discussed in detail elsewhere [24]. Because the inflammatory markers, AIx, and carotid-femoral pulse wave velocity (PWV) and brachial artery distensibility (BrachD) exposure-disease models had three different covariate sets, three ME-adjustment models were constructed. Based on the relationships estimated by these models, total energy (kcal/day) and fiber intake (g/day) in the SEARCH sample were predicted and these ME-adjusted dietary intakes were used in their respective exposure-disease models.

Given that this is a sample of children and adolescents, and that fiber recommendations are given in units of g/1000 kcal [25], for descriptive purposes participant characteristics were presented according to quartiles of ME-adjusted fiber in units of g/1000 kcal. The quartile cut points predicted using the inflammatory marker covariate set were used given that these quartile cut points were equivalent to those predicted by the PWV/BrachD covariate set and differed by only a tenth of a gram from those predicted by the AIx covariate set. All exposure-disease models specified ME-adjusted fiber in units of g/day (quartiles or continuous), controlling for ME-adjusted total energy intake (kcal/day).

Outcome Assessment

During the initial study visit, a fasting venipuncture was performed on metabolically stable participants, defined as no episode of diabetic ketoacidosis in the past month. Three inflammatory markers—IL-6, CRP, and fibrinogen—were analyzed in stored samples from this visit at the study Central Laboratory (Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington, Seattle, Washington). Specifically, IL-6 was assayed using the Human Adipokine panel B (Millipore Inc., Billerica, Massachusetts) on a Bio-Plex suspension array system (Bio-Rad Laboratories, Hercules, California), and CRP and fibrinogen were analyzed using Siemens reagent on a Siemens BNII nephelometer (Siemens Healthcare Diagnostics Inc., Newark, Delaware).

As part of a pilot study on CVD, measures of arterial stiffness were also collected on a subset of participants at two SEARCH sites. This CVD pilot study visit took place, on average, 19.4 ± 7.6 months after the SEARCH initial study visit. BrachD, a measure of vascular function of a peripheral muscular artery, was measured using a DynaPulse Pathway instrument (Pulse Metric, Inc., San Diego, California). PWV, a measure of pulse propagation representing central arterial stiffness, and AIx, a measure of wave reflections, were assessed using a SphygomCor SCOR-PVx System (Atcor Medical, Sydney, Australia) [14]. AIx was normalized to a heart rate of 75 beats per minute and expressed as a percent (AIx-75).

Covariate Assessment

Self-reported demographic covariates included gender, race/ethnicity, and estimated total annual household income. Smoking and physical activity questions were derived from the national Youth Risk Behavior Survey [26]. Participants were classified as “Current smokers” if they self-reported having smoked cigarettes on at least one of the 30 days preceding the survey; “Past smokers” if they had tried smoking or had smoked regularly (at least one cigarette every day for 30 days) but were not current smokers; and “Never smokers” if they had never smoked a whole cigarette. Participants who self-reported

participating in physical activity that made them breathe hard or sweat for at least 20 minutes, on average, 0-2 days per week were classified as “Physically inactive”; and 3-7 days per week as “Physically active”.

Body mass index (BMI) was calculated as measured weight (kg) divided by height squared (m^2), and obesity was defined as a BMI $\geq 95^{\text{th}}$ age- and sex-specific percentile for participants ≤ 20 years of age and BMI $\geq 30 \text{ kg}/m^2$ for participants > 20 years of age [27]. Systolic and diastolic blood pressure (SBP and DBP, respectively) were measured using a standard mercury sphygmomanometer in triplicate and the average was used in subsequent analyses.

Statistical Analysis

Log transformations were used to account for non-normality of the exposures (ME-adjusted energy and fiber intake) and the inflammatory marker outcomes (IL-6, CRP, and fibrinogen). Multivariable linear regression models were used to estimate the association of ME-adjusted dietary fiber intake with inflammation and arterial stiffness. Potential confounders were identified through a literature review and formally evaluated by assessing their relationships with the exposure and outcomes. The final adjustment set included ME-adjusted total energy intake, age, gender, race/ethnicity, diabetes duration, smoking status, and physical activity. Models predicting the arterial stiffness outcomes (PWV, AIx-75, and BrachD) were additionally adjusted for the time between assessment of diet (SEARCH initial study visit) and arterial stiffness (CVD pilot study visit), and mean arterial blood pressure (to account for background distending pressure) calculated as $[(2 \times \text{DBP}) + \text{SBP}]$ divided by 3. Models predicting AIx-75 were also adjusted for height given that height directly influences the distance from the heart of wave reflection sites. As a sensitivity analysis, exposure-disease models stratified by soluble and insoluble fiber intake were also explored. All analyses were conducted using SAS 9.2 (SAS Institute, Cary, North Carolina). Values are presented as mean \pm SD or %.

Results

Participants were 14.7 ± 3.0 years of age with a diabetes duration of 47.9 ± 43.2 months; 50.5% of participants were female (Table 1). The BMI-z score was 0.64 ± 0.89 ; 12.5% of participants were classified as obese. Estimated total dietary fiber from the SEARCH FFQ was 13.6 ± 7.1 g/day. Fiber intake was 14.7 ± 2.8 g/day as predicted by the ME model applied to the inflammatory marker covariate set; 14.5 ± 2.8 g/day for that applied to the AIx covariate set; and 14.5 ± 2.8 g/day for that applied to the PWV and BrachD covariate set.

Participants who were female, older, had shorter diabetes durations, had never smoked or were former smokers, and who exercised 3-7 days/week were more likely to be in the highest versus lowest quartile of ME-adjusted fiber intake (Table 1). There were no differences in race/ethnicity, BMI-z score, SBP, or DBP across dietary fiber quartiles and no clear association with obesity status was observed.

Mean unadjusted levels of markers of inflammation and arterial stiffness did not differ across quartiles of ME-adjusted dietary fiber intake (Table 1). Controlling for confounding

factors, multivariable linear regression models confirmed that ME-adjusted dietary fiber intake was not associated with markers of inflammation or arterial stiffness in this sample. This observation held true when fiber intake was specified as quartiles (Table 2; *Model 1*) or continuously (Table 2; *Model 2*).

When dietary fiber was stratified by solubility, though parameter estimates for soluble fiber intake were larger than those for insoluble fiber intake, effects remained nonsignificant (data not shown).

Discussion

No association was observed between dietary fiber intake and markers of inflammation or arterial stiffness among youth with T1D. While these results are in contrast with the preponderance of evidence relating to IL-6 and CRP among adults and adolescents without diabetes [1-4], the evidence remains mixed for fibrinogen. In the National Heart, Lung, and Blood Institute Family Heart Study, no association was observed between dietary fiber and fibrinogen [28]. A randomized crossover study among healthy adults did not find a difference at 4 weeks in fibrinogen between diets supplemented with cereal fiber (19 g/day) and control diets [29], and a parallel randomized controlled trial among overweight and obese adults reported no differences in IL-6, CRP, or fibrinogen at 3 months between diets supplemented with psyllium (7 or 14 g/day) compared to control diets [30]. Indeed, null results relating to the fiber-CRP relationship among adults have also been reported [2,31]. We suggest three primary hypotheses to explain these conflicting results: differences in 1) fiber dose, 2) fiber type, and 3) sample population.

Fiber dose

An important advantage of epidemiological studies is that they provide a “reality check” on whether exposures are occurring in the population such that one could anticipate the health benefits reported in clinical trials. Our results confirm that youth with T1D have low dietary fiber intakes relative to the current American Diabetes Association (ADA) recommendation of 14 g/1000 kcal [25]; in fact, the average dietary fiber intake was about half of what is recommended. Further, the dietary fiber intakes previously reported to have a protective effect against low-grade inflammation, CVD, and all-cause mortality among adults with T1D were substantially higher than the intakes in our sample population [20,32]. Our study therefore suggests that current fiber intakes of youth with T1D in the US may not be high enough to observe the previously reported protective effects of this nutrient.

Fiber type

Some studies have shown a stronger protective effect for soluble fiber compared to insoluble fiber [20,32]. However, our results remained non-significant when stratified by fiber solubility. Future research should explore the effects of specific types of fiber, considering not only solubility in water, but also microbial fermentation in the large intestine and viscosity, which may influence fiber action. Although the mechanisms underlying the potential beneficial effects of dietary fiber on proinflammatory and prothrombotic states have not been fully elucidated, a leading hypothesis involves the production of short-chain

fatty acids from fermentable dietary fiber in the gut. For example, butyrate inhibits the effect of nuclear factor- κ B, resulting in an overall decrease in the proinflammatory state [33], and acetate and propionate reduce IL-6 mRNA and proteins [34]. Dietary fibers, such as β -glucans, may also interact directly with immunoregulatory cells, resulting in anti-inflammatory phenotypes [35]. The mechanisms underlying a potential protective effect of dietary fiber on endothelial function have yet to be explored, but may be related to observed improvements in blood pressure, lipid profiles, and inflammation. In summary, though several biological mechanisms of specific fiber types have been explored, the mechanisms underlying previously observed inverse relationships between dietary fiber intake and inflammation and arterial stiffness are not well understood.

Sample population

To our knowledge, this is the first observational study to evaluate the association of dietary fiber with inflammation and arterial stiffness among youth with T1D. A recent observational study among 559 adolescents without T1D reported that dietary fiber intake was inversely associated with CRP and fibrinogen [8], but the levels of CRP and fibrinogen in their population were lower than those seen in our sample. The observed protective effect in their study was also of note given that the reported fiber intake was lower in their population compared to our sample. One explanation for these observations is that the higher level of systemic inflammation seen in adolescents with T1D may indicate that in this population there are factors with stronger causal effects on inflammation than dietary fiber, and this may mask any beneficial effects. Other study populations reporting protective effects of fiber on inflammation have included European adults with T1D (median disease duration of 14.4 years) in the EURODIAB cohort [20] and US adults in the NHANES cohort [3]. The variability in reported results from these diverse populations further justifies the need for population-specific research of the potential beneficial effects of dietary fiber on CVD risk.

A key strength of this analysis is the inclusion of multiple measurements of the outcomes of interest. Previous studies have focused on a single inflammatory marker, most frequently CRP due to its stability and ease of measurement. These CVD risk factors may be more strongly correlated with adverse outcomes compared to traditional risk factors, such as BMI. Another strength of this study was the inclusion of measures of arterial stiffness, an early marker of the development of vascular disease and therefore an important intervention point. Additionally, we used innovative methods to account for the ME associated with the FFQ, and therefore our estimates of fiber and energy intake are likely less biased than those reported in previous studies.

A limitation of this analysis is the potential for residual systematic error in estimated fiber intake that remains after ME-adjustment. Furthermore, we only had measures of the outcomes at a single timepoint (baseline for the inflammatory markers and approximately 19 months post-baseline for the arterial stiffness markers). The sample sizes, particularly for the measures of arterial stiffness, were small and therefore null findings may indicate a lack of power to detect an effect. Future analyses of the ongoing SEARCH Cohort Study will allow both longitudinal analyses and evaluation of the association with subclinical measures of vascular disease in a larger sample. However, the analysis presented here represents the

best available evidence on the relationship between dietary fiber and markers of early vascular disease development in youth with T1D.

The low dietary fiber intakes observed among youth with T1D in the US are not associated with measures of systemic inflammation or vascular stiffness. Clinical and public health efforts should focus on increasing these disconcertingly low dietary fiber intakes to meet current recommendations. Future research should involve clinical trials exploring feasible doses among youth with T1D and prospective observational studies in adults with longer T1D durations.

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Table 1

Participant characteristics across quartiles of ME^a-adjusted dietary fiber (g/1000 kcal) in the SEARCH Nutrition and Cardiovascular Disease Ancillary Studies.^b

Characteristic	ME-adjusted dietary fiber				P-value ^c	
	All n=1405	Quartile 1 < 6.2 g/1000 kcal n=352	Quartile 2 6.2 - < 7.2 g/1000 kcal n=350	Quartile 3 7.2 - < 8.3 g/1000 kcal n=352		Quartile 4 8.3 g/1000 kcal n=351
Age (yrs)	14.7 ± 3.0	14.9 ± 3.2	14.5 ± 3.0	14.3 ± 2.8	15.1 ± 2.9	0.001
Diabetes Duration (mos)	47.9 ± 43.2	74.3 ± 51.1	47.4 ± 39.3	38.1 ± 34.7	31.5 ± 32.6	<.0001
Gender						
Female	50.5 (709)	31.5 (111)	39.1 (137)	52.0 (183)	79.2 (278)	<.0001
Male	49.5 (696)	68.5 (241)	60.9 (213)	48.0 (169)	20.8 (73)	
Race/ethnicity						
White, non-Hispanic	78.9 (1108)	78.1 (275)	78.6 (275)	79.6 (280)	79.2 (278)	0.97
All other	21.1 (297)	21.9 (77)	21.4 (75)	20.5 (72)	20.8 (73)	
Household Income						
< \$25,000	10.6 (148)	11.4 (40)	10.9 (38)	7.4 (26)	12.6 (44)	0.01
\$25,000 to < \$50,000	19.8 (277)	21.6 (76)	23.9 (83)	18.2 (64)	15.5 (54)	
\$50,000 to < \$75,000	20.1 (282)	21.0 (74)	19.3 (67)	23.1 (81)	17.2 (60)	
\$75,000	41.9 (586)	36.9 (130)	40.2 (140)	45.3 (159)	45.0 (157)	
Don't know/refuse to answer	7.6 (107)	9.1 (32)	5.8 (20)	6.0 (21)	9.7 (34)	
Smoking						
Never	78.7 (1106)	72.4 (255)	79.7 (279)	82.7 (291)	80.1 (281)	0.0001
Former	13.5 (189)	13.9 (49)	12.3 (43)	12.2 (43)	15.4 (54)	
Current	7.8 (110)	13.6 (48)	8.0 (28)	5.1 (18)	4.6 (16)	
Physical Activity						
0-2 days/week	38.2 (536)	66.2 (233)	39.4 (138)	31.0 (109)	16.0 (56)	<.0001
3-7 days/week	61.9 (869)	33.8 (119)	60.6 (212)	69.0 (243)	84.1 (295)	
BMI Status ^d						
Non-obese	87.5 (1227)	86.0 (302)	90.6 (317)	83.5 (294)	89.7 (314)	0.02
Obese	12.5 (176)	14.0 (49)	9.4 (33)	16.5 (58)	10.3 (36)	
SBP (mmHg)	106.2 ± 10.7	107.2 ± 10.3	105.9 ± 11.4	106.2 ± 10.7	105.7 ± 10.6	0.24

Characteristic	ME-adjusted dietary fiber				P-value ^c	
	All n=1405	Quartile 1 < 6.2 g/1000 kcal n=352	Quartile 2 6.2 - < 7.2 g/1000 kcal n=350	Quartile 3 7.2 - < 8.3 g/1000 kcal n=352		Quartile 4 8.3 g/1000 kcal n=351
DBP (mmHg)	67.4 ± 9.7	68.2 ± 9.9	66.6 ± 9.9	67.4 ± 9.6	67.2 ± 9.5	0.17
IL-6 (pg/mL)	16.0 ± 22.8	17.4 ± 22.8	16.8 ± 24.4	16.3 ± 21.5	13.6 ± 22.5	0.12
CRP (mg/dL)	0.17 ± 0.41	0.20 ± 0.47	0.13 ± 0.32	0.17 ± 0.40	0.18 ± 0.44	0.15
Fibrinogen (mg/dL)	355.9 ± 68.0	352.9 ± 67.4	352.2 ± 63.8	355.8 ± 67.1	362.7 ± 73.2	0.17
Aix-75 (%) ^{e,f}	0.19 ± 12.3	1.31 ± 15.0	-0.52 ± 11.0	-0.89 ± 10.4	0.21 ± 10.4	0.80
PWV (carotid-femoral, m/sec) ^g	5.50 ± 0.88	5.54 ± 0.74	5.65 ± 1.26	5.24 ± 0.80	5.58 ± 0.58	0.14
BrachD (% change/mmHg) ^h	5.81 ± 1.10	5.89 ± 1.16	5.63 ± 0.94	5.85 ± 1.10	5.78 ± 1.15	0.70

^a Abbreviations used: measurement error (ME); systolic blood pressure (SBP); diastolic blood pressure (DBP); interleukin 6 (IL-6); C-reactive protein (CRP); augmentation index (Aix); pulse wave velocity (PWV); brachial distensibility (BrachD).

^b Values presented are mean ± SD or % (n).

^c Chi-square test for categorical variables and ANOVA for continuous variables.

^d Obesity defined as BMI 95th age- and sex-specific percentile for participants 20 years of age and BMI 30 kg/m² for participants > 20 years of age.

^e Normalized to heart rate of 75 beats/minute.

^f Available for n=180.

^g Available for n=184.

^h Available for n=177.

Table 2

Multivariable linear regression estimations for the association of ME^a-adjusted dietary fiber specified using quartiles (g/day; *Model 1*) and continuously (g/day; *Model 2*) with inflammation and arterial stiffness among youth with type 1 diabetes.

	IL-6 ^{b,c} n=1405		CRP ^d n=1387		Fibrinogen ^e n=1340		AIx-75 ^{f,g} n=180		PWV ^{h,i} n=184		BrachD ^j n=177	
	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value
<i>Model 1</i>												
ME-adjusted dietary fiber (g/day)	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-
Quartile 1	0.18 (0.12)	0.12	-0.07 (0.11)	0.55	0.009 (0.02)	0.56	-1.07 (2.66)	0.69	0.04 (0.16)	0.80	-0.15 (0.24)	0.54
Quartile 2	0.18 (0.13)	0.17	-0.12 (0.13)	0.35	0.0001 (0.02)	0.99	-0.20 (3.21)	0.95	-0.09 (0.19)	0.64	0.23 (0.28)	0.40
Quartile 3	0.28 (0.17)	0.08	-0.12 (0.16)	0.45	-0.008 (0.02)	0.73	0.79 (3.83)	0.84	0.12 (0.23)	0.59	0.17 (0.34)	0.61
<i>Model 2</i>												
ME-adjusted dietary fiber (g/day)	0.14 (0.35)	0.70	-0.14 (0.33)	0.67	-0.02 (0.05)	0.66	8.61 (7.12)	0.21	-0.42 (0.44)	0.33	0.58 (0.74)	0.43

^a Abbreviations used: measurement error (ME); interleukin 6 (IL-6); C-reactive protein (CRP); augmentation index (AIx); pulse wave velocity (PWV); brachial distensibility (BrachD); mean arterial pressure (MAP).

^b Log[IL-6 (pg/mL)].

^c Adjusted for ME-adjusted total energy intake, age, gender, race/ethnicity, diabetes duration, smoking status, and physical activity.

^d Log[CRP (mg/dL)].

^e Log[Fibrinogen (mg/dL)].

^f Normalized to heart rate of 75 beats/minute (%).

^g Adjusted for ME-adjusted total energy intake, age, gender, race/ethnicity, diabetes duration, smoking status, physical activity, time between the SEARCH initial patient visit and CVD pilot study visit, MAP, and height.

^h Carotid-femoral (m/s).

ⁱ Adjusted for ME-adjusted total energy intake, age, gender, race/ethnicity, diabetes duration, smoking status, physical activity, time between the SEARCH initial patient visit and CVD pilot study visit, and MAP.

^j Percent change/mmHg.