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Endothelial function, arterial stiffness, and adherence to the 2010 Dietary Guidelines for Americans: a cross-sectional analysis

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Abstract

Endothelial dysfunction and arterial stiffness are early predictors of cardiovascular disease. Intervention studies suggest that diet is related to vascular health, but most prior studies tested individual foods or nutrients and relied on small samples of younger adults. The purpose of this study was to examine relations between adherence to the 2010 Dietary Guidelines for Americans and vascular health in a large, cross-sectional analysis. In 5887 adults in the Framingham Heart

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Conflict of Interest

The authors declare that there are no conflicts of interest.

Authorship

The authors contributions were as follows: K.A.S. conducted the analysis and drafted the manuscript; D.N.P., M.C., P.F.J., L.M.T., N.W., N.M.H., J.A.V., R.S.V., G.F.M., and S.G.W. assisted in the creation, design, analysis, and interpretation of the project. All authors critically revised and approved the final manuscript.

Study Offspring and Third Generation cohorts, diet quality was quantified with the 2010 Dietary Guidelines for Americans Index (DGAI-2010). Endothelial function was assessed via brachial artery ultrasound and arterial stiffness via arterial tonometry. In age-, sex-, and cohort-adjusted analyses, higher DGAI-2010 score (greater adherence) was modestly associated with lower resting flow velocity, hyperemic response, mean arterial pressure, carotid-femoral pulse wave velocity, and augmentation index, but not associated with resting arterial diameter or flow-mediated dilation. In multivariable models adjusting for cardiovascular risk factors, only the association of higher DGAI-2010 with lower baseline flow and augmentation index persisted (β=−0.002, P=0.003 and β =−0.05 ± 0.02, P<0.001, respectively). Age-stratified multivariate-adjusted analyses suggested that the relation of higher DGAI-2010 scores with lower mean arterial pressure, pulse wave velocity, and augmentation index was more pronounced among adults younger than 50 years. Better adherence to the 2010 Dietary Guidelines for Americans, particularly in younger adults, is associated with lower peripheral blood flow velocity and arterial wave reflection but not flowmediated dilation. Our results suggest a link between adherence to the Dietary Guidelines and favorable vascular health.

Keywords

endothelial function; arterial stiffness; Dietary Guidelines for Americans; Framingham Heart Study

Introduction

Endothelial dysfunction and arterial stiffness are early predictors of atherosclerosis, hypertension, and cardiovascular disease $(CVD)^{(1,2)}$. There is strong evidence that diet is related to endothelial dysfunction^(3,4), and, to a lesser degree, arterial stiffness^(5,6). However, there is significant variation in the methods used to quantify diet in previous studies, with the majority examining intake of specific foods or nutrients rather than overall diet. Studies of chronic disease morbidity and mortality indicate that the use of dietary indices, or diet quality scores, is a comprehensive approach that can provide valuable insight into the relationship between diet and health $(\bar{7}, 8)$.

The Dietary Guidelines for Americans (DGA) are evidence-based recommendations that provide guidance for choosing an eating pattern that promotes health and prevents disease. The 2010 Guidelines emphasize greater intake of fruits, vegetables, low-fat dairy products, whole grains, and a variety of lean meats while maintaining appropriate weight through caloric balance and physical activity⁽⁹⁾. The Dietary Guidelines Adherence Index (DGAI) is a tool that quantifies the degree to which key DGA recommendations are met. Developed in reference to the 2005 $DGA^{(10)}$ and updated for the 2010 $DGA^{(11)}$, the DGAI provides an objective index of diet quality that is useful for standardizing dietary assessments across studies. To our knowledge, no studies have evaluated whether overall diet quality is associated with measures of vascular function, particularly in a large, community-based sample.

Vascular health declines with age despite control of traditional risk factors. It is unclear whether age-related decline in vascular function is part of a normal physiological aging

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process or a consequence of repeated exposure to lifestyle-related risk factors. Physiological changes with age likely interact with lifestyle risk factors to exacerbate arterial stiffness and endothelial dysfunction⁽¹²⁾. Given the burden of CVD on the United States' aging

population, there is a need for improved understanding of the interaction between age and lifestyle and its effect on vascular function.

Therefore, the purpose of this study was to determine if adherence to the 2010 DGA is associated with endothelial dysfunction and arterial stiffness in a cross-sectional sample of adults from the Framingham Heart Study. A secondary purpose was to determine whether age influences the association between diet quality and these measures of vascular health.

Experimental Methods

Subjects

The Framingham Heart Study is a longitudinal, community-based study of risk factors for CVD. The current study includes dietary and vascular data collected during the seventh examination cycle of the Offspring cohort $(1998 - 2001^{(13)})$ and the first examination cycle of the Third Generation cohort $(2002 - 2005^{(14)})$. Sample characteristics are presented in Table 1. The present analysis was approved by the Institutional Review Board at The Pennsylvania State University.

Dietary measurements

The Harvard semi-quantitative food frequency questionnaire $(FFQ)^{(15)}$ was mailed to participants prior to the examination and they were asked to bring the completed form to their appointment. The 126-item questionnaire assesses the consumption frequency of standard servings of foods and beverages during the last year with response selections ranging from "never or less than once per month" to "6+/day." The Harvard FFQ provides a space for participants to write-in up to three additional foods they frequently consumed that were not listed, and specifically asks for type of breakfast cereal and cooking oil regularly used. Nutrient intakes are calculated by multiplying average intake with nutrient content of individual foods, based on the United States Department of Agriculture food composition database and supplemented with other sources^{(16)}.

The DGAI-2010 was applied to the FFQ data to determine the extent to which participants' diets are consistent with the 2010 DGA (see Supplementary Material for further description and example calculation). The DGAI-2010 assesses intake of 14 food groups (fruit; dark green vegetables; orange and red vegetables; starchy vegetables; other vegetables; grains; milk; meat, protein, and eggs; seafood; nuts; legumes; sugar; variety in protein choices; and variety of fruits and vegetables) and 11 healthy choice or nutrient intake recommendations (amounts of total fat, saturated fat, trans fat, cholesterol, sodium, fiber, alcohol; and percentage of protein that is lean, milk that is low-fat, grains that are whole grains, and fruits that are whole fruits). Adherence to each DGAI-2010 item is scored on a continuous scale of 0–1, and the categories are summed and standardized to a range of 0–100 to create an overall score, with higher scores indicating greater adherence. An important component of the DGAI compared to other dietary quality assessment tools is the penalty assigned for

overconsumption, which is in line with the 2005 and 2010 DGA emphasis on weight management. That is, the DGAI avoids assigning a higher score to individuals who meet the recommended food intakes simply through eating more. Appropriate energy levels are calculated for each participant (based on height, weight, age, sex, and physical activity estimates) and participants are penalized for consuming more than the recommended daily intake of energy-dense foods (e.g. starchy vegetables, specific protein sources, grains, meat and beans, and dairy products) for their energy intake.

Vascular measurements

Endothelial function was assessed by brachial artery flow-mediated dilation (FMD). Methodology and reproducibility data have been previously published $(17,18)$. Briefly, brachial artery diameter (mm) was imaged in the supine position with high-resolution ultrasound at rest and one minute after reactive hyperemia that was induced by 5-minute cuff occlusion of forearm blood flow. Arterial diameter was measured offline using commercially-available edge-detection software. Brachial FMD was calculated as the percent change in brachial diameter during reactive hyperemia from the resting state (%FMD), with lower values indicating greater endothelial dysfunction. Baseline and postdeflation hyperemic flow velocity were assessed with Doppler imaging at baseline and for 15 seconds immediately post-deflation, as described previously⁽¹⁹⁾.

Central (aortic) arterial stiffness was assessed in the supine position with arterial tonometry as described previously⁽²⁰⁾. Briefly, blood pressure was obtained with an oscillometric (Offspring) or auscultatory (Third Generation) device, and mean arterial pressure was measured via brachial waveform planimetry. A tonometer recorded blood pulsations at the right carotid, brachial, radial, and femoral arteries. Transit distances were measured from the suprasternal notch to each recording site. Tonometry waveforms were signal-averaged offline and calibrated using cuff pressures as described previously. Carotid-femoral pulse wave velocity (PWV) was calculated from transit distances and tonometry waveforms as described previously $^{(21)}$, with greater PWV indicating greater arterial stiffness. Augmentation index was calculated from the carotid pressure waveform as described previously⁽²²⁾, with higher values reflecting greater relative wave reflection.

Covariates

Potential confounders of the relationship between diet and vascular health were considered in the present analysis in accordance with previous studies^{$(17,20)$}. All participants underwent routine medical examination at the time of vascular assessment to obtain the following characteristics: age, sex, race, body mass index, heart rate, fasting glucose, total/HDL cholesterol ratio, triglycerides, diabetes (defined as a fasting blood glucose of 126 mg/dL or treatment with insulin or an oral hypoglycemic agent), hypertension (defined as systolic blood pressure 140 mm Hg, diastolic blood pressure 90 mm Hg), or existing CVD (coronary heart disease, heart failure, stroke, transient ischemic attack, or intermittent claudication). Systolic and diastolic blood pressures were the average of two physicianmeasured readings at the Heart Study. Hormone replacement therapy, hypertension medication, lipid-lowering medication, and cigarette smoking (in the six hours prior to vascular testing) were determined by self-report. A variable representing the timing of a

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walk test (performed concomitantly at Offspring Exam 7) in relation to the vascular assessments (before vs. after or not done) was included. We also included variables denoting family relatedness (parent-child and sibling-sibling) and cohort.

Statistical analyses

Of the 7634 participants who attended the seventh Offspring exam (n=3539) or the first Third Generation exam (n=4095), complete dietary and covariate data were available for 5887. Of these, brachial FMD data were available for 5521, flow data were available for 5067, and tonometry data were available for 5379. To maximize power, participants were included in analyses for which complete data were available. To determine power for the present analysis, we reviewed an earlier Framingham Heart Study analysis of brachial FMD where a final model including 8 predictors yielded a multiple R^2 of 0.16 for %FMD⁽¹⁷⁾. In the present proposal, the sample size of 5521 (for brachial FMD data) provided >90% power with an alpha of 0.05 to detect a change in the model \mathbb{R}^2 of 0.01.

All analyses were conducted in SAS v9.3 (Cary, NC). The DGAI-2010 scores were divided into equal quintiles according to the full sample (n=5887 total, n=1174 or 1175 per quintile). Means and 95% confidence intervals of participant characteristics and potential covariates across quintile categories, adjusted for age and sex, were computed using general linear models. The statistical significance for trend was assessed using linear regression for continuous variables with DGAI-2010 entered as a continuous score.

The DGAI-2010 score and all vascular outcome variables were assessed for normality; baseline flow velocity and PWV were positively skewed. A natural log transformation was applied to baseline flow velocity and an inverse transformation to PWV (1000/PWV). Quintile category means and 95% confidence intervals of vascular characteristics, adjusted for clinical covariates (see below), were computed using general linear models. Analysis of the residual plots indicated that the assumption of linearity was met. The statistical significance for trend was assessed with DGAI-2010 entered as a continuous score, and the GEE (Generalized Estimating Equations) approach was applied to account for the familial correlations in the present sample. First order interactions between DGAI-2010 and age were assessed for each of the vascular characteristics using model 2 (described below); variables with statistically significant interactions were stratified $($or 50$ years) for further$ investigation.

For all vascular outcomes, two analyses were performed with family relatedness and cohort indicator variables included as covariates in all models. Model 1 adjusted for age and sex, and Model 2 additionally adjusted for relevant clinical covariates (body mass index, mean arterial pressure, heart rate, and smoking) $(17,20)$. We explored the effect of further adjusting for total: HDL cholesterol, triglycerides, diabetes, hypertension therapy, lipid therapy, hormone replacement therapy, prevalent CVD, and completing the walk test prior to vascular testing in a third model, but this analysis yielded the same results as Model 2 and is therefore not presented. For all analyses, P<0.05 was considered statistically significant. Unless otherwise noted, we report adjusted means (95% CI).

Results

Sample characteristics stratified by sex are presented in Table 1. The sample was 54% women with an average age of approximately 48 years for both men and women. Mean DGAI-2010 score was 55 in men and 61 in women. On average, both men and women were overweight but men tended to have a worse metabolic profile and higher use of antihypertensive and lipid-lowering medications. Increasing DGAI-2010 scores were significantly associated with increasing age $(p<0.001)$ and decreasing body mass index (p<0.001), heart rate (p<0.001), total: HDL cholesterol (p<0.001), triglycerides (p<0.001), and glucose ($p<0.001$); and were significantly higher among women ($p<0.001$) and nonsmokers (p<0.001) (data not shown).

Vascular characteristics according to DGAI-2010 quintile categories are reported in Table 2 (Model 1) and Table 3 (Model 2). Baseline brachial artery diameter and FMD were not significantly associated with DGAI-2010 scores in Models 1 or 2. Baseline mean flow velocity was lower with higher DGAI-2010 scores in both models. Surprisingly, hyperemic mean flow velocity was lower with higher DGAI-2010 scores in Model 1, though this association was blunted in the fully-adjusted model. Further analysis indicated that concurrent adjustment for heart rate, body mass index, and smoking (but not mean arterial pressure) attenuated the association between hyperemic mean flow velocity and diet, with the greatest attenuation seen when smoking status was added to the model. Mean arterial pressure and carotid-femoral PWV were lower with higher dietary quintile scores in Model 1 but the relations were attenuated in Model 2; further analysis indicated that adjustment for heart rate alone rendered the associations non-significant. Augmentation index was lower with increasing DGAI-2010 scores in both models.

We tested interactions between DGAI-2010 and age for vascular characteristics using Model 2 and found a significant interaction for mean arterial pressure, carotid-femoral PWV, and augmentation index. Stratified analyses (\langle or \rangle 50 years, Table 4) indicated that mean arterial pressure is lower with higher DGAI-2010 scores in younger adults ($\beta = -0.03$, $P=0.05$) but not in older adults ($\beta=0.04$, $P=0.09$). Similarly, stratified analyses suggested that carotid-femoral PWV is lower with higher DGAI-2010 scores in younger adults (β =–0.03, $P=0.01$) but not older adults ($\beta=0.001$, $P=0.06$), although neither association was statistically significant. Augmentation index in the younger group was significantly lower with higher DGAI-2010 scores (β =−0.05, P=0.01), and although a similar association was indicated in the older group, it did not reach statistical significance (β=–0.04, $P=0.06$).

Discussion

In a large, cross-sectional community-based cohort study, we have comprehensively evaluated the associations of adherence to the 2010 DGA with measures of vascular function. Vasodilator measures in both a conduit artery, assessed by brachial FMD, and the microvessels, assessed by reactive hyperemia, were not associated with dietary adherence. Resting brachial flow velocity but not diameter was related to dietary adherence. The association of central aortic stiffness with diet in unadjusted models appeared to be related to concomitant risk factors. However, wave reflection assessed by augmentation index was

The cross-sectional relations between selected dietary components and FMD was previously examined in over 3000 adults in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort and found that among women (but not men) regular fish intake was associated with higher $FMD⁽²³⁾$; however, fish intake was the only component of diet reported. Numerous clinical trials have reported beneficial effects of dietary interventions on FMD, such as interventions low in fat^{(24_27}), rich in unsaturated fat^{(24,28,29}), based on the Mediterranean diet^{(30_33}), or rich in protein⁽³⁴⁾. Additionally, a review of observational studies concluded that diets rich in fruits and vegetables are inversely associated with biomarkers of endothelial dysfunction (such as cellular adhesion molecules and other pro-inflammatory markers), whereas Westernized diets rich in meat were positively associated with biomarkers of endothelial dysfunction⁽³⁵⁾. In the present study, we found that a dietary pattern in line with the 2010 DGA was not related to baseline brachial diameter and FMD. It is possible that the food groups and nutrients highlighted by the DGA are not those most important to vascular function, at least when assessed by brachial FMD, as these guidelines were meant to promote general health rather than prevent a specific condition such as vascular disease. Thus, the use of an overall index may be masking the effects of specific foods and nutrients, including those previously shown to modify endothelial function and arterial stiffness (e.g. nuts, chocolate, tea, red wine, omega-3 fatty acids, sodium) $(3-6,36-42)$. Importantly, as the 2010 DGA index does not include a component specific to intake of fish rich in long-chain omega-3 fatty acids or overall polyunsaturated fatty acid consumption, we are unable to compare our findings to those reported in the MESA study described above. The differences between our results and previous intervention trials may be explained by the limitations of cross-sectional observational studies and FFQ in assessing diet. Short-term intervention studies that provide food to participants can more accurately measure consumption of a particular food or dietary pattern, and thereby establish efficacy in modifying endothelial function.

Brachial flow velocities at rest and during hyperemia reflect arterial properties in microcirculation. In the present analysis, we have shown that increased adherence to the 2010 DGA is associated with lower baseline (resting) flow velocity. In the fully-adjusted model, we observed a difference in mean baseline flow velocity between the bottom and top quintiles of diet scores of −0.5 cm/s. Prior studies in the present cohort and others have demonstrated associations between higher resting flow velocity and CVD risk factors (particularly metabolic risk factors)⁽⁴³⁾, and there is evidence that higher resting flow may induce small vessel damage (44) . The absolute difference in resting flow that we observed between quintile 1 and quintile 5 (0.5 cm/s) is similar in magnitude to the 0.39 cm/s increase predicted by every increase of 1.3 in total: HDL cholesterol ratio and to the 0.75 cm/s increase predicted by every increase of 4.6 kg/m² in body mass index in a prior analysis of the Framingham Heart Study(44) . Taken together, our results suggest that adherence to the 2010 DGA may be as important as other CVD risk factors in determining resting flow velocity.

Hyperemic flow reflects small vessel vasodilation in response to ischemia and also predicts CVD outcomes and correlates with CVD risk factors($45\frac{1}{47}$). We found an unexpected trend toward a negative association for adherence to the DGA and hyperemic flow velocity in the age- and sex-adjusted model that was blunted in the fully-adjusted model. Further analysis indicated that heart rate, body mass index, and smoking accounted for the association of DGAI-2010 scores and hyperemic flow velocity.

Prior observational studies indicate that diets rich in meat intake and high alcohol consumption are associated with greater arterial stiffness^{$(6,36)$}, whereas diets with moderate alcohol consumption^{(37_40}), low sodium intake⁽⁴¹), greater fruit and vegetable consumption⁽⁵⁾, and greater consumption of dairy products $(42,48)$ have been associated with lower arterial stiffness. In the present study, adherence to the DGA was related to mean arterial pressure, carotid-femoral PWV, and augmentation index in the age- and sex-adjusted model, but only augmentation index remained significantly associated with DGAI-2010 after further adjustment for CVD risk factors. On average, the difference in augmentation index (%) between the bottom and top quintiles of dietary scores was 1.3%, which is similar to the increase of 0.93% predicted by every 8.5 year increase in age within the present cohort⁽²¹). This finding is consistent with reduced wave reflection and ventricular ejection⁽⁴⁹⁾ with greater adherence to the DGA. Further analyses indicated that the relationship between PWV and diet observed in the age- and sex-adjusted model was no longer evident after adjustment for heart rate. Heart rate is an important potential confounder of associations with carotid-femoral $PWV^{(20)}$, and researchers are encouraged to adjust for this in future studies.

There was a significant interaction between DGAI-2010 and age for the vascular stiffness measures that persisted after adjustment for heart rate and the other covariates in Model 2. Age is the predominant risk factor for $CVD^{(12)}$ and advancing age increases risk despite control of modifiable lifestyle factors^{(50_53}). Stratified analyses indicated that mean arterial pressure and arterial wave reflection are lower with higher DGAI-2010 scores in adults younger than 50 years, but in those aged 50 and older, the associations were not as strong or statistically non-significant. While stratified analyses for PWV were non-significant for both age groups, the trend toward lower PWV with higher DGAI-2010 scores was notably stronger in the younger group. Collectively, our results indicate that for younger adults, following a diet that more closely resembles the 2010 DGA is associated with better vascular health. In contrast, for older adults, adherence to the 2010 DGA is unrelated to vascular health. Longitudinal studies and intervention studies with long-term follow-up are needed to understand the possible dietary contribution to vascular decline.

The goal of the present study was to examine the association between adherence to the DGA and vascular health. However, there may be limitations to this approach. The DGA are evidence-based recommendations that provide guidance for choosing an eating pattern that promotes health and prevents disease, but as noted above, these recommendations do not focus solely on vascular disease. Moreover, few individuals in this cohort consumed diets that closely adhered to the DGA, which may limit our ability to see benefits of this dietary pattern. Other limitations of the study include its cross-sectional nature that prevents us from drawing conclusions about causation and related mechanisms. The Framingham cohorts are

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overwhelmingly white; thus, generalization to other races or ethnicities is limited. However, the use of this large, well-characterized sample enables us to examine the relationship between diet and vascular health with consideration of CVD risk factors. In addition, the age range of this sample (19–89 years) allowed us to examine the relationship between diet quality and vascular health over a wide age range.

In conclusion, we have shown that adherence to the 2010 DGA is associated with measures of blood flow velocity and arterial wave reflection, but not related to brachial FMD. Importantly, we have demonstrated that diet may be particularly related to vascular health in adults younger than 50 years. Future studies should examine whether interventions that increase adherence to the DGA modify vascular health, especially among younger adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Sample characteristics*

HDL, high-density lipoprotein; CVD, cardiovascular disease.

 $^I\!{\rm{Means}} \pm {\rm{SD}}$ for continuous variables, percentage for dichotomous variables.

* DGAI-2010 range is 0–100 possible points.

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Table 2

Vascular characteristics according to quintile category of DGAI-2010 (Model 1), adjusted for age, sex, family relatedness, and cohort

Quintile category means (95% CI) derived with general linear models adjusted for age, sex, cohort, and family relatedness. Quintile category means (95% CI) derived with general linear models adjusted for age, sex, cohort, and family relatedness.

 2 Derived from general estimating equations with DGAI-2010 entered as a continuous score. Derived from general estimating equations with DGAI-2010 entered as a continuous score.

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Quintile category means (95% CI) derived with general linear models adjusted for age, sex, cohort, family relatedness, body mass index, mean arterial pressure, heart rate, and smoking. Quintile category means (95% CI) derived with general linear models adjusted for age, sex, cohort, family relatedness, body mass index, mean arterial pressure, heart rate, and smoking.

 2 Derived from general estimating equations with DGAI-2010 entered as a continuous score. Derived from general estimating equations with DGAI-2010 entered as a continuous score.

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Vascular characteristics according to quintile category of DGAI-2010, stratified by age ٦.

Quintile category means (95% CI) derived with general linear models adjusted for age (continuous), sex, body mass index, mean arterial pressure, heart rate, and smoking. Quintile category means (95% CI) derived with general linear models adjusted for age (continuous), sex, body mass index, mean arterial pressure, heart rate, and smoking.

 2 Derived from general estimating equations with DGAI-2010 entered as a continuous score. Derived from general estimating equations with DGAI-2010 entered as a continuous score.