Associations between markers of subclinical atherosclerosis and dietary patterns derived by principal components analysis and reduced rank regression in the Multi-Ethnic Study of Atherosclerosis (MESA)[1–3]

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ABSTRACT

Background: The association between diet and cardiovascular disease (CVD) may be mediated partly through inflammatory processes and reflected by markers of subclinical atherosclerosis.

Objective: We investigated whether empirically derived dietary patterns are associated with coronary artery calcium (CAC) and common and internal carotid artery intima media thickness (IMT) and whether prior information about inflammatory processes would increase the strength of the associations.

Design: At baseline, dietary patterns were derived with the use of a food-frequency questionnaire, and inflammatory biomarkers, CAC, and IMT were measured in 5089 participants aged 45–84 y, who had no clinical CVD or diabetes, in the Multi-Ethnic Study of Atherosclerosis. Dietary patterns based on variations in C-reactive protein, interleukin-6, homocysteine, and fibrinogen concentrations were created with reduced rank regression (RRR). Dietary patterns based on variations in food group intake were created with principal components analysis (PCA).

Results: The primary RRR (RRR 1) and PCA (PCA factor 1) dietary patterns were high in total and saturated fat and low in fiber and micronutrients. However, the food sources of these nutrients differed between the dietary patterns. RRR 1 was positively associated with CAC [Agatston score >0: OR (95% CI) for quartile 5 compared with quartile 1 = 1.34 (1.05, 1.71); ln(Agatston score = 1): *P* for trend = 0.023] and with common carotid IMT [≥1.0 mm: OR (95% CI) for quartile 5 compared with quartile 1 = 1.33 (0.99, 1.79); ln(common carotid IMT): *P* for trend = 0.006]. PCA 1 was not associated with CAC or IMT.

Conclusion: The results suggest that subtle differences in dietary pattern composition, realized by incorporating measures of inflammatory processes, affect associations with markers of subclinical atherosclerosis. *Am J Clin Nutr* 2007;85:1615–25.

KEY WORDS Dietary patterns, principal components analysis, reduced rank regression, carotid artery intima media thickness, coronary artery calcium

INTRODUCTION

Coronary artery calcium (CAC) and carotid artery intima media thickness (IMT) are considered early indicators of atherosclerotic disease (1–3) and have been associated with cardiovascular disease (CVD) events in large prospective cohort studies (4–7). Inflammatory biomarkers, such as C-reactive protein (CRP), interleukin-6 (IL-6), homocysteine, and fibrinogen, are associated with the development of overt CVD (8–13). Dietary intake also plays a role in the development of CVD, and studies have reported significant relations between dietary factors and subclinical atherosclerosis and inflammation. Plasma vitamin C (14) and dietary linolenic acid (15) have been shown to be inversely associated, whereas dietary saturated fat (16) has been shown to be positively associated, with CAC. Fiber and wholegrain intake have been shown to be associated with reduced progression of carotid artery IMT (17) or coronary artery stenosis (18). Diets rich in combinations of these individual components have also shown inverse associations with subclinical atherosclerosis markers (19–21). Randomized, multifactorial lifestyle interventions also support a beneficial role for dietary patterns in relation to the progression of atherosclerosis (22, 23). Similar associations between inflammatory biomarkers and nutrients, foods, and dietary patterns also exist (24–29), which suggests a potential intermediate pathway between diet and markers of atherosclerosis and, thus, CVD.

Dietary pattern analysis facilitates the examination of food and nutrient synergies in relation to disease, whereas traditional reductive approaches may not capture such synergies and associations (30, 31). Recently, Hoffmann et al (32) proposed the application of reduced rank regression (RRR) in dietary pattern analysis. In contrast with the commonly used principal components analysis (PCA), which produces a linear combination of food groups (a factor) that maximally explains variation in food group intake, RRR produces a linear combination of food groups

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that maximally explains variation in investigator-specified intermediate response variables. Thus, the technique allows hypotheses regarding pathways (represented by the response variables) between diet and disease to be evaluated (33). Although PCA has been successful, it may not achieve the full potential of dietary pattern analysis because it relies solely on intercorrelations among dietary variables, which may not optimally represent the diet qualities most relevant to specific disease etiology (32).

In the present study we used RRR to derive dietary patterns on the basis of their ability to maximally explain variation in biochemical markers related to inflammation (ie, CRP, IL-6, fibrinogen, and homocysteine). A comparison of the food group composition of behavior-based PCA patterns with the food group composition of inflammation-based RRR patterns will provide an interesting perspective on the value of the 2 methods, ie how much information is lost if patterns are based on behavior alone and do not take into account inflammatory processes? On the basis of previous successes of PCA in this (26) and other (34) cohorts, we hypothesized that both PCA and RRR techniques would produce dietary patterns associated with CAC and carotid artery IMT. However, by incorporating inflammatory intermediates in the RRR analysis, we hypothesized that the RRR method would produce dietary patterns more strongly associated with CAC and IMT than dietary patterns derived by PCA.

SUBJECTS AND METHODS

Subjects

The primary objectives of the Multi-Ethnic Study of Atherosclerosis (MESA) are to study the characteristics of subclinical CVD and the risk factors that predict progression to clinically overt CVD or progression of subclinical disease (35). The MESA population consists of an ethnically diverse group of 6814 white, black, Hispanic, and Asian men and women aged 45–84 y, who were recruited from 6 field centers across the United States (Baltimore City and County, MD; Chicago, IL; Forsyth County, NC; New York, NY; Los Angeles County, CA; and St Paul, MN). All participants were free of clinical CVD at baseline and gave informed consent. The MESA protocols were approved by each field center's institutional review board.

The current cross-sectional investigation includes data from 5089 participants enrolled in MESA, including 2407 men and 2682 women aged 45–84 y. This sample was chosen after the exclusion of individuals who were currently taking oral steroid or antiinflammatory asthma medications ($n = 134$), who had diabetes mellitus defined according to the American Diabetes Association 2003 criteria ($n = 919$) (36), and who provided insufficient or implausible dietary information ($n = 630$: 167 because of extreme energy intake and 463 because of implausible responses or improperly completed questionnaires; 26).

Carotid intima media thickness and coronary calcium

Thickness of the intima media layers of the common and internal carotid arteries was determined from images obtained by high-resolution B-mode ultrasonography (Logiq 700 ultrasound machine; GE Medical Systems, Waukesha, WI). Calculation of IMT was performed at the central MESA ultrasound reading center (Tufts–New England Medical Center, Boston, MA). In the present study, high IMT was defined as measures above the 75th percentile of the sample distribution, separately for each internal carotid IMT (1.3 mm) and common carotid IMT (1.0 mm).

Computed tomography (CT) of the coronary arteries was performed with cardiac-gated (at 80% of the R-R interval) electron beam scanners at 3 centers (Imatron C-150; Imatron Inc, San Francisco, CA) (37) and with a prospective electrocardiogram-triggered scan acquisition at 50% of the R-R interval with multidetector scanners (38) at the remaining 3 centers. These scanners are comparable in their ability to measure calcium (39). All scans were read at the central MESA CT reading center (Harbor-University of California Medical Center; Los Angeles, CA). CAC scores (Agatston scores) were determined by blinded CT analysts. Presence of CAC was defined as an Agatston score >0.

CRP, fibrinogen, interleukin-6, and homocysteine

CRP, fibrinogen, IL-6, and homocysteine concentrations were measured in blood samples collected at baseline, processed (40), and stored at −80 °C until analyzed. CRP and fibrinogen antigen were measured in plasma with a BNII nephelometer (N High Sensitivity CRP and N Antiserum to Human Fibrinogen; Dade Behring Inc, Deerfield, IL). IL-6 concentrations were measured by ultrasensitive enzyme-linked immunosorbent assay (Qantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis, MN). Plasma homocysteine was measured by polarization immunoassay with an IMx Analyzer (IMx Homocysteine Assay; Axis Biochemicals ASA; Oslo, Norway). Analytic CVs were 3.6%, 2.6%, 6.3%, and 4.5% for CRP, fibrinogen antigen, IL-6, and homocysteine, respectively.

Dietary assessment

At the baseline examination, each participant completed a self-administered, modified-Block style food-frequency questionnaire (FFQ) (26, 41, 42). The FFQ was provided in English, Spanish, or Chinese with staff assistance available on request. Responses were converted to servings/d and categorized into 47 food groups.

Dietary pattern analysis

Dietary patterns were derived from 47 food groups with the use of 2 different empirical methods: PCA (26) and RRR (32) (SAS PROC FACTOR with varimax rotation and SAS PROC PLS with the RRR method option, respectively). In the RRR analysis, the specified response variables were CRP, IL-6, fibrinogen, and homocysteine (natural log values due to nonnormal distribution of original values). For the PCA analysis, a 4-pattern solution was chosen after the evaluation of a scree plot of the eigenvalues and after the interpretability of the final solution was considered. For the RRR analysis, a 4-pattern solution was used in accordance with the number of response variables specified (32). The 4-factor PCA solution explained 26.2% of the variation in food group intake and 1.5% of the variation in response variables. The 4-factor RRR solution explained 12.6% of the variation in food group intake and 5.0% of the variation in response variables. To present data concisely and because other dietary patterns were not significantly associated with the outcomes, the results are presented for only the primary factor (dietary pattern) derived by the PCA and the primary factor derived by RRR.

A score was calculated for each participant for each PCA and RRR dietary pattern as a sum of the 47 food groups, each weighted

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according to the factor loadings. Participant scores were then categorized into quintiles separately for each dietary pattern. Thus, for each dietary pattern, quintile 5 was composed of persons whose diets conformed most closely to that particular pattern.

Assessment of other relevant variables

Information on demographics, education, medication use, smoking history, and physical activity were collected at the baseline examination with a combination of self-administered and interviewer-administered questionnaires. Waist circumference (cm) was measured at the umbilicus, and body mass index (BMI; in kg/m^2) was calculated from measured height and weight.

Statistical analysis

All analyses were conducted with SAS version 9.1 (SAS Institute Inc, Cary, NC). The percentage variance in total dietary pattern score explained by each food group was calculated as follows (32):

$$\text{Percentage of variation explained} = (\text{Pearson correlation coefficient between food group and dietary pattern}) \times (\text{standardized } \beta \text{ coefficient for the association between food group and dietary pattern}) \times 100 \quad (1)$$

Energy-adjusted Pearson correlations were calculated between nutrients and dietary patterns. Unadjusted Pearson correlations were calculated between CRP, fibrinogen, IL-6, and homocysteine and dietary patterns and between these biomarkers and select food groups. Participant characteristics were calculated according to quintiles of each dietary pattern by using general linear model regression.

Odds ratios (ORs) for risk of high internal (≥1.3 mm) and common (≥1.0 mm) carotid IMT and CAC presence (Agatston score >0) were calculated for quintiles 2–5 of each dietary pattern by using quintile 1 as the reference category. The PCA-derived and RRR-derived dietary patterns were each entered separately into the multivariable logistic regression model, and the *P* for trend across quintiles was calculated by treating the categorical dietary pattern variable as a continuous term in all analyses. A linear regression analysis was also performed with the continuous natural log-transformed values of mean IMT of the common carotid artery, internal carotid artery, and CAC score (adding 1 to each before transformation to accommodate zeroes and very small values) as the dependent variables and the dietary patterns (quintile variables) as the independent variables. Again, each dietary pattern was entered into the regression model separately, with adjustment for the appropriate covariates (defined below).

In addition to age- and energy-adjusted analyses (model 1), we adjusted for the following confounding variables: field center (Baltimore City and County, MD; Chicago, IL; Forsyth County, NC; New York, NY; Los Angeles County, CA; and St Paul, MN), sex (male or female), race-ethnicity (white, black, Hispanic, and Chinese), education level (less than high school, high school, more than high school), active leisure activity (metabolic equivalents in minutes per week, includes moderate and vigorous activities), inactive leisure activity (metabolic equivalent in minutes per week, including activities such as television watching and automobile transportation), smoking (never versus current and pack-years), and dietary supplement use (at least weekly use versus nonuse) (model 2). We further investigated potential mediating pathways using the following 2 models: *1*) main multivariable model listed above + waist circumference, and *2*) main multivariable model + CVD risk factors with dietary origins (systolic blood pressure, HDL cholesterol, LDL cholesterol, triacylglycerols, insulin, and glucose). Additional adjustment for statin or hypertension medication use did not appreciably affect risk estimates; therefore, these variables were not included. Furthermore, exclusion of statin users ($n = 656$) before analysis did not materially affect results. We did not consider excluding users of hypertension medications because of the large numbers ($n = 1646$).

To assess homogeneity of risk estimates, stratified analyses were also conducted for BMI (<25 or ≥25) and waist circumference (<88.9 or ≥88.9 cm for women; <101.6 or ≥101.6 cm for men). Formal tests of interaction between dietary patterns and race-ethnicity, sex, current smoking status, BMI, or waist circumference were assessed by adding cross product terms to the main multivariable model.

To assess whether the associations ascribed to a dietary pattern were driven by single food group components, we performed analyses similar to those described above with the individual food groups contributing most to dietary pattern score variance as the independent variables (categorical and continuous analyses).

RESULTS

Dietary patterns, foods, and nutrients

Pearson correlation coefficients between the dietary patterns and food groups that explained most of the variance in dietary pattern scores are presented in **Table 1**. As reported previously (26), the first PCA factor, "fats and processed meats" (PCA 1), was high in fats and oils, processed meats, fried potatoes, and desserts. RRR 1 was somewhat similar to PCA 1 and also high in processed meats and fats and oils, but other unique contributors to this pattern were nondiet sodas (high consumption) and soy foods and dark-yellow and cruciferous vegetables (low consumption). Percentage variance in scores explained by all food groups for each diet pattern are given in **Appendixes A** and **B**. PCA 1 and RRR 1 scores were significantly correlated (0.41; $P < 0.001$); however, the percentage agreement of quintile classification between PCA 1 and RRR 1 was low (32.3%).

Partial correlations between dietary patterns and nutrients were consistent with the food groups largely composing the patterns (Table 1). PCA 1 was positively correlated with total, saturated, monounsaturated, and *trans* fats but negatively correlated with fiber, carbohydrate, and several vitamins. RRR 1 was also positively correlated with saturated and *trans* fats, but correlations with total fat were not as strong as for PCA 1, and RRR 1 positively correlated with carbohydrate intake. However, carbohydrate contributors were of low quality, as evidenced by the negative correlations between RRR 1 and fiber, vitamin C, folate, and β-carotene.

Dietary patterns and CRP, IL-6, fibrinogen, and homocysteine concentrations

Both PCA 1 and RRR 1 were significantly and positively correlated with CRP, IL-6, fibrinogen, and homocysteine (Table 1), although the magnitudes of the correlations with RRR 1

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TABLE 1
Correlations between empirically derived dietary patterns and food groups, nutrients, and biomarkers of inflammation in 5089 men and women from the Multi-Ethnic Study of Atherosclerosis[1]

		Pearson correlations with dietary patterns and food groups[3]			
Pearson correlation with pattern score[2]		CRP	IL-6	Fibrinogen	Homocysteine
	r (% explained score variance)				
PCA 1		0.104	0.097	0.007[4]	0.070
Food group	—	—	—	—	—
Fats and oils	0.64 (11.8)	0.096	0.082	0.035	0.037
Processed meat	0.65 (11.2)	0.080	0.090	0.017[4]	0.070
Fried potatoes	0.60 (9.4)	0.061	0.040	−0.032	0.033
Salty snacks	0.50 (6.9)	0.028	0.038	−0.017[4]	0.038
Desserts	0.48 (6.2)	0.039	0.053	0.019[4]	−0.004[4]
Sweet breads	0.41 (4.8)	0.057	0.069	0.016[4]	0.048
Nutrient[5]	—	—	—	—	—
Carbohydrate	−0.35	—	—	—	—
Protein	−0.18	—	—	—	—
Total fat	0.40	—	—	—	—
Saturated fat	0.47	—	—	—	—
PUFA	0.01	—	—	—	—
MUFA	0.33	—	—	—	—
trans Fat	0.71	—	—	—	—
Cholesterol	0.27	—	—	—	—
Fiber	−0.62	—	—	—	—
Vitamin E	−0.36	—	—	—	—
Vitamin C	−0.44	—	—	—	—
Folate	−0.51	—	—	—	—
β-Carotene	−0.39	—	—	—	—
RRR 1	—	0.228	0.199	0.153	0.060
Food group	—	—	—	—	—
Cruciferous vegetables	−0.51 (11.0)	−0.13	−0.11	−0.034	−0.066
Fats and oils	0.39 (10.2)	0.096	0.082	0.035	0.037
Dark-yellow vegetables	−0.42 (9.7)	−0.11	−0.094	−0.021[4]	−0.051
Soy foods and beverages	−0.40 (9.0)	−0.097	−0.093	−0.031[4]	−0.052
Processed meat	0.36 (9.0)	0.080	0.090	0.017[4]	0.070
Nondiet soda	0.35 (8.4)	0.072	0.082	0.046	0.052
Nutrient[5]	—	—	—	—	—
Carbohydrate	0.076	—	—	—	—
Protein	−0.156	—	—	—	—
Total fat	0.171	—	—	—	—
Saturated fat	0.343	—	—	—	—
PUFA	−0.109	—	—	—	—
MUFA	0.116	—	—	—	—
trans Fat	0.306	—	—	—	—
Cholesterol	0.063	—	—	—	—
Fiber	−0.305	—	—	—	—
Vitamin E	0.143	—	—	—	—
Vitamin C	−0.087	—	—	—	—
Folate	−0.161	—	—	—	—
β-Carotene	−0.452	—	—	—	—

[1] PCA, principal components analysis; RRR, reduced rank regression; CRP, C-reactive protein; IL-6, interleukin-6; PUFA, polyunsaturated fatty acids; MUFA, monounsaturated fatty acids. $P < 0.05$ for all correlations except those marked otherwise.

[2] For consistency, Pearson correlations for the 6 food groups explaining the highest percentage of variation in dietary pattern score for each dietary pattern are given [% explained score variance = (correlation coefficient between food group and dietary pattern score) × (standardized β coefficient for food group regressed on dietary pattern score) × 100].

[3] Because of deviance from normality, CRP, IL-6, homocysteine, and fibrinogen were transformed to the natural log scale before analysis. All values are simple correlations (unadjusted) based on 5053 observations for CRP, 4953 for IL-6, 5073 for homocysteine, and 5054 for fibrinogen.

[4] $P > 0.05$ (NS).

[5] Partial Pearson correlation coefficients adjusted for total energy (kcal/d).

were approximately twice as large as those with PCA 1. The percentages of total biomarker variance (RRR response variables) explained by each PCA 1 (0.23%) and RRR 1 (3.0%) also differed to a similar degree. PCA 1 explained 0.55%, 0.36%, 0.002%, and 0.01% of the variation in CRP, IL-6, fibrinogen, and homocysteine, respectively, whereas for RRR 1, these values were considerably higher (5.3%, 4.0%, 2.4%, and 0.34%, respectively).

Dietary patterns and participant characteristics

The distribution of participant characteristics across quintiles of PCA 1 was different from that of RRR 1 (**Table 2**). For

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TABLE 2
Descriptive characteristics of quintiles (Q) 1, 3, and 5 for primary dietary patterns derived by principal components analysis (PCA) and reduced rank regression (RRR) in 5089 men and women from the Multi-Ethnic Study of Atherosclerosis[1]

	PCA 1 dietary pattern[2]				RRR 1 dietary pattern[3]			
	Q1 (n = 1017)	Q3 (n = 1018)	Q5 (n = 1018)	P for trend	Q1 (n = 1017)	Q3 (n = 1018)	Q5 (n = 1018)	P for trend
Dietary pattern score	−1.08 ± 0.27	−0.20 ± 0.13	1.55 ± 0.88	—	−1.62 ± 0.03	0.08 ± 0.004	1.48 ± 0.02	—
White (%)	24.7	46.8	51.1	< 0.001	37.0	50.0	33.8	0.005
Chinese (%)	31.1	7.5	1.4	< 0.001	47.7	1.4	0.10	< 0.001
Black (%)	13.6	25.5	35.5	< 0.001	9.0	25.4	38.6	< 0.001
Hispanic (%)	30.7	20.2	12.1	< 0.001	6.3	22.9	27.5	< 0.001
Age (y)	63.6 ± 0.3	61.6 ± 0.3	59.5 ± 0.3	< 0.001	60.9 ± 0.3	62.1 ± 0.3	62.1 ± 0.3	< 0.001
Female (%)	63.1	54.1	41.2	< 0.001	46.1	52.8	55.5	< 0.001
High school degree (%)	72.6	85.0	90.7	< 0.001	85.7	87.4	77.5	< 0.001
Supplement use (%)	66.6	60.8	48.6	< 0.001	65.5	59.4	47.2	< 0.001
Hormone therapy use (% of women)	26.0	30.5	27.4	0.33	25.8	33.9	25.3	0.92
Current smokers (%)	5.9	15.2	25.8	< 0.001	11.7	13.5	19.2	< 0.001
Smoking (pack-years)	5.6 ± 0.7	9.9 ± 0.7	18.1 ± 0.7	< 0.001	10.1 ± 0.7	11.2 ± 0.7	13.0 ± 0.7	0.011
Active leisure (MET-h/wk)	41.2 ± 1.6	40.8 ± 1.6	42.0 ± 1.6	0.72	42.7 ± 1.6	42.7 ± 1.6	36.6 ± 1.6	0.016
Inactive leisure (MET-h/wk)	24.4 ± 0.6	28.3 ± 0.6	31.5 ± 0.6	< 0.001	25.4 ± 0.6	27.9 ± 0.6	30.6 ± 0.6	< 0.001
BMI (kg/m^2)	26.3 ± 0.2	28.1 ± 0.2	29.5 ± 0.2	<0.001	25.7 ± 0.16	28.1 ± 0.16	29.6 ± 0.16	< 0.001
Waist circumference (cm)	92.3 ± 0.4	97.1 ± 0.4	101.8 ± 0.4	< 0.001	91.5 ± 0.42	97.1 ± 0.42	101.0 ± 0.42	< 0.001
CRP (mg/dL)[4]	1.44 (1.34, 1.55)	1.86 (1.73, 2.00)	2.10 (1.96, 2.26)	< 0.001	1.13 (1.06, 1.21)	2.00 (1.86, 2.14)	2.44 (2.28, 2.62)	< 0.001
IL-6 (pg/mL)[4]	1.06 (1.02, 1.11)	1.16 (1.11, 1.21)	1.29 (1.24, 1.34)	< 0.001	0.95 (0.91, 0.99)	1.20 (1.15, 1.25)	1.41 (1.36, 1.47)	< 0.001
Fibrinogen (mg/dL)[4]	334 (330, 338)	332 (328, 336)	336 (332, 341)	0.87	319 (315, 323)	336 (332, 340)	347 (343, 351)	< 0.001
Homocysteine (μmol/L)[4]	8.49 (8.33, 8.64)	8.78 (8.95, 8.19)	9.03 (8.86, 9.19)	< 0.001	8.62 (8.46, 8.77)	8.68 (8.53, 8.84)	9.15 (8.98, 9.31)	< 0.001
Internal carotid IMT ≥75th percentile (%)	17.0	22.2	24.5	< 0.001	16.1	23.4	25.3	< 0.001
Common carotid IMT ≥75th percentile (%)	18.3	18.0	21.0	0.041	13.8	19.0	23.8	< 0.001
CAC Agatston score >0 (%)	47.8	47.2	46.5	0.57	47.3	50.0	49.1	0.28

[1] Categorical variables are presented as percentages, and continuous variables are presented as $\bar{x}$ ± SEM based on general linear model regression. Tests for trend across quintiles were performed by treating the quintile variable as a linear term. MET-h/wk, metabolic equivalents in hours per week (energy needed per kilogram body weight per hour of activity divided by the energy need per kilogram of body weight per hour at rest); CRP, C-reactive protein; IL-6, interleukin-6; IMT, intima media thickness; CAC, coronary artery calcium.

[2] $\bar{x}$ ± SD for factor 1 derived by PCA = 0.0 ± 1.0 (by design, all PCA dietary patterns have a mean of 0 and SD of 1).

[3] $\bar{x}$ ± SD for factor 1 derived by RRR = 0.006 ± 1.14.

[4] Original values were log transformed and are presented as geometric means (95% CIs).

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TABLE 3
Odds ratios (and 95% CIs) for risk of subclinical atherosclerosis according to quintiles (Q) of dietary pattern score for primary dietary patterns empirically derived with principal components analysis (PCA) and reduced rank regression (RRR) in 5089 white, black, Hispanic, and Chinese men and women from the Multi-Ethnic Study of Atherosclerosis[1]

	Q1	Q2	Q3	Q4	Q5	*P* for trend
IMT internal carotid artery (<1.3 versus ≥1.3 mm)						
PCA 1						
Model 1	1.00	1.33 (1.05, 1.67)	1.67 (1.32, 2.11)	2.15 (1.69, 2.72)	2.23 (1.68, 2.95)	< 0.001
Model 2	1.00	1.09 (0.85, 1.40)	1.18 (0.91, 1.52)	1.33 (1.01, 1.73)	1.13 (0.82, 1.57)	0.15
RRR 1						
Model 1	1.00	1.37 (1.08, 1.75)	1.55 (1.23, 1.96)	1.64 (1.30, 2.07)	1.50 (1.18, 1.90)	< 0.001
Model 2	1.00	1.01 (0.77, 1.32)	1.03 (0.78, 1.36)	1.13 (0.86, 1.48)	1.01 (0.76, 1.34)	0.69
IMT common carotid artery (<1.0 versus ≥1.0 mm)						
PCA 1						
Model 1	1.00	1.05 (0.82, 1.33)	1.16 (0.91, 1.47)	1.38 (1.08, 1.76)	1.62 (1.21, 2.16)	< 0.001
Model 2	1.00	0.94 (0.73, 1.21)	0.96 (0.74, 1.24)	1.08 (0.82, 1.42)	1.12 (0.80, 1.56)	0.40
RRR 1						
Model 1	1.00	1.44 (1.11, 1.87)	1.40 (1.09, 1.81)	1.54 (1.20, 1.98)	1.71 (1.33, 2.20)	< 0.001
Model 2	1.00	1.21 (0.92, 1.61)	1.11 (0.83, 1.49)	1.24 (0.93, 1.67)	1.33 (0.99, 1.79)	0.087
CAC (Agatston score 0 versus >0)						
PCA 1						
Model 1	1.00	1.19 (0.98, 1.44)	1.20 (0.99, 1.46)	1.34 (1.09, 1.63)	1.45 (1.15, 1.84)	0.001
Model 2	1.00	1.05 (0.86, 1.29)	1.01 (0.81, 1.26)	1.03 (0.82, 1.31)	1.08 (0.81, 1.43)	0.73
RRR 1						
Model 1	1.00	0.91 (0.75, 1.11)	1.02 (0.84, 1.24)	0.87 (0.72, 1.05)	0.93 (0.76, 1.13)	0.35
Model 2	1.00	0.92 (0.74, 1.15)	1.13 (0.89, 1.42)	1.03 (0.82, 1.31)	1.34 (1.05, 1.71)	0.011

[1] Quintile 1 is the reference category based on logistic regression and adjusted for age (y) and total energy (kcal/d) in model 1 and for age, energy, study center (Baltimore County, MD; Forsyth County, NC; Los Angeles County, CA; New York, NY; or St Paul, MN), sex (male or female), race-ethnicity (white, black, Chinese, or Hispanic), and education (less than high school, high school, or more than high school), active leisure activity (metabolic equivalents in minutes per week), inactive leisure activity (metabolic equivalents in minutes per week), smoking (never versus current and pack-years), and supplement use (at least weekly use versus nonuse) in model 2. Tests for trend across quintiles were performed by treating the quintile variable as a linear term. IMT, intima media thickness; CAC, coronary artery calcium.

example, educational attainment was positively associated with PCA 1 scores, whereas educational attainment was negatively associated with RRR 1 scores. The directions of the associations for age, sex, and percentage Hispanic also differed between the 2 patterns (*P* for trend < 0.001 for all). However, both patterns were associated positively with inactive leisure, waist circumference, BMI, and smoking prevalence and negatively with supplement use (*P* for trend < 0.001 for all).

Dietary patterns and markers of subclinical atherosclerosis

The PCA-derived dietary pattern was not associated significantly with internal or common IMT or the presence of CAC after adjustment for demographic and lifestyle confounders (**Table 3**). However, RRR 1 was associated positively with the presence of CAC (Agatston score >0), independent of demographic and lifestyle confounders (*P* for trend = 0.011; Table 3). For persons in the fifth quintile, the odds of having CAC were ≈34% higher than for persons in the first quintile (OR: 1.34; 95% CI:.05, 1.71). Formal tests of interaction between dietary patterns and race, sex, current smoking status, waist circumference, or BMI were not statistically significant. The estimate for risk of high common carotid IMT based on RRR 1 scores in all participants was similar in magnitude to that of CAC > 0 (OR: 1.33), but the 95% CIs were wide (0.99, 1.79). If potential mechanistic variables were added to the main multivariable model, risk estimates for CAC > 0 were attenuated—modestly after adjustment for waist circumference [quintile 5 versus quintile 1 (OR: 1.28; 95% CI: 1.00, 1.64)] and more notably after adjustment for systolic blood pressure, HDL cholesterol, LDL cholesterol, triacylglycerols, insulin, and glucose [quintile 5 versus quintile 1 (OR: 1.19; 95% CI: 0.93, 1.53)], which suggests that any relations between this particular dietary pattern and CAC are mediated through the effects of diet on traditional CVD risk factors other than inflammatory processes. Results of regression analysis of the continuous variables [mean internal IMT (mm), common IMT (mm), and CAC (Agatston score)] across dietary pattern quintiles were similar to those for the dichotomized analyses. Mean CAC (Agatston score) and mean common carotid IMT increased across quintiles of RRR 1 (*P* for trend = 0.023 and 0.006 for CAC and common carotid IMT, respectively), although the range of values across quintiles was rather narrow (≈2% increase in common carotid IMT and ≈29% increase in CAC; **Table 4**). Again, PCA 1 was not associated with mean CAC or IMT (data not shown). As a supplementary sensitivity analysis, we also evaluated multivariable-adjusted associations between continuously modeled exposures (dietary patterns) and outcomes (log mean common and internal carotid IMT and Agatston score). Again, results showed a significant positive association between RRR 1 and CAC ($\beta \pm$ SE: 0.064 ± 0.031; $P = 0.039$) and a nearly significant positive association between RRR 1 and common carotid IMT (0.002 ± 0.001; $P = 0.054$), but not internal carotid IMT (0.0007 ± 0.003; $P =$

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TABLE 4
Intima media thickness (IMT) of the internal carotid artery and common carotid artery (CAC) and coronary artery calcium (CAC) scores according to quintiles (Q) of dietary pattern score for primary dietary patterns empirically derived by principal components analysis (PCA) and reduced rank regression (RRR) in 5089 white, black, Hispanic, and Chinese men and women from the Multi-Ethnic Study of Atherosclerosis[1]

	Q1	Q2	Q3	Q4	Q5	*P* for trend
IMT internal carotid artery (mm)						
PCA 1						
Model 1	0.89 (0.86, 0.91)	0.93 (0.90, 0.96)	0.99 (0.96, 1.02)	1.03 (1.00, 1.05)	1.04 (1.01, 1.07)	< 0.001
Model 2	0.96 (0.93, 0.99)	0.96 (0.93, 0.99)	0.99 (0.96, 1.01)	0.99 (0.96, 1.02)	0.97 (0.94, 1.00)	0.23
RRR 1						
Model 1	0.90 (0.87, 0.93)	0.98 (0.95, 1.01)	1.00 (0.97, 1.03)	1.00 (0.98, 1.03)	0.98 (0.95, 1.01)	< 0.001
Model 2	0.95 (0.92, 0.99)	0.98 (0.95, 1.00)	0.97 (0.95, 1.00)	0.99 (0.96, 1.01)	0.97 (0.94, 1.00)	0.45
IMT common carotid artery (mm)						
PCA 1						
Model 1	0.83 (0.82, 0.84)	0.84 (0.83, 0.85)	0.85 (0.84, 0.86)	0.86 (0.85, 0.87)	0.87 (0.86, 0.88)	0.025
Model 2	0.84 (0.83, 0.85)	0.84 (0.83, 0.85)	0.85 (0.84, 0.86)	0.85 (0.84, 0.86)	0.86 (0.84, 0.87)	0.13
RRR 1						
Model 1	0.83 (0.82, 0.84)	0.85 (0.84, 0.86)	0.85 (0.84, 0.86)	0.86 (0.85, 0.87)	0.87 (0.86, 0.88)	< 0.001
Model 2	0.84 (0.83, 0.85)	0.85 (0.84, 0.86)	0.85 (0.84, 0.86)	0.85 (0.84, 0.86)	0.86 (0.85, 0.87)	0.006
Agatston coronary calcium score						
PCA 1						
Model 1	4.98 (4.20, 5.89)	6.49 (5.52, 7.60)	7.04 (6.02, 8.20)	7.93 (6.81, 89.21)	9.04 (7.55, 10.80)	< 0.001
Model 2	6.37 (5.36, 7.53)	6.92 (5.92, 8.08)	7.04 (6.07, 8.14)	7.00 (6.02, 8.11)	7.46 (6.17, 8.98)	0.33
RRR 1						
Model 1	7.10 (6.09, 8.26)	7.32 (6.27, 8.52)	7.41 (6.35, 8.62)	6.83 (5.85, 7.96)	6.28 (5.32, 7.38)	0.24
Model 2	6.36 (5.34, 7.55)	6.29 (5.41, 7.30)	6.92 (5.95, 8.03)	7.11 (6.11, 8.25)	8.20 (7.00, 9.06)	0.023

[1] Original values were log transformed (1 was added before transformation to accommodate zeros and very small values). All values are geometric $\bar{x}$ (and 95% CIs) based on linear model regression and adjusted for age (y) and total energy (kcal/d) in model 1 and for age, energy, study center (Baltimore County, MD; Forsyth County, NC; Los Angeles County, CA; New York, NY; or St Paul, MN), sex (male or female), race-ethnicity (white, black, Chinese, or Hispanic), and education (less than high school, high school, or more than high school), active leisure activity (metabolic equivalents in minutes per week), inactive leisure activity (metabolic equivalents in minutes per week), smoking (never versus current and pack-years), and supplement use (at least weekly use versus nonuse). Tests for trend across quintiles were performed by treating the quintile variable as a linear term.

0.82). PCA 1 showed no significant associations with outcomes ($P = 0.43–0.98$).

Food groups and markers of subclinical atherosclerosis

No single food group was able to explain the associations ascribed to the RRR dietary pattern. Although age- and energy-adjusted models showed significant associations between food groups and markers of subclinical atherosclerosis in the expected directions [quintile 5 versus quintile 1: processed meat consumption (OR: 1.38; 95% CI: 1.13, 1.68); cruciferous vegetable consumption (OR: 0.82; 95% CI: 0.67, 0.99)], values were attenuated and 95% CIs included the null after full adjustment for demographic and lifestyle characteristics [processed meat consumption: (OR: 1.11; 95% CI: 0.89, 1.39); cruciferous vegetable consumption (OR: 1.10; 95% CI: 0.87, 1.39)].

DISCUSSION

In this cross-sectional analysis, a dietary pattern based on variation in CRP, IL-6, fibrinogen, and homocysteine (RRR 1) was significantly, although modestly, associated with IMT and CAC. However, a dietary pattern based on variation in food group intake (PCA 1) was not significantly associated with these subclinical disease markers. The RRR dietary pattern was high in fats and oils, processed meats, and soda and low in soy and vegetable food groups. Consistent with the hypothesized ill effects of diets rich in saturated and *trans* fats and low in fiber and micronutrients, RRR 1 scores were positively associated with the presence of CAC, marginally associated with high common carotid IMT, and associated with continuous measures of common carotid IMT and CAC. The results were independent of demographic and lifestyle confounders, but not of classic CVD risk factors, nor of CRP, IL-6, fibrinogen, or homocysteine (by design).

The associations noted in relation to our RRR dietary pattern are similar to those reported in the one other study that investigated the relation between empirically derived dietary patterns and IMT (20). In a cluster analysis in a cohort of white women, Millen et al (20) reported that women falling into dietary pattern clusters that were high in total and saturated fats and low in micronutrients and fiber had an increased risk of carotid artery atherosclerosis relative to women in a low-fat, high-fiber, and micronutrient-rich "heart healthy" dietary pattern cluster. Because our RRR dietary pattern was low in fiber and antioxidant vitamins but high in saturated fat, our findings are also consistent with the studies reporting the beneficial (14, 17, 18) and deleterious (saturated fat) (16) effects of these nutrients in relation to IMT, CAC, or both. Although our PCA dietary pattern also shared similar characteristics, it was not as discriminating as was the RRR dietary pattern in terms of inflammatory biomarker concentrations, which possibly explained the absence of associations between PCA 1 and IMT or CAC.

RRR applied to the nutritional discipline is currently fairly novel. One of our goals was to add to this smaller body of research by comparing the associations between IMT or CAC and an RRR dietary pattern with the associations between IMT or

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CAC and a dietary pattern derived by a more common method, PCA. We hoped that such a comparison would increase knowledge of the RRR method and also further our understanding of diet-disease relations. We found the RRR dietary pattern to be associated with CAC and common carotid IMT, whereas the PCA dietary pattern was not significantly associated with these markers. A comparison of these 2 dietary patterns may aid in identifying specific food groups with biological effects relevant to inflammation and the development of atherosclerosis. Several nutrients showed similar correlations with RRR 1 and PCA 1 (saturated fat, *trans* fat, fiber, and antioxidant vitamins), and intakes of the food groups fats and oils and processed meats were important determinants of both RRR 1 and PCA 1 dietary pattern scores. However, the consumption of cruciferous and dark-yellow vegetables, soy foods, and soda notably differed between RRR 1 and PCA 1 (as well as other food groups not among the highest score contributors; Appendixes A and B). It is possible that such subtle differences in dietary pattern composition are biologically relevant to the atherosclerotic process. For example, Adams et al (43) recently showed that diets high in green and yellow vegetables (freeze-dried peas, green beans, broccoli, corn, and carrots) inhibited aortic atherosclerosis in a mouse model of atherosclerosis. Soy protein-feeding studies in monkeys fed otherwise atherogenic diets showed reduced atherosclerosis compared with milk proteins (44, 45), which may have been due partly to modified monocyte-endothelial cell interactions in the early stages of atherosclerosis (46). Although soda consumption has not been evaluated previously in relation to atherosclerosis, its association with obesity and type 2 diabetes is well known (47, 48); thus, a negative effect on atherosclerosis would not be unexpected. However, in the present study, individual food groups were not associated with IMT or CAC, which suggests that all facets of the dietary pattern act synergistically. One important role of dietary pattern analysis is to guide further investigations at the food and nutrient level (30). Although it is likely that the effects of single constituents are partly dependent on the overall dietary context, randomized clinical studies are needed to disentangle the effects of single components from those of the larger dietary pattern.

The limitations of this study deserve discussion. First, this cross-sectional analysis may be confounded by recent dietary changes that are not reflective of lifetime dietary practices, which are influential in the development of atherosclerosis. Similarly, these cross-sectional data do not allow for mechanistic hypotheses to be tested, ie, "does diet impact the atherosclerotic process by influencing inflammatory processes? " We can only conjecture that all factors (diet, inflammation, and atherosclerotic disease) may be interrelated. Second, as a result of the number of statistical tests conducted, noted associations may have been significant by chance alone. Indeed, the ORs were small but were robust to adjustment for multiple confounders and were consistent across strata of several characteristics. Third, we caution that ORs overestimate the relative prevalence when outcomes are common, as was the case for CAC presence (≈48% of cohort). Fourth, it is possible that the collection of biomarkers used in our RRR procedure did not adequately represent inflammatory processes relevant in the development of atherosclerosis. It is possible that the use of different biomarkers may have produced larger risk estimates, such as those reported in relation to coronary artery disease when more traditional CVD risk factors were used (33). However, we chose these biomarkers because of general interest in novel disease pathways. Last, the relation between diet and atherosclerosis may be mediated through pathways other than inflammation, and likewise, the relation between diet and CVD events may be mediated through pathways other than those reflected by carotid artery IMT and CAC (49).

Because RRR patterns are not based on dietary behavior, the applicative value of the resulting patterns in real-world settings remains largely unknown. In contrast, PCA dietary patterns reflect real-world food usage patterns but do not take into account biological measures of health (eg, inflammatory markers). Nevertheless, PCA-derived dietary patterns have consistently shown relevant associations with many CVD-related outcomes (34), including subclinical biomarkers whose concentrations are typically unknown by participants (25, 26). The unresolved question then becomes whether it is more important to identify a dietary pattern that reflects how people really eat and how that pattern is associated with disease outcomes, or alternatively, to identify an artificial dietary pattern (collection of foods) that is associated with disease outcomes. Likely, a valuable role for each method exists, depending on the question at hand—eg, PCA for planning behavioral interventions and RRR for etiologic investigations.

Dietary pattern research continues to be an area of interest because of the potential for food and nutrient synergies (30), utility of dietary patterns for making public health recommendations (50), and values of dietary pattern change (51–54). Our study is unique in that we were able to study a large multiethnic cohort, with a well-characterized measure of overall dietary intake and validated measures of inflammation and subclinical atherosclerosis. We found that a dietary pattern derived by RRR and based on variations in CRP, IL-6, fibrinogen, and homocysteine was positively associated with CAC and common carotid IMT, but a dietary pattern derived by PCA was not significantly associated with CAC or carotid artery IMT. Food group differences between these patterns did not solely explain the difference in relations to outcomes, which suggests the importance of the overall dietary pattern and method of dietary pattern derivation.

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The authors' responsibilities were as follows—JAN: analytic design, data analysis, and manuscript preparation; LMS: critical review of the manuscript; MBS: data analysis and critical review of the manuscript; NSJ, RGB, and AGB: data acquisition and manuscript review; DRJ: data acquisition, critical review of the manuscript, and data analysis. None of the authors had a conflict of interest to report.

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Appendix A

Food group statistics for primary dietary patterns empirically derived by principal components analysis (PCA) in 5089 men and women from the Multi-Ethnic Study of Atherosclerosis

	PCA factor 1		
	Correlation coefficient[1]	Regression coefficient[2]	Contribution to total score variance[3]
			%
Food groups with positive correlations[4]			
Processed meat[5]	0.64	0.18	11.8
Fats and oils[5]	0.65	0.17	11.2
Fried potato[5]	0.60	0.16	9.4
Salty snacks[5]	0.50	0.14	6.9
Desserts[5]	0.48	0.13	6.2
Sweet breads[5]	0.41	0.12	4.8
Pasta and potato salad[5]	0.41	0.10	4.3
Ice cream[5]	0.40	0.11	4.3
Potatoes[5]	0.38	0.11	4.0
Pizza[5]	0.41	0.096	4.0
Nondiet soda	0.36	0.095	3.4
Sweet extras	0.36	0.090	3.2
Red meat	0.42	0.076	3.2
Eggs and omelets	0.34	0.092	3.2
Poultry	0.36	0.069	2.5
Chicken, tuna, and egg salads	0.30	0.078	2.4
Cream-based soups	0.29	0.073	2.1
Cheese and cheese and cream sauce	0.42	0.048	2.0
Coffee	0.29	0.065	1.9
Coffee and tea creamer	0.23	0.067	1.5
Beer	0.19	0.046	0.86
Tomatoes	0.11	−0.065	0.71
Fish	0.14	0.043	0.61
Refined grains	0.28	0.021	0.60
Other alcohol	0.12	0.030	0.35
Other soups	0.10	0.028	0.29
Seeds, nuts, and peanut butter	0.14	0.019	0.26
Whole milk	0.14	0.019	0.26
Hot chocolate	0.091	0.011	0.098
Fruit juice	0.054	−0.013	0.072
Diet soda	0.093	0.0077	0.071
Other vegetables	0.044	−0.014	0.061
Cottage and ricotta cheese	0.12	0.0049	0.059
Low-fat dairy desserts	0.036	0.0082	0.030
Meal-replacement drinks	0.038	0.0074	0.028
Yogurt	0.0095	−0.025	0.024
Green leafy vegetables	0.021	−0.010	0.022
Low-fat milk	0.0084	−0.016	0.014
High-fat Chinese dishes	0.053	0.0019	0.0099
Food groups with negative correlations[4]			
Avocados and guacamole	−0.15	−0.11	1.6
Fruit	−0.16	−0.078	1.3
Cruciferous vegetables	−0.18	−0.042	0.74
Dark-yellow vegetables	−0.15	−0.050	0.71
Legumes	−0.048	−0.11	0.51
Soy foods and beverages	−0.15	−0.028	0.41
Tea	−0.029	0.0047	0.014
Whole grains	−0.004	−0.027	0.011

[1] Values are unadjusted Pearson correlation coefficients between each food group and PCA dietary pattern score.

[2] Values are standardized β regression coefficients between each food group (servings/d) and the PCA dietary pattern score. Food groups were standardized to a mean of 0 and an SD of 1 and regressed on the continuous dietary pattern score variable.

[3] Percentage of total variance in PCA dietary pattern score explained by each food group = Pearson correlation coefficient × standardized β regression coefficient (column 1 value × column 2 value × 100).

[4] Food groups are listed in descending order according to the percentage of variation explained by PCA dietary pattern score. Food groups with positive correlation coefficients and negative correlation coefficients are listed separately.

[5] Food groups contributing the most to each dietary pattern score (based on percentage explained score variance).

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Appendix B

Food group statistics for primary dietary patterns empirically derived by reduced rank regression (RRR) in 5089 men and women from the Multi-Ethnic Study of Atherosclerosis

	RRR factor 1		
	Correlation coefficient[1]	Regression coefficient[2]	Contribution to total score variance[3]
			%
Food groups with positive correlations[4]			
Fats and oils[5]	0.39	0.26	10.2
Processed meat[5]	0.36	0.25	9.0
Nondiet soda[5]	0.35	0.24	8.4
Potatoes[5]	0.31	0.17	5.2
Beans[5]	0.23	0.20	4.6
Sweet breads	0.27	0.16	4.4
Poultry	0.20	0.21	4.1
Meal-replacement drinks	0.20	0.19	3.9
Sweet extras	0.25	0.14	3.5
Tomatoes	0.19	0.16	3.0
Chicken, tuna, and egg salads	0.18	0.13	2.3
Cheeses and cheese and cream sauce	0.26	0.073	1.9
Cottage and ricotta cheese	0.14	0.11	1.5
Cream-based soup	0.16	0.094	1.5
Fried potato	0.16	−0.084	1.4
Refined grains	0.044	−0.24	1.1
Yogurt	0.11	0.086	1.0
Fruit juice	0.12	0.059	0.68
Ice cream	0.18	0.032	0.58
Salty snacks	0.11	−0.044	0.49
Pasta and potato salads	0.17	0.024	0.41
Eggs and omelets	0.10	−0.040	0.40
Diet soda	0.063	0.059	0.37
Low-fat milk	0.052	0.064	0.33
Pizza	0.018	−0.15	0.38
Red meat	0.017	−0.12	0.21
Desserts	0.20	−0.00084	0.17
Coffee	0.012	−0.11	0.13
Whole milk	0.13	0.0070	0.091
Hot chocolate	0.087	0.010	0.084
Fruit	0.0056	0.095	0.053
Avocados and guacamole	0.031	−0.012	0.039
Food groups with negative correlations[4]			
Cruciferous vegetables[5]	−0.51	−0.22	11.0
Dark-yellow vegetables	−0.42	−0.23	9.7
Soy foods and beverages[5]	−0.40	−0.23	9.0
Fish[5]	−0.25	−0.20	4.9
Other alcohol[5]	−0.21	−0.24	4.9
Beer	−0.11	−0.29	3.2
Seeds, nuts, and peanut butter	−0.15	−0.18	2.8
Other vegetables	−0.20	−0.054	1.1
Whole grains	−0.073	−0.15	1.1
Tea	−0.16	−0.043	0.70
Other soups	−0.073	−0.072	0.53
High-fat Chinese dishes	−0.17	−0.018	0.30
Green leafy vegetables	−0.061	−0.030	0.18
Coffee and tea creamers	−0.0044	−0.084	0.037
Low-fat dairy desserts	−0.040	−0.00085	0.0033

[1] Values are unadjusted Pearson correlation coefficients between each food group and RRR dietary pattern score.

[2] Values are standardized β regression coefficients between each food group (servings/d) and the RRR dietary pattern score. Food groups were standardized to a mean of 0 and an SD of 1 and regressed on the continuous dietary pattern score variable.

[3] Percentage of total variance in RRR dietary pattern score explained by each food group = Pearson correlation coefficient × standardized β regression coefficient (column 1 value × column 2 value × 100).

[4] Food groups are listed in descending order according to the percentage of variation explained by RRR dietary pattern score. Food groups with positive correlation coefficients and negative correlation coefficients are listed separately.

[5] Food groups contributing the most to each dietary pattern score (based on percentage explained score variance).

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