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The Association of Fruit and Vegetable Consumption During Early Adulthood With the Prevalence of Coronary Artery Calcium After 20 Years of Follow-Up: The CARDIA Study

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Abstract

Background—The relationship between intake of fruits and vegetables (F/V) during young adulthood and coronary atherosclerosis later in life is unclear.

Methods and Results—We studied participants of the Coronary Artery Risk Development in Young Adults (CARDIA) study, a cohort of young, healthy black and white individuals at baseline (1985–1986). Intake of F/V at baseline was assessed using a semi-quantitative interview administered diet history and CAC was measured at year 20 (2005–2006) using computed tomography. We used logistic regression to adjust for relevant variables and estimate the adjusted odds ratios (OR) and 95% confidence intervals (CI) across energy-adjusted, sex-specific tertiles of total servings of F/V per day. Among our sample $(n=2,506)$, the mean (SD) age at baseline was 25.3 (3.5) years and 62.7% were female. After adjustment for demographics and lifestyle variables, higher intake of F/V was associated with a lower prevalence of CAC: OR (95% CI) $=1.00$ (reference), 0.78 (0.59–1.02), and 0.74 (0.56–0.99), from the lowest to the highest tertile of F/V , p-value for trend <0.001. There was attenuation of the association between F/V and CAC after adjustment for other dietary variables but the trend remained significant: OR (95% CI): 1.00 (reference), 0.84 (0.63–1.11), and 0.92 (0.67–1.26), p-value for trend <0.002].

Conclusions—In this longitudinal cohort study, higher intake of F/V during young adulthood was associated with lower odds of prevalent CAC after 20 years of follow-up. Our results

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reinforce the importance of establishing a high intake of F/V as part of a healthy dietary pattern early in life.

Keywords

Epidemiology; Nutrition; Diet; Coronary Disease; Atherosclerosis; Imaging

Introduction

Healthy lifestyle choices are essential for the prevention of cardiovascular disease (CVD). A dietary pattern high in fruits and vegetables (F/V) in middle-aged adults has been associated with reduced rates of coronary heart disease (CHD), stroke, and CVD mortality.^{1–6} Atherosclerotic plaque formation, the hallmark of CVD, is known to begin early in life,⁷ but if and how F/V intake in young individuals impacts this process is unclear.

Population based lifestyle interventions hold significant potential to reduce rates of CVD and will be increasingly relied upon as the US model of healthcare changes.^{8,9} Middle-aged adults, often motivated by the near-term risk of a CVD event, frequently adopt healthier lifestyle patterns, including dietary changes, though they may already have developed a significant atherosclerotic plaque burden. Adopting a healthy diet earlier in life holds the potential to have a greater impact on CVD risk reduction but evidence supporting this concept is lacking. Knowledge of the relationship between dietary patterns in young adults and future CVD is essential as public health strategies are developed to target the most efficacious dietary interventions.

Coronary artery calcium (CAC), a direct marker of coronary atherosclerosis, is a strong predictor of future CHD events and a powerful CVD risk stratification tool.^{10,11} CAC has been shown to predict mortality independent of age and even minimal amounts of coronary calcification (CAC score 1–10) have been associated with a substantial increase in mortality compared to individuals with no CAC.12,13

The Coronary Artery Risk Development in Young Adults (CARDIA) Study provides a unique opportunity to analyze the association between dietary factors during young adulthood and atherosclerosis later in life. In this study, we sought to define the relationship between dietary intake of F/V during young adulthood and the prevalence of CAC after 20 years of follow-up.

Methods

Study Design and Population

The CARDIA study is a prospective cohort designed to evaluate the progression of cardiovascular risk factors and CVD. Thorough descriptions of the study design and procedures have been previously published.^{14–16} Briefly, in 1985–1986, 5,115 black and white men and women, aged 18–30 years, were recruited from 4 urban sites across the United States: Birmingham, Alabama; Chicago Illinois, Minneapolis, Minnesota; and Oakland, California. Participants have been followed for more than 25 years with detailed demographic and clinical data, including anthropometric and laboratory measures, as well as

assessments of subclinical atherosclerosis. The retention rate for the surviving cohort was 72% at year 20. Examination protocols were reviewed and approved by institutional review boards at each site, and written informed consent was obtained from every participant at each examination.

Of the 3,549 individuals with follow-up data from the year 20 visit, 541 participants were excluded for the following reasons: 422 were missing CAC scores, 4 were missing F/V intake at year 0, 1 underwent a female-to-male transgender conversion, 113 were missing covariate data, and 1 was a significant outlier for reported F/V intake. Of the remaining 3,008 participants, we excluded 502 individuals due to extreme reported energy intake (<800 or >4,000 kcal/d), leaving 2,506 participants for the primary analysis.

Assessment of diet and F/V intake

Diet was assessed at year 0 and year 20 using the interviewer-administered CARDIA Diet History.^{17,18} Interviewers asked questions about dietary consumption of various food groups within the past month. A positive response would trigger additional information-gathering questions. For example, a positive response to the question "Do you eat fresh fruit?" would trigger the additional questions "Which fruits from the following list do you eat and how often" and "How much do you typically eat". The fruits and vegetables included in the diet history are listed in Table 1. Data on consumption of frozen and canned fruits and vegetables was also collected. Potatoes, including fried potatoes, were not included as vegetables, nor were legumes which consistent of dried beans, dried peas, and lentils. All reported foods were grouped according to the nutritional data system for research, 2005 food groups (modified United States department of agriculture food grouping scheme) developed at the nutrition coordinating center at the University of Minnesota.17,18 Reported foods were assigned to one of 165 subgroups within 9 major food groups, including each of fruit and vegetables. Intake of each food group was calculated as the sum of the servings a food in each food group was eaten per day. In addition, standard serving sizes for all foods were calculated based on gram weight information obtained from the nutritional data system for research software program and the United States department of agriculture pyramid servings database.17,18 Therefore, for each participant, the number of servings for each reported food was calculated based on a standard serving (gram weight given the form of the food). Foodgroup intake was calculated as servings per day. All servings of fruits and vegetables were combined into a single category to determine the servings of F/V per day. This value was then energy adjusted to a dietary intake of 2,000 kcal/d.

Assessment of CAC

CAC was assessed using computed tomography (CT) and analyzed as either present or absent (CAC=0 vs CAC>0) for all individuals who underwent CAC scanning at the year 20 follow-up. The CT protocol at the year 20 exam consisted of 2 sequential non-contrast CT scans performed on electron beam CT scanners (Chicago and Oakland centers: Imatron C-150, GE Healthcare, Waukesha, Wisconsin) or multidetector CT scanners (Birmingham center: GE Lightspeed, GE Healthcare, Waukesha, Wisconsin; Minneapolis center: Volume Zoom, Siemens Medical Solutions, Erlangen, Germany). The methodology and validity of the CAC assessment process has been previously described in detail.^{19,20} Scans were read

by a trained reader who was blinded to the participant's characteristics. The CAC score was totaled from the amount of measured plaque in the epicardial coronary arteries using the modified Agatston method to account for slice thickness.21 The presence of CAC was defined as having a positive, non-zero score, using the average of the two scans. Discordant scans were infrequent (3.6%) and independently adjudicated by two CARDIA investigators.

Other covariates

Information on age, gender, race, education, cigarette smoking, alcohol intake, and physical activity was obtained by using a structured interview and self-administered questionnaires. Participants reported highest grade of school completed and education was classified into 5 categories (less than high school, high school graduate, some college, college degree, and post-graduation education). Income was not collected at baseline but was collected at the year 5 follow-up and was categorized into 3 categories (\leq \$25,000, \$25,000–\$50,000, and > \$50,000). Smoking was classified as never, former, or current smoker. Alcohol consumption was analyzed in 5 categories based on self-reported consumption of alcoholic drinks per week $\left($ <1, 1–2, 3–6, 7–14, 14+). Physical activity was self-reported and classified into 5 categories based on the question, "Compared to other people your age and sex, what number would you choose for rating your physical activity during the past year: 1=physically inactive, 2, 3=moderately active, 4, 5=very active". Height and weight were measured at baseline and the year 20 exam and recorded to the nearest 0.5cm and 0.2 kg, respectively. Body mass index (BMI), in kg/m², was derived from these measures. Seated blood pressure was obtained after 5 minutes of rest with a random-zero sphygmomanometer at year 0 and an automated device (Omron) at year 20. Three blood pressure measurements were taken and the average of the 2nd and 3rd measurements was used as the measured blood pressure. Patients were asked to fast for 12 hours before blood was collected for measurement of serum lipids and glucose.

Statistical Analysis

Baseline characteristics were determined according to sex-specific tertiles of energy adjusted intake of F/V as calculated from the baseline exam. Baseline characteristics are described as mean (SD) or median (range) for continuous variables based on normality and number (percentage) for categorical variables. We dichotomized CAC into zero and nonzero scores given the strong predictive value of a CAC score of zero and the increased CVD risk for individuals with even minimal CAC.¹³

Logistic regression was used to calculate prevalence odds ratios (OR) for CAC across energy adjusted, sex-specific tertiles of F/V intake. We built sequential models based on a priori knowledge. Model 1 was adjusted for age and race. Model 2 was adjusted for age, race, BMI, smoking, alcohol, physical activity, income, center and education. We obtained a p-value for linear trend by creating a new variable that was assigned the median F/V intake in each tertile and fitting the new variable into the regression model. We analyzed this association in the total sample as well as in a sex-stratified approach. We chose to include the sex-stratified analysis because the prevalence of CAC is known to vary by sex , 10 and two previous studies suggested the relationship between F/V intake and CHD varies according to sex.^{2,3} Given that the prevalence of CAC (16.6%) was somewhat higher than

what is typically considered a "rare outcome", we also performed a relative risk regression model to estimate adjusted prevalence ratios of CAC with corresponding 95% confidence interval.

We performed several additional analyses to try and isolate the effect of F/V intake during young adulthood from other dietary factors by including F/V intake at the year 20 exam as well as other dietary factors from the baseline exam. We chose additional dietary variables based on a prior knowledge and clinical relevance including dairy, nuts, legumes, eggs, fish, beef, refined grain bread, refined grain pasta, cakes/cookies/doughnuts, fried potatoes, salt intake, sugar sweetened soft drinks, and frequency of fast food intake for further exploration of confounding. Finally, we included potential mediators in a model including systolic blood pressure, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, and fasting blood sugar as measured at the year 20 follow-up.

Results

The mean age of the 2,506 participants at baseline was 25.3 (SD 3.5) years, and 1,571 (62.7%) were women. The baseline characteristics of the women and men in the study according to energy-adjusted tertiles of F/V intake are shown in Table 2. Women and men with higher intake of F/V were more likely to be older, white, more educated, and less likely to smoke. The median intake of F/V adjusted to a 2,000-kcal/d diet was 8.9 servings per day in women in the top tertile compared to 3.3 servings per day in the bottom tertile. F/V intake was slightly lower in men (7.2 servings per day in the top tertile versus 2.6 servings per day in the bottom tertile). Baseline dietary intake of the women and men in the study according to energy-adjusted tertiles of F/V intake are shown in Table 3. Individuals in our study with a high intake of F/V had a higher intake of fish, and lower intake of refined carbohydrates, salt, and fast food compared to those with low intake of F/V.

In an age and race-adjusted model analyzed according to sex-specific tertiles, F/V intake was inversely associated with prevalent CAC and this association persisted and remained statistically significant after adjustment for BMI, smoking, alcohol, physical activity, income, center and education (Table 4). The correlation between F/V intake at baseline and year 20 was modest (Spearman r-value 0.33, p<0.0001). Updating F/V intake at year 20 did not appreciably alter the results [OR (95% CI): 1.00 (reference), 0.76 (0.57–1.02), and 0.73 $(0.53-1.00)$, p-value for trend across tertiles <0.001].

There was attenuation of the association between F/V and CAC after adjustment for other dietary factors that might be associated with CAC development (dairy, nuts, legumes, eggs, fish, beef, refined grain bread, refined grain pasta, cakes/cookies/doughnuts, fried potatoes, salt intake, sugar sweetened soft drinks, and frequency of fast food intake) but the trend remained significant: OR (95% CI): 1.00 (reference), 0.84 (0.63–1.11), and 0.92 (0.67– 1.26), p-value for trend across the tertiles 0.002. The inclusion of legumes as a vegetable did not meaningfully change the results of the analysis (results not shown).

Adjusting for potential mediators including systolic blood pressure, LDL and HDL cholesterol, and fasting blood sugar did not meaningfully alter the relationship: OR (95%

CI): 1.00 (reference), 0.79 (0.60–1.04), and 0.78 (0.58–1.03), p-value for trend <0.001. Repeating the multivariable analysis (model 2) using relative risk regression yielded similar results [OR (95% CI): 1.00 (reference), 0.83 (0.67–1.02), 0.80 (0.64–1.00), p-value for trend across the tertiles <0.001].

A multivariable-adjusted analysis of intake of F/V separately showed a similar benefit for fruits and vegetables respectively: OR (95% CI) were 1.00 [reference], 0.92 [0.70–1.20], and 0.85 [0.64–1.12] from lowest to highest tertiles of fruit intake (p-value for trend 0.002), and 1.00 [reference], 0.84 [0.64–1.12], 0.81 [0.61–1.08] for corresponding tertiles of vegetable intake (p-value for trend <0.001).

When stratified by sex, the inverse association between F/V intake and CAC appeared limited to women compared to men (p-value for interaction 0.05 in the multivariable model). In the multivariable model, women in top tertile of F/V intake were 45% less likely to have prevalent CAC compared to women in the bottom tertile: OR (95% CI) 1.0 (ref), 0.73 (0.48– 1.10), and 0.55 (0.35–0.87), p-value for trend 0.01, Figure 1. Conversely, reported intake of F/V did not appear to be associated with prevalent CAC among men: OR (95% CI) 1.0 (ref), 0.77 (0.52–1.12), 0.89 (0.60–1.31), p-value for trend 0.67, p-value for interaction 0.05, Figure 1.

In women, a model with the additional examination of other dietary factors (dairy, nuts, legumes, eggs, fish, beef, refined grain bread, refined grain pasta, cakes/cookies/doughnuts, fried potatoes, salt intake, sugar sweetened soft drinks, and frequency of fast food intake) did not alter the trend seen between F/V intake and CAC: OR (95% CI) were 1.00 [reference], 0.74 (0.48–1.14), and 0.56 (0.34–0.94), from lowest to highest tertiles of F/V intake in women, p-value for trend 0.03. There was minimal attenuation of the relationship between F/V intake during young adulthood and CAC at year 20 in women with the updated use of year 20 F/V data: OR (95% CI), 1.00 [reference], 0.74 [0.47–1.16], and 0.58 [0.35– 0.97], for corresponding tertiles of F/V intake. Also, the relationship between F/V and CAC in women did not appear to be significantly mediated by SBP, LDL cholesterol, HDL cholesterol, or fasting blood sugar, as addition of these variables (measured at the year 20 follow-up) did not alter the relationship: OR (95% CI) 1.00 (reference), 0.75 (0.49–1.14), and 0.58 (0.37–0.93), from lowest to highest tertiles in women). The addition of other dietary variables, F/V intake at year 20, as well as potential mediators did not substantially alter the non-significant relationship between F/V and CAC in men (results not shown).

Discussion

We found a significant inverse association between F/V intake during young adulthood and the prevalence of CAC later in life. After adjustment for relevant variables, young adults in the top tertile who averaged 7–9 servings per day of F/V at baseline were approximately 25% less likely to have any CAC after 20 years of follow-up compared to the bottom tertile who averaged 2–4 servings of F/V per day. An analysis of F/V individually showed a similar benefit for each food group. There was attenuation of the association between F/V and CAC after additional adjustment for other dietary factors but the trend in the association

Previous studies demonstrating an inverse association between F/V intake and CHD and CVD have largely been limited to middle-aged adults. A meta-analysis of observational cohorts (mean age \sim 50 years) found that each additional serving of F/V was associated with a risk reduction of 4% (95% CI: 1% to 4%) for a CHD event.⁴ An analysis from the National Health and Nutritional Examination Survey evaluated the relationship between F/V and CVD, finding that individuals who reported consuming F/V three or more times per day was associated with a 37% (95% CI: 21% to 49%) lower rate of CVD mortality compared to individuals who reported consuming $F/V < 1$ time per day.⁶ In both of these studies, the benefit of F/V intake was similar for men and women.

The lack of association between F/V intake and CAC in men in our study may be due to a lack of power, as our study included only 935 male participants. However, a less significant association between CVD and F/V intake in men has been seen in other studies. Data from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Heart study demonstrated a 15% (95% CI: 6% to 23%) lower risk for CHD mortality per 80gram/day increase in fruit and vegetable intake in women, but a non-significant 2% (95% CI: −2% to $+2\%$) CHD mortality reduction in men (p-value for heterogeneity 0.007).² Similar findings were reported in a cohort of Japanese women and men.³ In the CHD risk factor study INTERHEART, the 3 lifestyle behaviors associated with a lower risk of CHD were F/V intake, exercise, and moderate alcohol consumption, and the protective effects of exercise and moderate alcohol consumption were larger in women compared to men with a trend towards F/V intake being more protective in women as well.²² Although the protective benefit of lifestyle behaviors against CHD may be more pronounced in women, the results of our study should not be used to minimize the potential health benefits of F/V intake for men, as several other studies have found positive associations from F/V intake for men, including lower rates in CVD, cancer, and all-cause mortality.1,4–6,23,24 Individuals in our study with a high intake of F/V generally had a healthier dietary pattern overall, including a higher intake of fish, and less intake of refined carbohydrates, salt, and fast food compared to those with low intake of F/V. The association between F/V and CAC may be influenced by a corresponding decrease in intake of unhealthy substances as opposed to a direct benefit of F/V, and adjustment for multiple dietary variables did result in some attenuation of the association between F/V and CAC although the trend remained significant. This finding is consistent with a recent global analysis that suggested that insufficient intake of healthy foods is responsible for a larger burden of chronic disease than what is due to excessive intake of unhealthy foods.²⁵

There are multiple potential mechanisms by which F/V intake could lead to a reduction in atherosclerotic plaque formation, including improved lipids, lower blood pressure, and increased intake of various antioxidant micronutrients.26 Observational studies have suggested more optimal lipid values in individuals with higher F/V intake, 27 but randomized trials have failed to confirm this relationship.^{28,29} Two randomized trials demonstrated a reduction in systolic blood pressure with increased intake of F/V.^{28,30} In our study, adjusting for systolic blood pressure, HDL cholesterol, and LDL cholesterol did not substantially

attenuate the relationship between F/V intake and CAC, suggesting alternative mechanisms. Vitamins and other antioxidant micronutrients have long been hypothesized to have significant cardiovascular benefits, 31 but multiple randomized trials evaluating various supplemented micronutrients have failed to show CVD benefit.^{32,33} The results of our study lend further support to the importance of emphasizing consumption of whole foods, including F/V, as opposed to use of nutritional supplements. F/V contain multiple components beyond antioxidants that may confer a cardiovascular benefit, including multiple different vitamins, phytochemicals, and electrolytes.³⁴

Our analysis has several strengths including a large sample, extensive data on traditional cardiovascular risk factors, and a standardized approach to CAC assessment. It also has limitations. Given the observational nature of our study and the variance in the baseline characteristics across the F/V tertiles, residual confounding may still be present in the multivariable model. Equal numbers of men and women were enrolled in CARDIA at baseline but, due to a greater retention of women over time, our analysis contained significantly more women than men. Also, CAC is a surrogate marker of CHD, representative of subclinical atherosclerosis as opposed to actual CHD events, and we only analyzed a single measurement of CAC, thereby preventing analysis of the relationship between F/V intake and CAC progression. Additionally, not all exposures with established associations with CHD have been found to have a similar association with subclinical atherosclerosis. For instance, moderate alcohol consumption has a well-established association with a lower risk of CHD events but is associated with an increase in the prevalence of CAC35,36, suggesting a non-atherosclerotic mechanism. However, CAC is a strong predictor of future CHD events and was recently shown to be the only novel predictor with the capacity to substantially improve discrimination above and beyond traditional risk assessment.11 CAC has been shown to highly correlate with total atherosclerotic plaque burden, even more so than luminal stenosis.37,38

A sub-optimal diet is one of the leading contributors to the global burden of CVD, and methods to improve dietary patterns hold the potential to significantly impact CVD rates, even if those methods only lead to a modest shift in population CVD risk.¹² The recently released American College of Cardiology/American Heart Association lifestyle guidelines encourage a diet that includes a high intake of F/V as a Class 1-Grade A recommendation to lower cardiovascular risk.⁹ Our results support this recommendation, reinforce the value of establishing healthy behaviors early in adulthood, and provide further credence for public health initiatives aimed at increasing F/V intake in adolescents and young adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Prevalence of CAC at the year 20 exam according to energy-adjusted tertiles of servings of F/V per day at the baseline exam in men and women in CARDIA.

Table 1

Fruits and vegetables included in the interviewer-administered CARDIA Diet History.

Table 2

Baseline characteristics of women and men in CARDIA according to energy-adjusted tertiles of fruit and vegetable intake.

Energy (kcal/d) 2755 ± 722 2685 ± 701 2630 ± 741 0.03

Table 3

Baseline dietary characteristics of women and men in CARDIA according to energy-adjusted tertiles of fruit and vegetable intake.

*** Dietary variables are reported in servings per day unless specified otherwise

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Table 4

Adjusted prevalence odds ratios (95% CI) for CAC at the year 20 exam according to energy-adjusted, sex-specific tertiles of servings of F/V per day at Adjusted prevalence odds ratios (95% CI) for CAC at the year 20 exam according to energy-adjusted, sex-specific tertiles of servings of F/V per day at the baseline exam in CARDIA. the baseline exam in CARDIA.

Model 1 is adjusted for age and race. Model 1 is adjusted for age and race.

Model 2 is adjusted for age, race, body mass index, smoking, alcohol, physical activity, income, center, and education. Model 2 is adjusted for age, race, body mass index, smoking, alcohol, physical activity, income, center, and education.

Model 3 is adjusted for the variables in model 2 as well as intake of fruits and vegetables at year 20. Model 3 is adjusted for the variables in model 2 as well as intake of fruits and vegetables at year 20.

Model 4 is adjusted for the variables in model 2 as well as multiple dietary variables assessed at baseline including intake of dairy, nuts, legumes, eggs, fish, beef, refined grain bread, refined grain pasta, Model 4 is adjusted for the variables in model 2 as well as multiple dietary variables assessed at baseline including intake of dairy, nuts, legumes, eggs, fish, beef, refined grain bread, refined grain pasta, cakes/cookies/doughnuts, fried potatoes, salt intake, sugar sweetened soft drinks, and frequency of fast food intake. cakes/cookies/doughnuts, fried potatoes, salt intake, sugar sweetened soft drinks, and frequency of fast food intake.

Abbreviations: CI - Confidence Interval, CAC - Coronary Artery Calcium, F/V - Fruits and Vegetables, CARDIA - Cardiae Artery Risk Development in Young Adults Abbreviations: CI – Confidence Interval, CAC – Coronary Artery Calcium, F/V – Fruits and Vegetables, CARDIA – Cardiac Artery Risk Development in Young Adults