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ORIGINAL RESEARCH

IMAGING

Associations of Dietary Calcium and Phosphorus With Vascular and Valvular Calcification

The ARIC Study

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ABSTRACT

BACKGROUND High dietary calcium and phosphorus may accelerate vascular calcification, but epidemiological data are inconsistent. Most of those studies assessed diet at one point and have not been systematically evaluated.

OBJECTIVES The purpose of this study was to assess the associations of dietary calcium and phosphorus intakes in middle age with coronary artery and extra-coronary calcification at older age.

METHODS We studied 1,914 participants from the ARIC (Atherosclerosis Risk In Communities) study (mean age 80.5 years) without coronary heart disease who underwent chest computed tomography scans at visit 7 (2018-2019) and completed a 66-item food frequency questionnaire at 2 earlier visits (visit 1 [1987-1989] and visit 3 [1993-1995]). Dietary calcium and phosphorus intakes were averaged between these 2 visits. Calcification was quantified by the Agatston score in coronary artery, ascending aorta, descending aorta, aortic valve ring, aortic valve, and mitral valve.

RESULTS Dietary calcium intake was inversely associated with coronary artery and ascending aorta calcification, whereas the association was not significant for other measures of extra-coronary calcification. For example, the highest vs lowest quartile of calcium intake showed an adjusted OR of 0.66 (95% CI: 0.45-0.98) for coronary artery calcification (Agatston score ≥75th percentile). Dietary phosphorus intake demonstrated similar results, but the magnitude of the association was weaker than dietary calcium intake.

CONCLUSIONS Dietary calcium and phosphorus intakes at middle age were not positively associated with vascular and valvular calcification at over 75 years old. Our findings did not support the link between a calcium or phosphorus-rich diet and vascular and valvular calcification. (JACC Adv 2024;3:100993) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CAC = coronary artery calcification

CHD = coronary heart disease

CKD = chronic kidney disease

CT = computed tomography

CVD = cardiovascular disease

ECC = extra-coronary calcification

eGFR = estimated glomerular filtration rate

FFQ = food frequency questionnaire

HDL-C = high-density lipoprotein cholesterol

RDA = recommended dietary allowance

Calcium and phosphorus are essential to maintain bone structure and cellular functions.[1-3] Approximately 1,000 to 1,200 g of calcium and 700 to 800 g of phosphorus are in the human adult body, mainly (99% of calcium and 85% of phosphorus) in bones and teeth as a form of hydroxyapatite.[2-4] The remaining 1% of total calcium is in soft tissues, intracellular, and extracellular fluid, whereas the remaining 14% of total phosphorus is in soft tissues and intracellular, and only 1% in extracellular fluid.[2-4]

The Institute of Medicine sets the Recommended Dietary Allowance (RDA), the intake level sufficient to meet nutritional requirements, as 1,000 mg/day[5] for calcium and 700 mg/day[6] for phosphorus among adults. Clinical guidelines recommend a dietary calcium intake of 1,000 to 1,200 mg/day for the prevention and treatment of osteoporosis, depending on age and sex.[7] In the United States, phosphorus intake is above the recommended amount in both men and women, while calcium intake is below the recommended amount in women.[8]

There is also a concern about their excess intake; the tolerable upper intake levels are 2,000 mg/day for calcium and 4,000 mg/day for phosphorus.[5,6] Development of cardiovascular disease (CVD) is part of this concern[9] since passive precipitation of calcium and phosphate may induce vascular calcification.[10] Indeed, many previous studies have shown the positive associations of their serum levels with CVD outcomes in the general population.[11-15] In addition, elevated serum levels of calcium and phosphorus have been associated with vascular and valvular calcification as well.[16-18]

Although serum calcium and phosphorus levels have been robustly associated with adverse CVD outcomes, the data on dietary intake of calcium and phosphorus and CVD have been conflicting. For example, 2 recent meta-analyses reported no evident positive association between dietary calcium intake and CVD incidence and mortality,[19,20] while a U.S. community-based study showed an elevated risk of CVD mortality related to higher phosphorus intake.[21] Moreover, a few studies including the Framingham Offspring Study and the MESA (Multi-Ethnic Study of Atherosclerosis) did not find positive associations of dietary calcium with coronary artery calcification (CAC).[15,22-25] For phosphorus, its intake has been positively associated with CAC in a study of individuals with chronic kidney disease (CKD),[26] but not in a large Korean population-based study.[15]

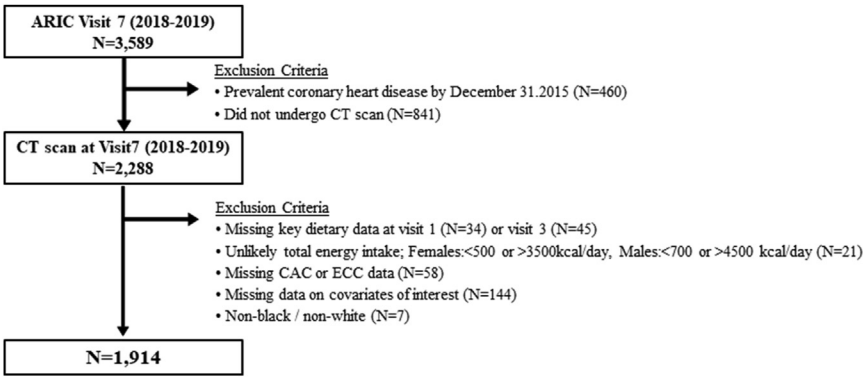
However, most of those previous studies relied on dietary assessment at one time point. Also, those studies evaluated only CAC, while a growing body of evidence indicates that the pathophysiological process can be heterogeneous across different vascular beds (eg, smoking impacts leg arteries more than coronary artery[27]). To overcome these caveats of previous literature, we aimed to comprehensively investigate the associations of dietary calcium and phosphorus intakes using a validated food frequency questionnaire (FFQ) at 2 time points over ~6 years during middle age with CAC and extra-coronary calcification (ECC) (ie, aortic valve, aortic ring, ascending and descending aorta, and mitral valve) at older age using longitudinal data of the ARIC (Atherosclerosis Risk In Communities) study.[28]

METHODS

STUDY POPULATION. The ARIC study enrolled 15,792 participants aged 45 to 64 years at baseline (1987-1989) from 4 U.S. communities: Forsyth County, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland. Participants were invited to follow-up examinations in 1990 to 1992 (visit 2), 1993 to 1995 (visit 3), 1996 to 1998 (visit 4), 2011 to 2013 (visit 5), 2016 to 2017 (visit 6), 2018 to 2019 (visit 7), 2019 to 2020 (visit 8), 2021 to 2022 (visit 9), and 2022 to 2023 (visit 10). Participants provided written informed consent at each visit. The study complied with the Declaration of Helsinki and was approved by the institutional review board at each study site.

In the ARIC study, the FFQ was administered at visits 1 and 3, and a noncontrast cardiac computed tomography (CT) was systematically conducted for the first time at visit 7. Among the 3,589 participants at visit 7, 460 were not eligible for chest CT due to their previous history of coronary heart disease (CHD) before December 31, 2015 (reflecting the lag time between CHD events and the ARIC case adjudication). Of the remaining 3,129 participants, 2,288 (73.1%) underwent chest CT scans. Of those, we excluded participants missing key dietary data at visit 1 (n = 34) or visit 3 (n = 45), those with unrealistic total energy intake (<500 or >3,500 kcal/day in females and <700 or >4,500 kcal/day in males) (n = 21), those with missing information on all of CAC and ECC data (n = 58), those missing data on covariates of interest (n = 144), and racial groups other than Black or White

FIGURE 1 Flow Chart of Study Population



ARIC = Atherosclerosis Risk In Communities; CAC = coronary artery calcification; CT = computed tomography; ECC = extra-coronary calcification.

due to a small number (n = 7). The final study population was 1,914 participants (Figure 1).

DIETARY DATA MEASUREMENTS. We used the average dietary calcium and phosphorus intakes between visits 1 and 3. Daily intakes of nutrients were estimated and quantified from a 66-item FFQ and alcoholic beverages. The ARIC 66-item FFQ was based on the 61-item Harvard FFQ originally validated.[29,30] Supplements were not included in this dietary data. Based on food and its portions (almost never to more than 6 times per day) described by a trained interviewer, participants responded how often they ate each item during the past year on average. The reliability of the ARIC FFQ was assessed by a previous study from a random subsample of 443 participants at visits 1 and 2.[31] The median reliability coefficients were 0.69 in White men, 0.52 in White women, 0.45 in Black men, and 0.26 in Black women for dietary calcium intake, and 0.70 in White men, 0.48 in White women, 0.50 in Black men, and 0.46 in Black women for dietary phosphorus intake.

CAC/ECC MEASUREMENTS. Across the 4 ARIC field centers, 64-slice scanners were used to conduct cardiac-gated CT scans. Calcified lesions were defined based on attenuation ≥130 HU and area ≥1 mm^2 in each slice level. Agatston calcification score[32] was quantified for coronary artery (ie, CAC) and 5 extra-coronary sites: ascending aorta, descending aorta, aortic ring (aortic root or annulus at the level of the aortic ring), aortic valve, and mitral valve.

COVARIATES. We included the following variables as covariates: total dietary energy intake, age, sex, race, field center, education level, income level, alcohol intake, smoking habits, physical activity, body mass index (BMI), systolic blood pressure, antihypertensive medication, total cholesterol level, high-density lipoprotein cholesterol (HDL-C) level, cholesterol-lowering medication, estimated glomerular filtration rate (eGFR), use of aspirin, and prevalent diabetes mellitus. Demographic characteristics, income level, alcohol intake, smoking status, physical activity, and medication and supplement use were based on self-report at visit 3. Participants brought medication containers to the visit for inspection, and medications were coded by research staff. Education level was assessed at visit 1 and was divided into 3 categories: less than high school education, high school graduate or equivalent, and at least some college. Annual household income levels were categorized into <$12,000, $12,000 to 24,999, $25,000 to 49,999, and ≥$50,000. Alcohol intake and smoking status were dichotomized as current or not. The physical activity index was based on a modified version of the Baecke questionnaire and ranged from 1 (lowest) to 5 (highest). Diabetes was defined as fasting blood glucose ≥126 mg/dL, nonfasting blood glucose ≥200 mg/dL, a self-reported history of diabetes diagnosed by a physician, or use of diabetes medication in the past 2 weeks. BMI was calculated as weight (kg) divided by height (m^2). Blood pressure was measured 3 times after 5 minutes of rest in a seated position, and the average of the second and third measurements was recorded. Total cholesterol, HDL-C, and serum creatinine were measured using an enzymatic method, and eGFR was calculated based on the 2021 CKD Epidemiology Collaboration creatinine-based equation.[33]

TABLE 1 Baseline Characteristics Stratified by Quartiles of Dietary Calcium Intake

		Q1 (n = 478)	Q2 (n = 479)	Q3 (n = 479)	Q4 (n = 478)
		Dietary Calcium Intake Quartiles (mg/day)[a]			
	Overall (N = 1,914)	<437.23	437.23-600.14	600.15-806.08	>806.08
Total energy intake (kcal/day)[a]	1,597.8 ± 495.3	1,241.8 ± 344.3	1,485.9 ± 412.9	1,717.4 ± 431.5	1,946.3 ± 482.1
Dietary phosphorus intake (mg/day)[a]	1,075.3 ± 356.3	723.6 ± 172.8	935.8 ± 160.2	1,149.6 ± 182.9	1,492.3 ± 310.9
Dietary vitamin D intake (IU/day)[a]	232.3 ± 122.3	134.5 ± 68.6	186.7 ± 65.1	245.6 ± 93.6	362.6 ± 115.7
Age at visit: 1 (y)	50.3 ± 4.2	49.7 ± 4.0	50.4 ± 4.4	50.5 ± 4.3	50.5 ± 4.3
Age at visit: 3 (y)	56.2 ± 4.2	55.7 ± 4.0	56.3 ± 4.4	56.5 ± 4.3	56.5 ± 4.2
Age at visit: 7 (y)	80.5 ± 4.3	79.9 ± 4.0	80.6 ± 4.4	80.6 ± 4.4	80.7 ± 4.3
Male	737 (38.5)	152 (31.8)	187 (39.0)	187 (39.0)	211 (44.1)
Black race	373 (19.5)	123 (25.7)	101 (21.1)	94 (19.6)	55 (11.5)
ARIC field center					
Forsyth	443 (23.2)	101 (21.1)	127 (26.5)	127 (26.5)	88 (18.4)
Jackson	335 (17.5)	116 (24.3)	91 (19.0)	78 (16.3)	50 (10.5)
Minneapolis	652 (34.1)	140 (29.3)	123 (25.7)	154 (32.2)	235 (49.2)
Washington	484 (25.3)	121 (25.3)	138 (28.8)	120 (25.1)	105 (22.0)
Education					
Less than high school	164 (8.6)	42 (8.8)	45 (9.4)	42 (8.8)	35 (7.3)
High school graduate or equivalent	792 (41.4)	228 (47.7)	199 (41.5)	202 (42.2)	163 (34.1)
At least some college	958 (50.1)	208 (43.5)	235 (49.1)	235 (49.1)	280 (58.6)
Income level					
< $12,000	102 (5.3)	39 (8.2)	22 (4.6)	28 (5.9)	13 (2.7)
$12,000-24,999	230 (12.0)	63 (13.2)	59 (12.3)	59 (12.3)	49 (10.3)
$25,000-49,999	683 (35.7)	158 (33.1)	179 (37.4)	166 (34.7)	180 (37.7)
≥ $50,000	899 (47.0)	218 (45.6)	219 (45.7)	226 (47.2)	236 (49.4)
Current drinker	1,180 (61.7)	285 (59.6)	288 (60.1)	281 (58.7)	326 (68.2)
Current smoker	217 (11.3)	65 (13.6)	59 (12.3)	46 (9.6)	47 (9.8)
Physical activity index score	2.6 ± 0.8	2.5 ± 0.8	2.6 ± 0.8	2.6 ± 0.8	2.7 ± 0.8
Body mass index (kg/m^2)	27.9 ± 5.0	27.5 ± 4.9	27.5 ± 4.8	28.3 ± 5.3	28.0 ± 4.9
Systolic blood pressure (mm Hg)	117.8 ± 15.8	118.4 ± 16.0	117.4 ± 15.8	118.2 ± 16.4	117.0 ± 15.1
Diastolic blood pressure (mm Hg)	71.6 ± 10.0	72.2 ± 10.9	71.1 ± 9.5	71.9 ± 9.9	71.2 ± 9.5
Estimated glomerular filtration rate	92.2 ± 12.4	92.2 ± 13.1	91.5 ± 12.6	91.7 ± 12.1	93.3 ± 11.6
Total cholesterol (mg/dL)	203.3 ± 35.5	205.7 ± 36.1	201.6 ± 34.9	202.1 ± 36.3	203.7 ± 34.7
HDL-cholesterol (mg/dL)	55.2 ± 18.3	56.4 ± 17.1	55.7 ± 19.4	53.2 ± 18.3	55.4 ± 18.5
Hypertension	468 (24.5)	137 (28.7)	112 (23.4)	129 (27.2)	90 (18.9)
Diabetes	104 (5.4)	29 (6.1)	19 (4.0)	30 (6.3)	26 (5.4)
Antihypertensive medication use	419 (21.9)	117 (24.5)	97 (20.3)	112 (23.4)	93 (19.5)
Lipid-lowering medication use	106 (5.5)	27 (5.7)	23 (4.8)	31 (6.5)	25 (5.2)
Aspirin use	942 (49.2)	235 (49.2)	239 (49.9)	229 (47.8)	239 (50.0)
Calcium supplement use	354 (18.5)	88 (18.4)	89 (18.6)	90 (18.8)	87 (18.2)
Vitamin D supplement use	88 (4.6)	24 (5.0)	21 (4.4)	22 (4.6)	21 (4.4)

Values are mean ± SD or n (%). [a]Dietary data (calcium, phosphorus, vitamin D, and total energy) were estimated using the average intake of visit 1 (1987-1989) and visit 3 (1993-1995). The other characteristics were assessed at visit 3 (1993-1995) except for education level. Estimated glomerular filtration rate in ml/min/1.73 m^2.

ARIC = Atherosclerosis Risk In Communities; HDL = high-density lipoprotein.

STATISTICAL ANALYSIS. Baseline characteristics were summarized as mean ± SD for continuous variables and number (percentage) for categorical variables across quartiles of dietary calcium and phosphorus intakes. Between-group differences for continuous and categorical variables were compared using analysis of variance and chi-squared test, respectively.

We first ran linear regression models to evaluate the association of dietary calcium and phosphorus intakes with ln (CAC+1) or ln (ECC+1) as continuous dependent variables. Since the Agatston score of CAC and ECC can be zero, we added 1 and then log-transformed them given their skewed distributions, as commonly done.[34,35] The p for trend values were determined with a linear term in quartile number. Subsequently, we evaluated the OR of having CAC and ECC ≥75th percentile[36] using logistic regression models. Dietary calcium and phosphorus

TABLE 2 Multivariable Linear Regression of Dietary Calcium and Phosphorus Intakes With Log-Transformed CAC and ECC

	Q1 (n = 478)	Q2 (n = 479)			Q3 (n = 479)			Q4 (n = 478)			
	Dietary Calcium Intake Quartiles (mg/day)										
	<437.23	437.23-600.14			600.15-806.08			>806.08			
		β	SE	*P* Value	β	SE	*P* Value	β	SE	*P* Value	*P* Value for trend
Coronary artery	Ref.	**−0.28**	**0.14**	**0.036**	**−0.32**	**0.14**	**0.028**	**−0.44**	**0.16**	**0.0062**	**0.0087**
Ascending aorta	Ref.	0.0016	0.11	0.88	−0.14	0.12	0.24	**−0.26**	**0.13**	**0.047**	**0.026**
Aortic valve ring	Ref.	0.013	0.14	0.92	−0.19	0.14	0.19	**−0.40**	**0.16**	**0.014**	**0.0071**
Aortic valve	Ref.	0.26	0.15	0.070	−0.062	0.16	0.69	0.080	0.17	0.64	0.87
Descending aorta	Ref.	−0.12	0.15	0.45	−0.13	0.16	0.45	−0.23	0.18	0.21	0.24
Mitral valve	Ref.	−0.059	0.18	0.74	0.023	0.19	0.90	−0.31	0.21	0.15	0.22
	Q1 (n = 478)	**Q2 (n = 479)**			**Q3 (n = 479)**			**Q4 (n = 478)**			
	Dietary Phosphorus Intake Quartiles (mg/day)										
	<818.25	818.25-1,030.08			1,030.09-1,274.85			>1,274.85			
		β	SE	*P* Value	β	SE	*P* Value	β	SE	*P* Value	*P* Value for trend
Coronary artery	Ref.	−0.087	0.14	0.54	−0.22	0.16	0.17	**−0.40**	**0.20**	**0.041**	**0.036**
Ascending aorta	Ref.	0.083	0.12	0.47	−0.036	0.13	0.78	−0.055	0.16	0.73	0.55
Aortic valve ring	Ref.	0.10	0.14	0.47	−0.048	0.16	0.76	−0.37	0.20	0.063	0.055
Aortic valve	Ref.	−0.026	0.15	0.86	−0.18	0.17	0.30	−0.14	0.21	0.50	0.36
Descending aorta	Ref.	0.14	0.16	0.36	0.22	0.18	0.21	−0.072	0.22	0.75	0.94
Mitral valve	Ref.	0.33	0.19	0.074	0.078	0.21	0.71	−0.023	0.26	0.93	0.67

Models were adjusted for total dietary energy intake, age, sex, race, center, alcohol intake, smoking status, physical activity, body mass index, education level, income level, systolic blood pressure, total cholesterol level, HDL-cholesterol level, eGFR, use of aspirin, antihypertensive medicine, cholesterol-lowering medicine, and prevalent diabetes mellitus. **Bold** indicates statistical significance.

CAC = coronary artery calcification; ECC = extra-coronary calcification; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; SE = standard error.

intakes were initially modeled categorically (ie, quartiles). Furthermore, we visualized the continuous associations of dietary calcium and phosphorus intakes with CAC and ECC using restricted cubic spline models. We put 3 knots at the 25th, 50th, and 75th percentiles and set a reference at the 5th percentile of dietary calcium and phosphorus intakes. Models were adjusted for total dietary energy intake, age, sex, race, the ARIC field centers, alcohol intake, smoking status, physical activity, BMI, education level, income level, systolic blood pressure, total cholesterol level, HDL-C level, eGFR, use of aspirin, antihypertensive medicine, and cholesterol-lowering medicine, and diabetes status.

We performed subgroup analyses by sex or race using linear and logistic regression models. In this analysis, to obtain reliable estimates in each sex subgroup, we modeled dietary calcium and phosphorus intakes as continuous variables with a unit of 1-SD increment. Statistical interactions were assessed by likelihood ratio tests. We also repeated the analysis after excluding participants taking calcium or vitamin D supplements and using CAC Agatston score >100[37] as an outcome variable. Two-sided statistical significance was defined as $P < 0.05$. All statistical analyses were performed using the SAS system (Release 9.4, SAS Institute).

RESULTS

PARTICIPANT CHARACTERISTICS. Of the 1,914 participants, 39% were men and 20% were Black. The age was 50.3 ± 4.2 years at visit 1, 56.2 ± 4.2 years at visit 3, and 80.5 ± 4.3 years at visit 7. The dietary calcium intake was 660 ± 311 mg/day (693 mg/day for men and 638 mg/day for women, respectively), with 651 mg/day at visit 1 and 669 mg/day at visit 3. Only 257 participants (13.4%) consumed dietary calcium over its RDA of 1,000 mg/day, and 5 participants (0.3%) consumed over its recommended upper limit of 2,000 mg/day. There were 354 participants (18.5%) taking calcium supplements and 88 participants (4.6%) taking vitamin D supplements at visit 3. Participants with higher dietary calcium intake were more likely to have higher intake of total energy, phosphorus, and vitamin D (Table 1). They were also likely to be older, male sex, White race, more educated, current drinkers, more physically active, and have higher income levels, higher BMI, lower prevalence of hypertension, and lower HDL-C levels. Similar

TABLE 3 OR of Having ≥75th Percentile of Calcification in Different Sites by Quartiles of Dietary Calcium and Phosphorus Intakes

	Q1 (n = 478)	Q2 (n = 479)	Q3 (n = 479)	Q4 (n = 478)
	Dietary Calcium Intake Quartiles (mg/day)			
	<437.23	437.23-600.14	600.15-806.08	>806.08
Coronary artery	Ref.	0.78 (0.56-1.09)	0.76 (0.54-1.09)	**0.66 (0.45-0.98)**
Ascending aorta	Ref.	1.04 (0.77-1.41)	0.80 (0.57-1.11)	**0.67 (0.46-0.99)**
Aortic valve ring	Ref.	1.04 (0.76-1.43)	0.78 (0.55-1.10)	0.82 (0.56-1.20)
Aortic valve	Ref.	1.32 (0.96-1.82)	1.01 (0.71-1.43)	1.16 (0.79-1.68)
Descending aorta	Ref.	1.31 (0.95-1.81)	0.91 (0.64-1.29)	0.97 (0.66-1.43)
Mitral valve	Ref.	0.93 (0.68-1.27)	0.93 (0.67-1.30)	0.77 (0.53-1.12)
	Q1 (n = 478)	Q2 (n = 479)	Q3 (n = 479)	Q4 (n = 478)
	Dietary Phosphorus Intake Quartiles (mg/day)			
	<818.25	818.25-1,030.08	1,030.09-1,274.85	>1,274.85
Coronary artery	Ref.	0.87 (0.61-1.23)	0.77 (0.52-1.14)	0.62 (0.38-1.02)
Ascending aorta	Ref.	1.15 (0.83-1.59)	0.94 (0.65-1.36)	0.93 (0.58-1.47)
Aortic valve ring	Ref.	1.19 (0.85-1.67)	0.94 (0.64-1.37)	0.86 (0.53-1.38)
Aortic valve	Ref.	1.09 (0.77-1.52)	1.03 (0.70-1.50)	1.08 (0.68-1.72)
Descending aorta	Ref.	1.23 (0.88-1.74)	1.01 (0.69-1.49)	0.86 (0.53-1.39)
Mitral valve	Ref.	1.16 (0.84-1.61)	1.03 (0.71-1.48)	0.90 (0.57-1.43)

Values are OR (95% CI). Models were adjusted for total dietary energy intake, age, sex, race, center, alcohol intake, smoking status, physical activity, body mass index, education level, income level, systolic blood pressure, total cholesterol level, HDL-cholesterol level, eGFR, use of aspirin, antihypertensive medicine, cholesterol-lowering medicine, and prevalent diabetes mellitus. **Bold** indicates statistical significance.

eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein.

patterns were observed across quartiles of dietary phosphorus intake (Supplemental Table 1). The dietary phosphorus intake was 1,075 ± 356 mg/day (1,146 mg/day for men and 1,030 mg/day for women), with 1,076 mg/day at visit 1 and 1,074 mg/day at visit 3. Most participants (n = 1,669 [87%]) consumed dietary phosphorus over its RDA of 700 mg/day, and no participant consumed over its upper limit of 4,000 mg/day.

DIETARY CALCIUM AND PHOSPHORUS INTAKES AND CAC AND ECC. With log-transformed CAC and ECC as continuous dependent variables, dietary calcium intake was significantly and inversely associated with CAC (P for trend = 0.0087), ascending aorta calcification (P for trend = 0.026), and aortic valve ring calcification (P for trend = 0.0071) (**Table 2**). The highest quartile of dietary calcium showed a statistically significant association with lower calcification in these 3 vascular beds. For CAC, the second and third quartiles reached statistical significance as well. When we repeated the same analysis with dietary phosphorus, there was a significant inverse association only with CAC (P for trend = 0.036) (**Table 2**). We observed generally consistent results when using CAC and ECC ≥75th percentile as dichotomous dependent variables, although statistical significance was restricted to CAC and ascending aorta for dietary calcium (adjusted OR: 0.66 [95% CI: 0.45-0.98]) and adjusted OR: 0.67 [95% CI: 0.46-0.99], respectively), and the association between dietary phosphorus and CAC became borderline significant (P = 0.060) (**Table 3**). When CAC Agatston score >100 was used as an alternative outcome variable, the results were slightly weaker than the primary analysis, but the general patterns were consistent (Supplemental Table 2).

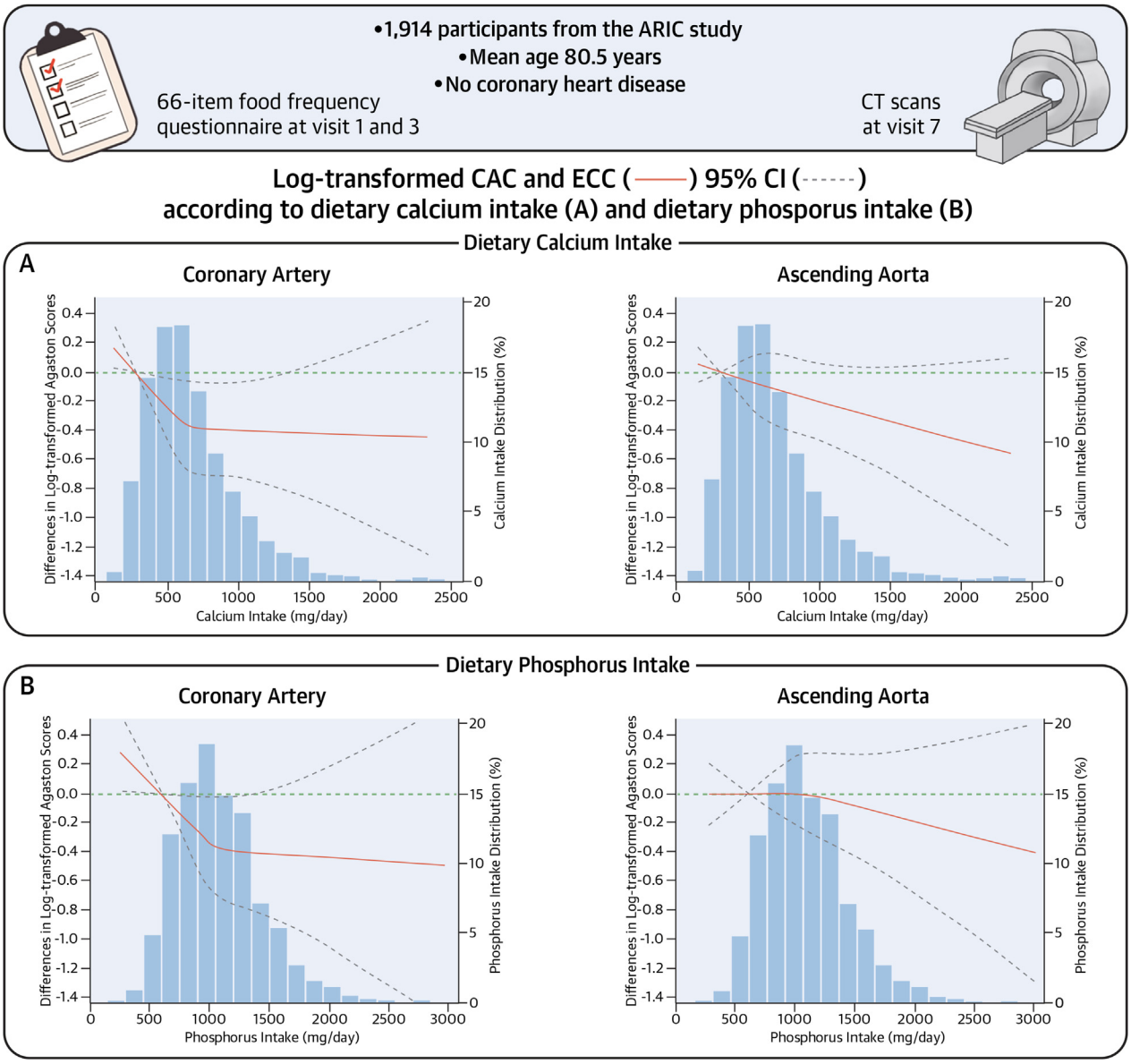
We did not observe any positive associations with CAC and ECC, even when we explored the full spectrum of dietary calcium and phosphorus intakes with their spline terms (**Central Illustration**). We observed generally consistent results for CAC and ECC ≥75th percentile as dependent variables (Supplemental Figures 1 and 2).

SUBGROUP ANALYSIS. In general, the inverse associations appeared stronger in men than in women (Supplemental Tables 3 and 4). For example, dietary phosphorus intake was inversely associated even with aortic valve ring in men. However, there was no statistically significant interaction between sex with dietary calcium and phosphorus intake quartiles overall. We observed similar patterns in logistic regression models with CAC and ECC ≥75th percentile as dependent variables and dietary calcium and phosphorus intakes as continuous independent variables (per 1-SD increment) (**Figure 2**). The results were generally consistent without any significant interaction by racial groups (Supplemental Figure 3). The exclusion of participants taking calcium or vitamin D supplements did not materially alter the results (Supplemental Tables 5 and 6). When we compared CAC and ECC in participants taking calcium supplements vs those not taking them, we did not observe any positive associations (Supplemental Table 7).

DISCUSSION

In our community-based study, we did not observe any positive associations of dietary calcium and phosphorus intakes with CAC and ECC. Rather, we observed their inverse associations with the calcifications of some vascular beds. More specifically, in the overall study population, calcium intake was inversely associated with calcification of coronary artery, ascending aorta, and aortic valve ring, and so was phosphorus intake with CAC. The results were generally consistent when we stratified by sex or race, although some inverse associations appeared stronger in men than in women. The exclusion of participants taking calcium or vitamin D supplements did not materially alter the results.

CENTRAL ILLUSTRATION **Calcium and Phosphorus Intakes With Coronary Artery Calcification and Extra-Coronary Calcification in the Ascending Aorta**

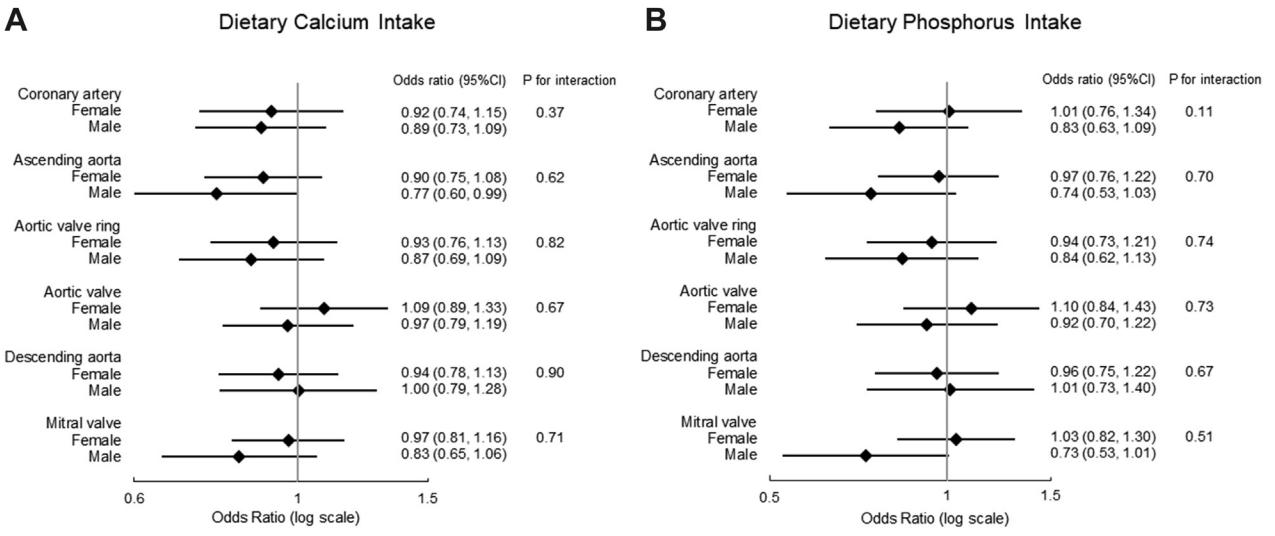


Nohara-Shitama Y, et al. JACC Adv. 2024;3(7):100993.

Log-transformed CAC and ECC (solid red line) and 95% CIs (dashed grey lines) according to dietary calcium intake (A) and dietary phosphorus intake (B). The reference value was set at 5th percentile with 3 knots (25th, 50th, and 75th percentiles). Models were adjusted for total dietary energy intake, age, sex, race, center, alcohol intake, smoking status, physical activity, body mass index, education level, income level, systolic blood pressure, total cholesterol level, HDL-cholesterol level, eGFR, use of aspirin, antihypertensive medicine, cholesterol-lowering medicine, and prevalent diabetes mellitus. CAC = coronary artery calcification; ECC = extra-coronary calcification; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein.

The inverse association between dietary calcium intake and CAC in the present study is consistent with data from MESA (Multi-Ethnic Study of Atherosclerosis),[25] reporting a lower incidence of CAC over 10 years according to higher dietary calcium intake. Nonetheless, there are a few unique aspects of our study. First, our exposure to dietary calcium was based on the average dietary information collected twice over 6 years, which should reduce the risk of misclassification. Second, leveraging data on ECC, we

FIGURE 2 ORs of Having ≥75th Percentile of CAC and ECC by Sex



The adjusted OR of CAC and ECC scores above 75th percentile per 1-SD increment in dietary (A) calcium and (B) phosphorus intakes by sex. Models were adjusted for total dietary energy intake, age, race, center, alcohol intake, smoking status, physical activity, body mass index, education level, income level, systolic blood pressure, total cholesterol level, HDL-cholesterol level, eGFR, use of aspirin, antihypertensive medicine, cholesterol-lowering medicine, and prevalent diabetes mellitus.
CAC = coronary artery calcification; ECC = extra-coronary calcification; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein.

found inverse associations of dietary calcium intake with ascending aorta and aortic valve ring in addition to CAC, which further support different pathophysiology across different vascular beds[27] and valves.[38] Third, we uniquely linked dietary calcium intake at middle age and vascular calcification at older age, approximately 30 years apart.

Our findings of no evident positive associations of dietary phosphorus intake with vascular calcification are consistent with a previous Korean study of individuals with a glomerular filtration rate of ≥60 ml/min/1.73 m^2.[15] On the other hand, a Brazilian study of patients with CKD reported a positive association between high dietary phosphorus intake and CAC.[26] This discrepancy between CKD vs non-CKD populations seems to be in line with the physiology of phosphorus and the pathophysiology of vascular calcification. Specifically, a positive association of dietary phosphorus intake with CAC in CKD patients may reflect bone mineral disorders in which vascular calcification due to the transition of vascular smooth muscle cells into osteoblasts[39] is induced by hyperphosphatemia.[10] In our study, the majority of participants did not have reduced kidney function at visit 3.

As noted above, some inverse associations of dietary calcium and phosphorus with vascular calcification tended to be stronger in men than in women. However, we should carefully interpret these results since there was no statistically significant interaction by sex. Also, we evaluated multiple potential interactions without a prespecified hypothesis. Nonetheless, it would be worth exploring sex-specific results when future studies investigate dietary calcium or phosphorus in the context of cardiovascular health.

There are a few implications for our study. Many adults in the United States (particularly women) do not take calcium adequately.[8] Given the importance of calcium intake for bone health and the low likelihood of its adverse effects on the cardiovascular system, further promotion of increasing dietary calcium intake is warranted. Of note, there are several studies showing potential protective effects of dietary calcium intake on the cardiovascular system, such as reducing blood pressure,[40] increasing insulin sensitivity,[41] and improving lipid profile.[42] Unlike calcium intake, phosphorus intake is already above the recommended amount in both males and females in the United States.[8] Furthermore, inorganic phosphate is contained in food additives used in instant foods, processed foods, and fast foods[43] and is also easily absorbed in the gut.[43] Thus, a modest inverse association of dietary phosphorus with CAC in our study should not be simply interpreted as a potential benefit of dietary phosphorus intake. Also, our observation further supports the emerging concept that the pathophysiological process differs across

different vascular beds[27] (eg, lipids are more strongly associated with CHD than cerebrovascular disease[44]).

STUDY LIMITATIONS. There are several limitations to the present study. First, while FFQ is a useful tool for the measurement of most nutrients in general,[45,46] there may be potential measurement errors in the assessment of dietary data. Indeed, a few studies have reported the possibility of underestimating phosphorus intake using FFQ.[47,48] Second, we did not have baseline measures of CAC and ECC and could not evaluate their changes over time. Third, we studied participants without CHD and also those who could undergo chest CT scans at visit 7, which may include healthier participants among the ARIC participants. Fourth, although we had self-reported data on the use of calcium supplements, the ARIC did not collect the dose of calcium supplements. Fifth, we included only White and Black participants in this study, and thus the extrapolation of our findings to other racial/ethnic groups should be done carefully. Finally, we cannot deny the possibility of residual confounding (eg, participants with higher dietary calcium intake may be engaging in other healthy behaviors).

CONCLUSIONS

Dietary calcium and phosphorus intakes at middle age were not positively associated with vascular and valvular calcification at over 75 years old. Our findings did not support the link between a calcium or phosphorus-rich diet and vascular and valvular calcification.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Among 1,914 ARIC participants, we observed an inverse association between dietary calcium intake and vascular and valvular calcification. Dietary phosphorus intake demonstrated similar results, but the magnitude of the association was weaker than dietary calcium intake.

TRANSLATIONAL OUTLOOK: Our findings suggest that a calcium-rich diet would not cause vascular calcification and have important implications since many U.S. older adults are not taking enough calcium and are at risk of osteoporosis.

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KEY WORDS **Agatston score, computed tomography, coronary artery calcification, extra-coronary calcification, epidemiology, food frequency questionnaire**

APPENDIX **For supplemental tables and figures, please see the online version of this paper.**