Nutrition impacts the prevalence of peripheral arterial disease in the United States

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Objective: **Traditional recommendations for peripheral arterial disease (PAD) risk factor reduction include smoking cessation, low-fat/low-salt diet, exercise, and optimal medical management of chronic disease. Little attention has been paid to the role of dietary supplementation of specific nutrients in the prevention of PAD.**

Methods: **This cross-sectional study used the National Health and Nutrition Examination Survey (NHANES) to determine specific nutrients that are associated with prevalent PAD in the United States (US) population. NHANES data include nationwide sampling of the US population, using physical examination, questionnaire, and laboratory testing. PAD status was defined by an ankle-brachial index (ABI) of <0.9. Nutritional information was collected by 24-hour dietary recall using the US Department of Agriculture dietary collection instrument. Data were linked to a database of foods and their nutrient composition. Univariate and multivariate logistic regression analyses were performed to evaluate associations between specific nutrient intake and the presence of PAD. Multivariate models adjusted for the effects of age, gender, hypertension, coronary vascular disease, diabetes, and smoking.**

Results: **NHANES data for 1999 to 2004 included 7203 lower extremity examinations, of which 422 individuals had prevalent PAD (5.9%). Examinees with PAD had significantly higher rates of hypertension, coronary artery disease, diabetes, and smoking than those without PAD. Univariate analysis revealed that consumption of all nutrients considered were associated with lower odds of PAD, including antioxidants (vitamins A, C, and E), folate, other B vitamins (B_6, B_{12}), fiber, and polyunsaturated and saturated fatty acids. After adjustment for traditional risk factors, nutrients associated with reduced prevalence of PAD were vitamin A (odds ratio [OR], 0.79; $P = .036$), vitamin C (OR, 0.84; $P < .001$), vitamin E (OR, 0.78; $P = .011$), vitamin B_6 (OR, 0.71; $P = .023$), fiber (OR, 0.65; $P < .001$), folate (OR, 0.67; $P = .006$), and ω-3 (α-linolenic) fatty acid (OR, 0.79; $P = .028$).**

Conclusions: **Improved nutrition is associated with a reduced prevalence of PAD in the US population. Higher consumption of specific nutrients, including antioxidants (vitamin A, C, and E), vitamin B_6, fiber, folate, and ω-3 fatty acids have a significant protective effect, irrespective of traditional cardiovascular risk factors. These findings suggest specific dietary supplementation may afford additional protection, above traditional risk factor modification, for the prevention of PAD. (J Vasc Surg 2008;48:897-904.)**

Peripheral arterial disease (PAD) is a potentially life- or limb-threatening condition affecting 5.9% of the United States (US) population aged >40 years, roughly 16.5 million Americans (present study). Prevention and treatment of PAD has focused on modification of cardiovascular risk factors, which include smoking, hypertension, diabetes, and hyperlipidemia. Life-style modification includes programs for smoking cessation, graduated exercise regimens, and dietary changes. Medical intervention involves the treatment of chronic disease using cholesterol-lowering agents (statins), and antiplatelet agents, and antihypertensive medicines, including angiotensin-converting enzyme inhibitors and β-blockers.[1] Despite these guidelines, patients with PAD are relatively under-treated with regard to reduction of risk factors compared with patients with coronary heart disease.[2]

General dietary interventions often call for a low-fat, low-salt diet for secondary treatment of cardiovascular disease, but recommendations for consumption of specific nutrients are often lacking. The World Health Organization (WHO) Study Group[3] proposed guidelines for the prevention of cardiovascular disease include a diet low in total fat (<30% of calories) and saturated fat (<10% of calories), and devoid of trans-fatty (saturated) acids. Salt intake should be reduced to <5 g/d (90 mmol/d). Consumption of a broad range of fruits, vegetables, and grain (>400 g/d) is encouraged. However, no recommendation could be made for intake of vitamins B, C, E, and folic acid due to a paucity of clinical evidence.

We have conducted a population-based study to examine the association between consumption of certain nutrients and the prevalence of PAD within the US population. Data from the National Health and Nutritional Examination Survey (NHANES)[4] from 1999 to 2004 was used to gather information on the dietary habits in the United States. Nutrients examined in this study had previous evidence of protective effect in the literature and include antioxidants (vitamins A, C, and E), folate and B vitamins, polyunsaturated fatty acids (PUFA), and dietary fiber. As-

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sociations between specific nutrient consumption and PAD were explored using univariate and multivariate models. Adjustment for the presence of cardiovascular risk factors was performed to determine which nutrients might have a protective effect in addition to traditional risk factor modification.

METHODS

Data source. NHANES conducts series of cross-sectional surveys among the civilian, noninstitutionalized US population by using a complex, stratified, multistage, probability-sampling design. Data for this study included NHANES 1999 to 2000, 2001 to 2002, and 2003 to 2004. Extracted data files included demographic information, the ankle-brachial index (ABI) examination, 24-hour dietary recall interview (total nutrient intake), and disease history. These data files were obtained from the NHANES Website[4] and combined to create a single data set.

Ankle-brachial index measurements. Detailed description of the ABI measurement procedure can be found on the NHANES Website.[4] All study participants aged ≥40 years were invited to participate in the lower extremity examination. Exclusion criteria included people weighing ≥400 pounds or with bilateral amputation. Other reasons for nonparticipation in the lower extremity examination included (1) casts, ulcers, dressings or other conditions of the participant that interfered with the testing, (2) participant could not understand the test instructions, (3) participant became ill and the test could not be performed, (4) an equipment failure occurred, (5) the participant refused, (6) the participant that came late or left early from the mobile examination center and the lower extremity disease exam could not be performed, or (7) some other reason.

Supine systolic pressure was measured twice in the arm (brachial artery) and both ankles (posterior tibial or dorsalis pedis arteries, or both). The ABI was calculated by dividing the systolic blood pressure at the ankle by the mean systolic blood pressure in the arm. The smallest of the left or right ABI calculations was used for this study to maximize numbers of prevalent peripheral arterial disease (PAD), defined as an ABI <0.9.[5]

Nutrition variables. The variables include vitamins A, C, E, B_6, B12, fiber, folate, total polyunsaturated fatty acids, linoleic acid, α-linolenic acid, and total saturated fatty acids. These were collected from the NHANES 1999 to 2004 first day dietary interview examination files. Quantitative dietary intake data was obtained for all subjects by means of a 24-hour dietary recall interview using the NHANES computer-assisted dietary data interview system. The 24-hour dietary recall collected a list of all the foods and beverages consumed within a 24-hour period, the time of consumption and the name of the eating occasion, detailed food descriptions and amounts of the reported foods, where the food was obtained, and whether it was eaten at home or not. The recall was then followed by a set of health-related questions. The data were collected with the US Department of Agriculture's (USDA) dietary data collection instrument, the Automated Multiple Pass Method.

These data were then coded and linked to a database of foods and their nutrient composition. Calculations of total daily nutrient intakes were derived from these data. Reference nutrient values were based on recommendations by the US Department of Health and Human Services, the USDA,[6] and the Food and Nutrition Board, Institute of Medicine, National Academies,[7] which incorporates recommended daily allowances and adequate intakes and vary for individual life stage groups. The USDA five-step, multiple-pass method of 24-hour dietary recall has been validated for both men and women.[8]

Associated risk factors. Age, sex, and comorbidities of hypertension, coronary artery disease (CAD), diabetes, and smoking were examined concomitantly with all nutrient variables. Age in years was used as a continuous variable. Hypertension was defined as self-reported medical history of hypertension or systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg on physical examination. CAD was defined as self-reported medical history of coronary artery disease, angina, or stroke. Status of diabetes was defined as self-reported medical history of diabetes. Smoking status was defined as positive for participants consuming more than 100 cigarettes over a lifetime.

Statistical analysis. All statistical analyses were conducted with SAS 9.1 software (SAS Institute Inc, Cary, NC). Because of the NHANES complex probability sampling of the US population, sample weights, stratification, and clustering of the sampling design were incorporated into all SAS survey procedures to ensure the correct estimation of standard errors, confidence intervals, and *P* values. A 6-year sample weight was created according to the NHANES analytic guidelines[4] for the combined 1999 to 2004 data by assigning one-third of the 2-year weight for 2003 to 2004 if a participant was sampled in 2003 to 2004 and merging it with the 1999 to 2002 4-year weight for those sampled in 1999 to 2002. The stratification and clustering variables used in all analyses were SDMVSTRA and SDMVPSU, respectively.

All nutrient variables were highly skewed and thus normalized by log-transformation before statistical analysis. Pearson correlation coefficients between nutrient variables were calculated. Descriptive statistics included two-sided Student *t* tests and Wald χ^2 analysis, where appropriate. Univariate analyses were conducted to determine crude associations between putative predictor variables and PAD. Multivariate logistic regression was used to examine the potential protective effects of a nutrient on PAD prevalence, with adjustment for known risk factors. Adjusted bivariate analysis, stratified by quartiles of nutrient consumption levels, was used to determine a dose–response effect, with comparisons made to available governmental nutritional guidelines. Statistical significance was set at $P < .05$ or odds ratios (OR) and 95% confidence intervals (CI) that excluded 1.

RESULTS

Demographics. Results of the population characteristics of the United States are summarized in Table I. This study included 7203 lower extremity examination partici-

Table I. Population characteristics by peripheral arterial disease status, National Health and Nutrition Examination Survey, 1999 to 2004 (N = 7203)[a]

Characteristic[b]	*PAD (ABI <0.90)*		P[c]
	Yes (n = 422)	*No (n = 6781)*	
Age, years	67.6 ± 0.57	55.0 ± 0.14	<.001
Female sex, %	56.1 ± 3.68	51.6 ± 0.64	.266
Hypertension, %	65.6 ± 3.22	34.6 ± 1.87	<.001
CAD, %	11.2 ± 1.67	2.67 ± 0.29	<.001
Diabetes, %	21.1 ± 2.76	8.6 ± 0.41	<.001
Smoking, %	68.6 ± 3.52	53.3 ± 1.01	<.001
Obesity, %	18.6 ± 2.11	18.5 ± 1.02	.637
Body mass index, kg/m^2	28.9 ± 0.42	28.2 ± 0.09	.589
Nutrients			
Total calories, Kcal	1742 ± 44.3	2100 ± 15.8	<.001
Vitamin A, ug	567.2 ± 37.0	616.7 ± 10.0	.316
Vitamin C, mg	78.5 ± 4.03	94.0 ± 1.15	.007
Vitamin E, mg	5.80 ± 0.25	7.15 ± 0.08	.001
Vitamin B_6, mg	1.64 ± 0.05	1.84 ± 0.01	.004
Vitamin B_{12}, μg	4.96 ± 0.34	5.15 ± 0.11	.736
Fiber, g	13.9 ± 0.50	16.3 ± 0.12	<.001
Folate, μg	338.0 ± 10.9	393.4 ± 2.83	<.001
Total PUFA, g	13.8 ± 0.45	16.9 ± 0.14	<.001
Linoleic acid, g	12.2 ± 0.40	14.9 ± 0.13	<.001
α-Linolenic acid, g	1.24 ± 0.04	1.50 ± 0.01	<.001
Total saturated fatty acids, g	22.7 ± 0.73	25.9 ± 0.20	.001

ABI, Ankle-brachial index; *CAD,* coronary artery disease; *PAD,* peripheral arterial disease; *PUFA,* polyunsaturated fatty acid.
[a]Six-year weight variable used for two-sided *t* test and Wald χ^2 analyses.
[b]Values are percentages ± standard error or mean ± standard error.
[c]Statistical significance at $P < .05$.

pants from the years 1999 to 2004, of which 422 had prevalent PAD. Comparisons are made between participants with PAD (ABI <0.90) and those without PAD (ABI ≥0.90). Participants with PAD were older than those without (mean age, 67.6 vs. 55.0 years; $P < .001$). Gender distribution between the two groups was not significantly different, and reflected the gender distribution of the overall population.

Traditional cardiovascular risk factors were more prevalent in the group with PAD. This includes a greater prevalence of hypertension (65.6% ± 3.22% vs 34.6% ± 1.87%; $P < .001$), CAD (11.2% ± 1.67% vs 2.67% ± 0.29%; $P < .001$), diabetes (21.1% ± 2.76% vs 8.6% ± 0.41%; $P < .001$), and smoking (68.6 ± 3.52% vs 53.3% ± 1.01%; $P < .001$) in the PAD group.

Total caloric intake was lower in the group with PAD than in those without (mean, 1742 vs 2100 Kcals; $P < .001$). Consumption of most nutrients assayed was also significantly lower in the group with PAD. This includes a lower consumption of antioxidants (vitamins A, C, and E), folate and vitamins B_6 and B_{12}, fiber, and polyunsaturated fatty acids (linoleic and α-linolenic acid) and total saturated fatty acids. This reflects generalized poor nutrition among participants with PAD.

Bivariate and multivariate analyses. Results of the bivariate analyses are summarized in Table II. The odds of PAD were generally lowered with increased consumption of all nutrients. This reflects an association between improved nutrition and lower odds of PAD. This association reached statistical significance for all nutrients examined except for vitamin A (OR, 0.85; $P = .051$) and vitamin B_{12} (OR, 0.88; $P = .174$).

Multivariate analyses are summarized in Table II. Traditional cardiovascular risk factors were used as covariates in the model, including age, gender, hypertension, CAD, diabetes, and smoking. By using this adjustment, the potential protective effect of nutrient consumption can be determined, irrespective of the effect of traditional risk factors. The point estimates (ORs) for all nutrients were <1, except for total saturated fat consumption. This implies that consumption of these nutrients showed some trend toward a protective effect. Nutrients which showed a significant association towards reduced OR of PAD included vitamin A (OR, 0.79; $P = .036$), vitamin C (OR, 0.84; $P < .001$), vitamin E (OR, 0.78; $P = .011$), vitamin B_6 (OR, 0.71; $P = .023$), fiber (OR, 0.65; $P < .001$), folate (OR, 0.67; $P = .006$) and α-linolenic fatty acid (OR, 0.79; $P = .028$).

Quartile analysis. Results of unadjusted bivariate analyses, stratified by quartile of consumption, are summarized in Table III. This stratification was performed to determine whether a dose–response effect could be seen in participants consuming larger quantities of certain nutrients. Threshold values for recommended consumption are listed to evaluate the quartiles meeting or exceeding these limits.

Results of these analyses are similar to the multivariate analyses. A dose–response relationship was seen, with higher levels of vitamin C consumption conferring a lower likelihood of PAD (25.3 to 60 mg/d: OR, 0.65; $P < .046$). A significant protective effect was also seen in quartiles meeting or exceeding the threshold values for vitamin E (>8.58 mg/d: OR, 0.60; $P = .039$), vitamin B_6 (1.08 to 1.58 mg/d: OR, 0.47; $P = .002$), fiber (13.3 to 19.4 g/d: OR, 0.65; $P = .036$), and folate (344 to 492 μg/d: OR, 0.66; $P = .019$).

DISCUSSION

There is mounting evidence from experimental and clinical studies that diet can have a profound effect on the process of atherosclerosis. Diet not only affects the levels of circulating blood lipids but can also modulate the immune and inflammatory processes present in the epithelium that affects the development of atherosclerotic plaque.[9] This has led to a number of putative nutritional targets that may afford protection or secondary intervention in patients with PAD. However, many clinical studies have conflicting results with regard to specific nutrient supplementation.[10] Dietetic guidelines are often tailored for overall *cardio*vascular health and do not specifically focus on *peripheral* arterial disease.[11]

One major finding of this study is the association between poor caloric intake and a higher risk of PAD. Among people in the United States *without* PAD, there is a general increase in

Table II. Unadjusted and adjusted bivariate logistic regression analysis[a]

	Unadjusted analysis for PAD			*Adjusted analysis for PAD*		
Nutrients[b]	*OR*	*95% CI*	P[c]	*OR*	*95% CI*	P[c]
Vitamin A	0.85	0.73-1.00	0.051	0.79	0.63-0.99	0.036
Vitamin C	0.88	0.81-0.96	0.002	0.84	0.76-0.92	<0.001
Vitamin E	0.66	0.56-0.78	<0.001	0.78	0.65-0.94	0.011
Vitamin B_6	0.68	0.55-0.83	<0.001	0.71	0.53-0.95	0.023
Vitamin B_{12}	0.88	0.73-1.06	0.174	0.94	0.72-1.21	0.626
Fiber	0.66	0.56-0.77	<0.001	0.65	0.53-0.79	<0.001
Folate	0.62	0.51-0.75	<0.001	0.67	0.52-0.88	0.006
Total PUFA	0.68	0.59-0.80	<0.001	0.83	0.68-1.01	0.061
Linoleic acid	0.70	0.61-0.81	<0.001	0.85	0.70-1.03	0.091
α-Linolenic acid	0.72	0.60-0.85	<0.001	0.79	0.65-0.98	0.028
Total saturated fatty acids	0.76	0.65-0.90	0.001	1.07	0.84-1.36	0.596

CI, Confidence intervals; *OR*, odds ratio; *PAD,* peripheral arterial disease; *PUFA,* polyunsaturated fatty acid.
[a]Models adjusted for age, gender, hypertension, diabetes, and smoking. Six-year weight variable used for analysis.
[b]See Table III for intake levels of the various nutrients.
[c]Statistical significance at $P < .05$.

total calories consumed and in all specific nutrient intakes, including saturated and polyunsaturated fatty acids. People with PAD had reported *decreased* total calorie and nutrient intake and had a higher prevalence of comorbid conditions, including hypertension, CAD, and diabetes. This trend towards poor caloric intake in patients with PAD and critical limb ischemia has been previously reported.[12]

In contrast, improved nutrition and freedom from PAD has also been associated. The Edinburgh Artery study evaluated the effect of dietary factors on ABI in a prospective trial of 1592 adults.[13] This showed an association between higher ABI and increased consumption of cereal fiber, meat, alcohol, and vitamins C and E. Our study finds a similar pattern of poor dietary habits and higher prevalence of PAD. Alarmingly, most Americans do not meet the US Food and Drug Administration (FDA)–required intake of most nutrients; this difference is more pronounced among the population with PAD. However, the association between nutrition and PAD can be confounded by other coexistent medical conditions, such as age, diabetes, CAD, and smoking. We conducted further analyses in attempt to adjust for other coexisting medical conditions to independently evaluate the effect of nutrition.

Antioxidants. Vitamin A (most commonly retinol) is a fat-soluble antioxidant that is important in vision, bone growth, and immune function. It is found in many yellow and orange vegetables, as well as butter, eggs, and liver.

Vitamin C (ascorbic acid) is water-soluble antioxidant, most commonly found in citrus fruit. It is a well known for its role in scurvy prevention as well as its importance in immune function and maintenance of the redox state. Previous clinical studies have shown vitamin C levels are reduced in PAD patients and correlates with reduced walking distance and systemic inflammation (C-reactive protein).[14] However, not all clinical trials involving vitamin C supplementation have shown positive effects on PAD.[15]

Vitamin E (tocopherol) is a membrane-bound antioxidant that has been linked to reduction in cellular damage seen in cardiovascular disease. It is found most commonly in nuts, vegetable oils, and fish. Vitamin E supplementation has long been used as preventative treatment for cardiovascular disease. In the Rotterdam study,[16] improved vitamin E intake was correlated with a reduction in PAD and increased ABI. However, in the large, randomized Heart Outcomes Prevention Evaluation (HOPE) trial,[17] dietary supplementation with vitamin E showed no decrease in cardiovascular events among patients with diabetes or vascular disease.

We found that increased consumption of antioxidants, vitamins A, C, and E, was associated with reduced odds of PAD in unadjusted analyses (Table II). In multivariate analyses (Table II), when the effect of traditional cardiovascular risk factors is adjusted, the association between antioxidant intake and lower odds of PAD is maintained. In quartile analysis (Table III), the benefit of higher levels of vitamin C consumption was seen in a dose–response relationship, lending some support to higher levels of vitamin C supplementation. Additional benefit was also seen in the highest quartile of vitamin E consumption (≥8.58 mg/d: OR, 0.60; $P = .039$).

This strong association observed in the United States population between improved antioxidant intake and reduced PAD disease should not be misinterpreted as a cause-and-effect relationship. More definitive evidence for antioxidant use will be provided by clinical trials, such as Critical Leg Ischemia Prevention Study (CLIPS), evaluating both vitamin C and E supplementation.

Folate and other B vitamins. Hyperhomocysteinemia is a known independent risk factor for the development of PAD.[18] About 30% of patients with PAD have hyperhomocysteinemia, and their severity of disease is correlated with plasma homocysteine levels.[19] Folate supplementation has been shown to reduce plasma homocysteine levels in PAD patients,[20] and the addition of vitamins B_6 and B_{12} may potentate this effect. In addition, many observational studies have reported a strong relationship between B vitamin

Table III. Multivariate logistic regression analysis for nutrient value quartiles [a]

Nutrients	*Dietary Health Guidelines*[b]	*Dietary Reference Intake/day*[c]	*OR of PAD*	*95% CI*	P[d]
Vitamin A, μg					
<260			1.00		
260-463			0.95	0.59-1.54	.839
464-756	700-900	700-900	0.67	0.40-1.13	.132
≥757	700-900	700-900	0.65	0.35-1.20	.167
Vitamin C, mg					
<25.3			1.00		
25.3-60.0			0.65	0.42-0.99	.046
60.1-125.1	75-90	75-90	0.65	0.47-0.90	.009
≥125.2			0.51	0.34-0.75	<.001
Vitamin E, mg					
<3.63			1.00		
3.63-5.57			0.81	0.53-1.25	.337
5.58-8.57			0.83	0.58-1.20	.326
≥8.58	15	15	0.60	0.37-0.97	.039
Vitamin B_6, mg					
<1.08			1.00		
1.08-1.58	1.3-1.7	1.3	0.47	0.29-0.76	.002
1.59-2.33			0.72	0.49-1.04	.078
≥2.34			0.56	0.33-0.96	.034
Vitamin B_{12}, μg					
<2.18			1.00		
2.18-3.85	2.4	2.4	0.98	0.62-1.55	.932
3.86-6.29			0.71	0.46-1.09	.118
≥6.30			0.99	0.59-1.65	.971
Fiber, g					
<8.67			1.00		
8.67-13.2			0.87	0.62-1.22	.403
13.3-19.4			0.65	0.44-0.97	.036
≥19.5	28	25-38	0.51	0.33-0.79	.002
Folate, μg					
<233			1.00		
233-343			0.76	0.55-1.05	.098
344-492	400	400	0.66	0.47-0.93	.019
≥493			0.63	0.38-1.04	.070
Total PUFAs, g	NA	NA			
<8.94			1.00		
8.94-14.2			0.77	0.50-1.18	.225
14.3-21.7			0.86	0.56-1.33	.496
≥21.8			0.72	0.47-1.11	.136
Linoleic acid, g					
<7.74			1.00		
7.74-12.3	12-14		0.74	0.48-1.15	.225
12.4-19.0	12-14	12-17	0.87	0.57-1.34	.496
≥19.1			0.68	0.44-1.04	.136
α-Linolenic acid					
<0.75			1.00		
0.75-1.20	1.1-1.6	1.1-1.6	0.98	0.69-1.38	.893
1.21-1.88	1.1-1.6	1.1-1.6	0.95	0.63-1.44	.814
≥1.89			0.70	0.48-1.03	.068
Total saturated fatty acids, g		Minimal			
<15.6			1.00		
15.6-23.7	20		1.00	0.64-1.56	.998
23.8-35.1			1.24	0.80-1.92	.332
≥35.2			1.00	0.60-1.64	.986

CAD, Coronary artery disease; *CI,* confidence interval; *OR,* odds ratio; *PAD,* peripheral arterial disease; *PUFA,* polyunsaturated fatty acid.
[a]Models adjusted for age, sex, hypertension, CAD, diabetes, and smoking. Six-year weight variable used for analysis.
[b]US Department of Health and Human Services, US Department of Agriculture; based on a 2000 calorie diet; ranges are female-male values.
[c]Based on criteria by Food and Nutrition Board, Institute of Medicine, National Academies, which incorporates Recommended Daily Allowances (RDAs) and Adequate Intakes; ranges are females-male values and for individuals aged ≥40 years.
[d]Statistical significance at $P < .05$.

intake and protection from PAD. Folate and vitamin B_6 consumption are predictors of PAD in men aged >50 years, independent of other cardiovascular risk factors.[21] The Health Professionals Follow-up Study also observed a relationship between folate and B_6 consumption and PAD risk.[22] In fact, a meta-analysis suggested that lowering homocysteine levels in patients with cardiovascular disease by 3 μmol/L would reduce the risk of cardiac events by 16%.[23]

The results of randomized trials have not been as encouraging, however. In the HOPE trial,[17] high-risk cardiovascular patients were randomized to treatment with combination therapy (folate, vitamin B_6, and B_{12}) or placebo. Despite reduction in homocysteine levels, there was no observed reduction in overall cardiovascular events. In fact, in the Norwegian Vitamin Trial (NORVIT),[24] supplementation with B vitamins actually *increased* the risk of cardiac events. It should be noted that these trials were specifically designed to evaluate *cardiac* outcomes, and PAD end points were not evaluated.

Our study evaluated the relationship to B-vitamin consumption and prevalence (OR) of PAD. We found that increased folate intake was associated with reduced odds of PAD in both unadjusted (OR, 0.62; $P < .001$) and adjusted (OR, 0.67; $P = .006$) analyses. Vitamin B_6 also showed positive associations in the unadjusted (OR, 0.68; $P < .001$) and adjusted models (OR, 0.71; $P = .023$). No significant trends were observed for vitamin B_{12}. Quartile analysis showed consumption at FDA-recommended levels of folate (344 to 492 μg/d: OR, 0.66; $P = .019$) and vitamin B_6 (1.08 to 1.58 mg/d, OR, 0.47; $P = .002$) conferred additional protective effect.

These results suggest that dietary intake of folate and vitamin B_6 may be beneficial in the prevention of PAD. However, the discrepancy between the findings of observational studies and randomized trial evidence in the cardiac literature should not be overlooked. Further trials evaluating the effect of B-vitamin supplementation on specific peripheral vascular outcomes are forthcoming.

Fiber. There is considerable observational evidence for the beneficial role of dietary fiber. The Edinburgh Artery study[13] found a positive association between cereal fiber intake and increased ABI measurements. A similar positive association between cereal fiber and increased ABI was seen in the Health Professional's Follow-up Study.[25] In addition, there is some suggestion that increased fiber consumption may exert anti-inflammatory effects. In a study using the 1999 to 2000 NHANES data, a strong association was seen between fiber intake and C-reactive protein levels.[26] Randomized trial evidence for fiber supplementation and PAD risk reduction is lacking.

Our study shows a strong protective effect of fiber consumption on PAD risk in both unadjusted (OR, 0.66; $P < .001$) and adjusted analyses (OR, 0.65; $P < .001$). There is some suggestion that higher levels of fiber intake have additional protective effect in quartile analysis (13.3 to 19.4 g/d: OR, 0.65; $P = .036$). It should be noted that the highest quartile of fiber consumption in the US population began at 19.5 gm/d, a value that is well below those suggested by the Dietary Health Guideline (28 g/d) and the Dietary Reference Intake (25 to 38 g/d).

Overall, it is difficult to isolate the specific effect of fiber supplementation. Food, such as cereal, that is high in fiber is also high in other nutrients, such as folate and vitamin E. With the use of the USDA Automated Multiple Pass Method used in this study, the effect of fiber alone could be evaluated in PAD risk reduction.

Dietary fat. Polyunsaturated fats (PUFA) can be classified as ω-3, commonly derived from fish oils, and ω-6, which is found in olive oils and in the Mediterranean diet. The primary role of PUFA in the reduction of cardiovascular risk is mainly due to an anti-inflammatory effect. Both ω-3 and ω-6 PUFAs participate in the arachidonic acid pathway and alter the ratio of prostaglandin and leukotriene production.[27] This anti-inflammatory effect has been experimentally shown to help stabilize atherosclerotic plaque and promote plaque repair.[28]

Dietary consumption of ω-3 fatty acid was supported by the FDA in 2006, when it released a qualified health claim that ω-3 PUFAs may reduce the risk of coronary heart disease. This statement was based on evidence from meta-analyses that showed the use of fish and fish oil supplements reduced cardiovascular events and overall mortality.[29] The protective effect seen in the Mediterranean diet is thought to come from ω-6 PUFA, especially in the form of olive oil. Olive oil has been shown to lower plasma cholesterol and serum low-density lipoprotein cholesterol, as well as have and anti-inflammatory effect.[30]

In our study we chose to represent ω-3 PUFA consumption with α-linolenic acid, and ω-6 PUFA with linoleic acid. In unadjusted population-level analysis, we found people with PAD had a reduced consumption of PUFAs (including α-linolenic and linoleic acids) and saturated fatty acids. This reflects a generally poor nutrition in participants with PAD. In unadjusted analysis, both PUFAs (OR, 0.68; $P < .001$) and saturated fatty acids (OR, 0.76; $P < .001$) conferred a protective effect against PAD. This observed *protective* effect of *saturated* fatty acids may be confounded with improved overall nutrition associated with improved caloric intake. In adjusted analysis, however, saturated fatty acid consumption did not show a protective effect (OR, 1.07; $P = .596$). Adjusted analyses did show a protective effect of ω-3 fatty acid (α-linolenic; OR, 0.79; $P = .028$), whereas ω-6 fatty acid (linoleic) did not (OR, 0.85; $P = .091$). No benefit was seen in higher levels of consumption of fatty acids in quartile analyses. These findings lend support to the FDA claim that a diet low in saturated fats and high in PUFAs (especially ω-3 fatty acids) may confer a protective effect against CAD and PAD.

Limitations. The use of the NHANES data set has allowed us to explore the relationship between the consumption of specific nutrients and the prevalence of PAD within the US population. By using survey data, we are able

to overcome the selection bias inherent in smaller group studies and extrapolate our findings to the dietary habits in the entire population.

The use of this type of data is not without limitations, however. Because the data are a cross-sectional observational representation, causality between nutrient consumption and the development of PAD cannot be determined. The data presented are also subject to the methodologic constraints posed by the conduct of NHANES and are themselves subject to selection bias because not all participants who were selected underwent the lower extremity examination or dietary analysis. Furthermore, a 24-hour dietary recall can be a restricted measure of overall nutrition and is subject to inaccuracies and recall bias. Finally, because of the large number of participants in the NHANES study, small differences in nutrient intake or small differences in ABI measurements can lead to statistical significance. It is incumbent on the reader to determine their relative clinical significance.

In our multivariate model, only traditional risk factors for PAD, including age, gender, CAD, diabetes, and smoking were included as covariates. This adjustment was done to determine the effect of nutrient intake independent of traditional cardiovascular risk factors. Certain variables were excluded from these models because we believed this would lead to over-adjustment and reduced discrimination. These factors include total caloric intake, body mass index (BMI), obesity, and race. Tables IV (online only) and V (online only) evaluate the effect of these variables on the model.

The prevalence of obesity and mean BMI is not statistically different between participants with or without PAD (Table I), so this factor was not included as a covariate. The effect of obesity or BMI may be confounded by other important factors, such as exercise, which are not well coded in the NHANES data set. Racial and socioeconomic effects were also not included in multivariate models (Tables IV, online only, and V, online only). The NHANES survey purposefully under-samples racial minorities based on their prevalence within the US population. We believe that true disparities may exist in racial and socioeconomic access to proper nutrition, and this may have an impact on PAD. However, this must be considered in a separate study designed to look for these differences.

Conclusive evidence for dietary supplementation in PAD must come from randomized trial evidence. Our findings suggest multiple nutrients must be supplemented to achieve a balanced nutritional approach. In a recently published small Spanish trial that used these methods,[31] 60 patients with PAD were randomly assigned to receive a supplement containing PUFAs, and vitamins A, B_6, D, and E. At 1 year, they were able to show significant improvements in serologic markers, walking distance, and ABI measurement. We believe in the validity of this approach and encourage larger clinical trials to be performed in the United States.

CONCLUSIONS

Despite these limitations, we believe our data give strong observational evidence to the role of nutrition in the prevalence of PAD. We found that in adjusted models, antioxidants (vitamins A, C, and E), B vitamins (folate and B_6), and fiber intake were associated with a protective effect going beyond that explained by traditional cardiovascular risk factors. In addition, a diet low in saturated fats and high in ω-3 fatty acids may also confer a protective effect against PAD. Among the 16.5 million Americans with PAD, our study showed extremely poor dietary habits, with average levels of nutritional intake far below the FDA suggested dietary guidelines. This allows for considerable dietary improvement on a nationwide scale.

AUTHOR CONTRIBUTIONS

Conception and design: JL, CM, KL, TC, DH, SG
Analysis and interpretation: JL, CM
Data collection: JL, CM
Writing the article: JL, CM, KL, TC, DH, SG
Critical revision of the article: JL, CM, KL, TC, DH, SG
Final approval of the article: JL
Statistical analysis: CM
Obtained funding: JL, DH, SG
Overall responsibility: JL

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Table IV. (online only). Additional adjusted bivariate logistic regression analysis for body mass index, kilocalories, and race[a]

	Body mass index (kg/m^2)			*Kilocalories*			*Race*		
Nutrients[b]	*OR of PAD*	*95% CI*	P[c]	*OR of PAD*	*95% CI*	P[c]	*OR of PAD*	*95% CI*	P[c]
Vitamin A	0.76	0.59-0.98	0.032	0.75	0.56-1.00	0.053	0.76	0.59-0.97	.025
Vitamin C	0.81	0.71-0.94	0.004	0.87	0.75-1.01	0.068	0.86	0.75-0.99	.030
Vitamin E	0.81	0.58-1.13	0.209	0.92	0.64-1.34	0.675	0.88	0.66-1.18	.390
Vitamin B_6	0.70	0.47-1.04	0.075	0.74	0.48-1.14	0.168	0.74	0.53-1.03	.077
Vitamin B_{12}	0.96	0.74-1.25	0.757	0.97	0.65-1.44	0.873	0.92	0.66-1.28	.631
Fiber	0.61	0.44-0.84	0.003	0.70	0.51-0.95	0.022	0.71	0.56-0.91	.007
Folate	0.61	0.41-0.89	0.011	0.63	0.44-0.91	0.014	0.66	0.49-0.89	.006
Total PUFA	0.84	0.60-1.17	0.304	0.93	0.68-1.29	0.681	0.87	0.67-1.13	.299
Linoleic acid	0.85	0.61-1.18	0.331	0.95	0.70-1.30	0.767	0.89	0.69-1.14	.346
α-Linolenic acid	0.85	0.60-1.20	0.353	0.83	0.57-1.21	0.332	0.81	0.61-1.07	.144
Total saturated fatty acids	0.95	0.66-1.35	0.759	1.37	0.83-2.28	0.218	1.03	0.75-1.42	.864

CI, Confidence interval; *OR,* odds ratio; *PAD,* peripheral arterial disease; *PUFA,* polyunsaturated fatty acids.
[a]All models adjusted for age, gender, hypertension, diabetes, and smoking. Six-year weight variable used for analysis.
[b]See Table III for intake levels of the various nutrients.
[c]Statistical significance at $P < .05$.

Table V. (online only). Additional adjusted bivariate logistic regression analysis for obesity, kilocalories, and race[a]

	Obesity (≥30 kg/m^2)			*Kilocalories*			*Race*		
Nutrients[b]	*OR of PAD*	*95% CI*	P[c]	*OR of PAD*	*95% CI*	P[c]	*OR of PAD*	*95% CI*	P[c]
Vitamin A	0.76	0.60-0.97	.024	0.75	0.56-1.00	.053	0.76	0.59-0.97	.025
Vitamin C	0.86	0.75-0.98	.026	0.87	0.75-1.01	.068	0.86	0.75-0.99	.030
Vitamin E	0.88	0.65-1.18	.379	0.92	0.64-1.34	.675	0.88	0.66-1.18	.390
Vitamin B_6	0.74	0.53-1.03	.072	0.74	0.48-1.14	.168	0.74	0.53-1.03	.077
Vitamin B_{12}	0.92	0.67-1.28	.631	0.97	0.65-1.44	.873	0.92	0.66-1.28	.631
Fiber	0.71	0.56-0.90	.005	0.70	0.51-0.95	.022	0.71	0.56-0.91	.007
Folate	0.66	0.49-0.88	.005	0.63	0.44-0.91	.014	0.66	0.49-0.89	.006
Total PUFA	0.87	0.67-1.13	.296	0.93	0.68-1.29	.681	0.87	0.67-1.13	.299
Linoleic acid	0.88	0.69-1.14	.340	0.95	0.70-1.30	.767	0.89	0.69-1.14	.346
α-Linolenic acid	0.81	0.62-1.07	.134	0.83	0.57-1.21	.332	0.81	0.61-1.07	.144
Total saturated fatty acids	1.04	0.75-1.43	.833	1.37	0.83-2.28	.218	1.03	0.75-1.42	.864

CI, Confidence interval; *OR,* odds ratio; *PAD,* peripheral arterial disease; *PUFA,* polyunsaturated fatty acids.
[a]All models adjusted for age, gender, hypertension, diabetes, and smoking. Six-year weight variable used for analysis.
[b]See Table III for intake levels of the various nutrients.
[c]Statistical significance at $P < .05$.