Greater Fish, Fruit, and Vegetable Intakes Are Related to Lower Incidence of Venous Thromboembolism

The Longitudinal Investigation of Thromboembolism Etiology

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Background—Little is known about the role of dietary intake in the development of deep vein thrombosis or pulmonary embolus (venous thromboembolism [VTE]). Homocysteine, factor VIII, and von Willebrand factor levels, risk factors for VTE, are influenced by dietary intake. We tested the hypothesis that foods rich in B vitamins and ω-3 fatty acids are negatively associated and meat intake is positively associated with incidence of VTE.

Methods and Results—In a prospective study over 12 years, 14 962 middle-aged adults participating in the Atherosclerosis Risk in Communities study were followed up for incident VTE. All hospitalizations were identified, and 196 VTEs were validated by chart review. A food frequency questionnaire assessed dietary intake at baseline and year 6. In separate proportional hazards regression analyses, risk of developing VTE was computed across quintiles of selected nutrients, major food groups, and the Western diet pattern, with adjustment for demographic and lifestyle factors, body mass index, and diabetes. Hazard ratios and 95% confidence intervals of VTE incidence across quintiles of fruit and vegetable intake were 1.0 (reference), 0.73 (0.48 to 1.11), 0.57 (0.37 to 0.90), 0.47 (0.29 to 0.77), and 0.59 (0.36 to 0.99) ($P_{trend}=0.03$). Eating fish 1 or more times per week was associated with 30% to 45% lower incidence of VTE for quintiles 2 to 5 compared with quintile 1, suggestive of a threshold effect. Hazard ratios of VTE across quintiles of red and processed meat intake were 1.0, 1.24 (0.78 to 1.98), 1.21 (0.74 to 1.98), 1.09 (0.64 to 1.87), and 2.01 (1.15 to 3.53) ($P_{trend}=0.02$). Hazard ratios were attenuated only slightly after adjustment for factors VIIc and VIIIc and von Willebrand factor.

Conclusions—A diet including more plant food and fish and less red and processed meat is associated with a lower incidence of VTE. **(*Circulation*. 2007;115:188-195.)**

Key Words: diet ■ epidemiology ■ fish ■ folate ■ fruit and vegetables ■ venous thromboembolism ■ vitamin B6

Little is known about the role of dietary intake in the development of venous thromboembolism (VTE); thus, there are no dietary recommendations for VTE. Homocysteine,[1] factor VIII coagulant activity (FVIIIc), and von Willebrand factor (vWF), putative risk factors for VTE,[1–3] are affected by dietary intake.[4–9] Supplemental folic acid, alone or in combination with vitamin B_{12} and vitamin B_6, as well as foods rich in these vitamins, including fruit, vegetables, and cereal, reduce homocysteine levels.[4–6] Levels of FVIIIc[7] and vWF,[8] coagulation factors that also relate to blood viscosity and vascular function, may be influenced by dietary intake.[7–9] Recently, plasma levels of coagulation factor VII (FVIIc)[3] and fibrin fragment D-dimer[10] have been suggested as risk factors for VTE and may be responsive to dietary fat[7] or vitamin B intake.[11]

Clinical Perspective p 195

In Norway, the rate of postoperative thrombosis emboli decreased considerably during World War II (1940–1944), although the rate increased again after 1944.[12] During this same period, food rationing changed food consumption patterns.[13] With food rationing, consumption of cholesterol, total fat, and calories decreased because of a reduced intake of meat, whole milk, cream, margarine, cheese, eggs, and fruit, whereas intake increased for fish, cod liver oil, skimmed milk, whole grain bread, potatoes, and fresh vegetables, thus increasing intakes of ω-3 fatty acids, vitamin B_6, and folate.[13] These ecological data provide a hypothesis that changes in dietary pattern beneficially influenced coagulation balance, resulting in a lower VTE rate.

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Although folate and vitamins B_6 and B_{12} reduce homocysteine levels and ω-3 fatty acids improve vascular function, it is unknown whether dietary intake of these nutrients is related to risk of developing VTE. Furthermore, the relations of foods and dietary patterns with risk of developing VTE are even less well understood. We therefore examined the relations of (1) nutrients (folate, vitamins B_6 and B_{12}, and ω-3 and saturated fatty acids); (2) foods rich in these nutrients; and (3) dietary patterns with incidence of VTE in a prospective study of middle-aged black and white men and women. We hypothesized a priori that foods rich in B vitamins and ω-3 fatty acids are negatively associated and intakes of saturated fatty acid and meat are positively associated with incidence of VTE.

Methods

Study Design and Population

The Longitudinal Investigation of Thromboembolism Etiology (LITE) is a prospective study of VTE occurrence in 2 population-based cohorts: the Atherosclerosis Risk in Communities (ARIC) study and the Cardiovascular Health Study.[3,14] Similar methods were used in data collection for both studies; however, different instruments were used to assess dietary intake, and thus it was not feasible to pool the diet data from the 2 studies. For this report, we used data from the ARIC cohort only. ARIC examined 15 792 45- to 64-year-old black and white male and female residents recruited in between 1987 and 1989 from Forsyth County, North Carolina; the city of Jackson, Miss; selected suburbs of Minneapolis, Minn; and Washington County, Maryland.[15]

Data Collection

The institutional review boards of the 4 participating centers approved this study. Study participants underwent a comprehensive baseline examination for cardiovascular disease risk factors and up to 3 triennial reexaminations.[15] Height and weight were measured. Fasting blood specimens were collected, centrifuged at 4°C, and frozen at −70°C until analysis in a central laboratory. FVIIc, FVIIIc, and vWF levels were measured at baseline.[16] Body mass index (BMI) was calculated as weight in kilograms divided by the square of standing height in meters. Diabetes status (yes or no) was defined at baseline as fasting glucose ≥126 mg/dL,[17] nonfasting glucose ≥200 mg/dL, or a history of or treatment for diabetes. Information was obtained about vitamin supplement intake.

Usual dietary intake was assessed with the use of the Willett 66-item semiquantitative food frequency questionnaire, interviewer-administered at baseline and 6 years later (examination 3).[18] For each food, participants were asked to report the frequency of consumption in 9 categories, ranging from never or less than once per month to ≥6 times per day. Interviewers obtained additional information, including the brand name breakfast cereal usually consumed. Data were analyzed for selected nutrient and food intakes. Nutrients in these analyses included folate, vitamins B_6 and B_{12}, fiber, and saturated and ω-3 fatty acids.

Foods were grouped into whole grain, refined grain, fruit and vegetables, dairy, fish, and red and processed meat. The whole and refined grain groups were formed according to previously developed procedures.[19,20] Food items classified as whole grain were dark bread and whole grain cold breakfast cereal, in which whole grain cold cereals contained at least 25% whole grain or bran by weight. Food items classified as refined grain included cold breakfast cereal with <25% whole grain or bran, cooked cereal (oatmeal, cream of wheat, and cream of rice, which were queried in a single item, could not be separated), white bread, bagels, doughnuts, pastry, muffins, biscuits, cookies, cake, brownies, pasta, and rice (brown rice and wild rice were not separately queried). The fruit and vegetable food group comprised 6 fruit categories (fresh apples or pears; oranges; orange or grapefruit juice; peaches, apricots, or plums; bananas; and other fruit) and 12 vegetable categories (green beans; broccoli; cabbage, cauliflower, or brussel sprouts; carrots; corn; spinach, collards, or other greens; peas or lima beans; dark yellow or winter squash; sweet potatoes; beans or lentils; tomatoes; and potatoes, not including french fries), which were listed on the food frequency questionnaire. Small amounts of vegetables included in mixed dishes were not recorded.

Case Ascertainment

Study participants were followed for VTE (deep vein thrombosis [DVT] or pulmonary embolism) end points through December 31, 2001, via annual telephone calls and surveillance of community hospitals.[3,14] For all hospitalizations, *International Classification of Diseases, Ninth Revision, Clinical Modification* discharge codes were recorded and used to abstract medical records for possible VTE. Medical records were reviewed by 2 physicians, VTE events were classified independently, and differences were resolved through discussion. VTE required objective evidence from imaging or autopsy. DVT was nearly always defined as a positive duplex ultrasound or venogram or rarely, in the earliest years, by a positive Doppler ultrasound or impedance plethysmography. Pulmonary embolism nearly always was defined by a ventilation-perfusion scan with multiple segmental or subsegmental mismatched defects or a positive pulmonary angiogram or computed tomographic scan.

Statistical Analysis

Of the 15 792 ARIC participants, we excluded from the analyses those with prevalent VTE at baseline (n=236), use of warfarin at baseline (n=73), or cancer-related incident VTE (n=72). We further excluded 26 individuals with missing dietary information and 375 individuals with energy intake <500 and <700 kcal for women and men, respectively, or >3500 and >4500 kcal for women and men, respectively. These cut points approximate the lower and upper 1% distribution of energy intake. Forty-eight individuals were excluded because they were not white or black, leaving 14 962, including 2482 black and 5771 white women and 1531 black and 5178 white men.

All analyses were conducted with the use of the statistical software package SAS, version 8.0 (SAS Institute, Cary, NC). Follow-up time was calculated as time from baseline to incident VTE, death, last follow-up contact, or through December 31, 2001, whichever occurred first. For participants with no VTE before examination 3 (year 6 of follow-up), we averaged diet data from examination 1 and examination 3.[21] Those with VTE by examination 3 were censored. Nutrient and food intakes between examinations 1 and 3 were moderately correlated with Spearman r values ranging from 0.49 to 0.56 ($P<0.001$). When well-known within-person variation in response to diet questionnaires of the food frequency questionnaire type is considered, the correlations suggest considerable tracking (lack of change over time), although they could also represent some change in diet over 6 years.[21] From 32 food subgroups, principal components analysis was performed, which yielded scores for 2 diet patterns, which we labeled as prudent (healthy) and Western.[22] The Western diet pattern was characterized by a diet rich in red and processed meat, fast food, and high-fat dairy products and low in fish, fruit, and vegetables; the opposite characterized the prudent diet pattern.

The selected nutrients, food groups, and diet pattern scores were categorized into quintiles of intake. Means or proportions were computed to describe baseline characteristics of participants. Cox proportional hazards regression analyses were used to estimate the hazard ratio for developing VTE across quintiles of intake of (1) nutrients (folate, vitamins B_6 and B_{12}, and saturated and ω-3 fatty acids); (2) food groups (whole grains, refined grains, fruit and vegetables, dairy, red and processed meat, and fish); and (3) diet pattern scores (prudent or healthy and Western patterns). To consider whether collinearity might be a problem in the statistical models, Spearman correlations were calculated. Spearman correlations between the food groups ranged from −0.28 (meat versus fruit/vegetables) and 0.27 (fish versus fruit/vegetables) and between −0.32 (saturated fat and folate) and 0.58 (folate and vitamin B_6) for nutrients. We concluded that collinearity was not an issue.

TABLE 1. Mean (SE) or Prevalence of Baseline Characteristics Across Quintiles of Fruit and Vegetable Intake Among ARIC Study Participants, 1987–1989 (N=14 962)

	Quintiles of Fruit and Vegetable Intake					
Characteristic	1	2	3	4	5	*P*
Demographic factors						
Age, y	53.3 (0.11)	53.9 (0.11)	54.2 (0.10)	54.4 (0.10)	54.8 (0.11)	<0.001
Women, %	46	52	56	59	62	<0.001
Blacks, %	32	26	25	23	28	0.17
Education, >high school, %	37	43	45	47	48	<0.001
Current smokers, %	36	29	24	21	21	<0.001
Clinical characteristics*						
BMI, kg/m^2	27.5 (0.10)	27.5 (0.10)	27.6 (0.09)	27.9 (0.09)	27.9 (0.10)	<0.001
Overweight/obese (BMI ≥25), %	65	65	67	69	67	<0.001
Waist circumference, cm	96.8 (0.25)	96.6 (0.25)	96.6 (0.25)	97.0 (0.25)	97.4 (0.25)	<0.001
Diabetes status, %	9	10	12	14	14	<0.001
FVIIc, % standard	120.1 (0.53)	117.9 (0.53)	119.0 (0.53)	119.5 (0.53)	118.9 (0.53)	0.62
FVIIIc, % standard	132.1 (0.70)	130.1 (0.69)	131.0 (0.69)	132.0 (0.69)	130.3 (0.70)	0.36
vWF, % standard	117.6 (0.86)	117.8 (0.84)	116.9 (0.84)	118.5 (0.84)	117.6 (0.85)	0.40
Daily nutrient intake†						
Energy intake, kcal	1318 (10)	1496 (10)	1595 (10)	1747 (10)	1982 (10)	<0.001
Total fat, g	63.9 (0.23)	62.6 (0.23)	61.1 (0.22)	58.6 (0.23)	53.6 (0.24)	<0.001
Saturated fat, g	23.7 (0.10)	23.2 (010)	22.4 (0.10)	21.3 (0.10)	19.3 (0.10)	<0.001
ω-3 fatty acids, g	0.18 (0.004)	0.21 (0.005)	0.25 (0.005)	0.27 (0.005)	0.35 (0.005)	<0.001
Protein, g	66.6 (0.31)	69.0 (0.30)	71.6 (0.30)	72.8 (0.30)	76.5 (0.31)	<0.001
Fiber, g	11.7 (0.10)	14.3 (0.09)	16.6 (0.09)	19.1 (0.09)	24.3 (0.10)	<0.001
Folate, μg	162.1 (1.33)	199.4 (1.29)	222.7 (1.28)	252.9 (1.29)	307.2 (1.34)	<0.001
Vitamin B_6, mg	1.35 (0.008)	1.54 (0.008)	1.69 (0.008)	1.85 (0.008)	2.13 (0.008)	<0.001
Vitamin B_{12}, μg	7.07 (0.07)	7.45 (0.07)	7.67 (0.07)	7.87 (0.07)	8.26 (0.07)	<0.001
Food intake (servings per day)†						
Whole grain	0.95 (0.02)	1.11 (0.02)	1.24 (0.02)	1.4 (0.02)	1.5 (0.02)	<0.001
Refined grain	2.8 (0.03)	2.7 (0.02)	2.4 (0.02)	2.3 (0.02)	1.8 (0.03)	<0.001
Fruit and vegetables	2.0 (0.03)	3.0 (0.02)	3.8 (0.02)	4.8 (0.02)	6.7 (0.03)	<0.001
Fish	0.21 (0.005)	0.24 (0.005)	0.28 (0.005)	0.31 (0.005)	0.40 (0.005)	<0.001
Dairy	1.6 (0.02)	1.6 (0.02)	1.6 (0.02)	1.7 (0.02)	1.7 (0.02)	<0.001
Red and processed meat	1.22 (0.01)	1.15 (0.01)	1.08 (0.01)	1.00 (0.01)	0.84 (0.01)	<0.001

*Adjusted for age, gender, race, and field center.
†Adjusted for age, gender, race, field center, and energy intake.

Regression models were adjusted for age (continuous), race (black, white), gender (male, female), energy intake (continuous), vitamin supplement use (any, none), BMI (continuous), diabetes (yes, no), and other dietary factors (continuous; see table footnotes for details). To determine whether associations of dietary factors with incident VTE might be mediated by FVIIc, FVIIIc, or vWF, we further adjusted for these potential explanatory factors in a supplemental model. Test for linear trend across increasing quintiles of dietary intake was performed with the use of the continuous variable of nutrient, food, or diet score as the level of exposure.

All authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Over an average 12.5 years of follow-up, 197 incident non–cancer-related VTE events were validated among ARIC study participants. At baseline (Table 1), the average age of study participants was 54 years. The average BMI was 27.7, 67.7% were overweight or obese, and 11.7% had diabetes. Mean intake of folate was below the recommended daily intake of 400 μg for US adults, but intakes of vitamins B_6 and B_{12} were above the recommended levels of 1.5 to 1.7 mg and 2.4 μg, respectively. Men and women consumed an average of 4.3 servings per day of fruit and vegetables, which is below the recommended number of servings per day. Mean intake of red and processed meat was 1.1 servings per day, and daily fish intake was 0.25 servings.

Relations Between Dietary Intake and Incident VTE

Nutrient Intake

Incidence of VTE was 34% to 51% lower among individuals consuming ≥160 μg of folate per day (quintiles 2 to 5) than

TABLE 2. Hazard Ratios of VTE Across Quintiles of Nutrient Intake Among ARIC Study Participants, 1987–2001 (N=14 962)

	Quintiles of Daily Nutrient Intake					
	1	2	3	4	5	P_{trend}
Folate, μg/d						
Quintile ranges	<160	160–206	206–249	249–310	>310	
No. of cases	57	34	40	32	34	
HR (95% CI)	1.0	0.58 (0.37–0.91)	0.66 (0.41–1.05)	0.49 (0.28–0.86)	0.49 (0.24–1.02)	0.06
Vitamin B_6, mg/d						
Quintile ranges	<1.25	1.25–1.57	1.57–1.86	1.86–2.26	>2.26	
No. of cases	54	40	38	33	32	
HR (95% CI)	1.0	0.66 (0.43–1.02)	0.57 (0.35–0.93)	0.44 (0.25–0.78)	0.37 (0.17–0.80)	0.007
ω-3 Fatty acids, g/d						
Quintile ranges	<0.1	0.1–0.16	0.16–0.24	0.24–0.39	>0.39	
No. of cases	57	32	38	31	39	
HR (95% CI)	1.0	0.56 (0.36–0.87)	0.64 (0.42–0.99)	0.54 (0.34–0.85)	0.70 (0.43–1.13)	0.37
Saturated fatty acids, g/d						
Quintile ranges	<13.5	13.5–17.7	17.7–22.0	22.0–28.1	>28.1	
No. of cases	38	48	30	46	35	
HR (95% CI)	1.0	1.29 (0.81–2.06)	0.84 (0.46–1.51)	1.40 (0.72–2.73)	1.14 (0.43–3.00)	0.78

Adjusted for age, race, gender, field center, energy intake, vitamin supplement use, BMI, diabetes, and the other nutrients in the table.

HR indicates hazard ratio.

among those consuming <160 μg per day (P_{trend}=0.06) (Table 2). There was a decreasing dose-response relation between vitamin B_6 and VTE incidence (P_{trend}=0.007), with the hazard ratio for the highest versus lowest quintile being 0.37 (95% CI, 0.17 to 0.80). For ω-3 fatty acid intake, the pattern suggests a threshold of 30% to 46% lower risk of VTE in quintiles 2 to 5 compared with quintile 1, with the 95% CIs excluding 1 in quintiles 2 to 4 but including 1 in quintile 5. A linear trend was tested but was not significant (P=0.37). VTE was not related to intakes of fatty acids (Table 2) or vitamin B_{12} (data not shown).

Food Intake

Compared with eating <2.5 servings per day of fruit and vegetables, eating ≥2.5 servings per day was associated with a 27% to 53% lower risk of VTE (P_{trend}=0.03) (Table 3). Eating ≥0.1 serving of fish per day (or ≥1 serving per week for quintiles 2 to 5) was associated with 30% to 45% lower risk of VTE than eating <0.1 servings of fish per day, suggestive of a threshold pattern effect but not a linear trend (P_{trend}=0.30). Intakes of dairy and refined grain (data not shown) and whole grain were not related to VTE risk. Individuals consuming >1.5 servings of red and processed meat per day had 2 times higher risk of developing VTE than those consuming <0.5 servings per day (P_{trend}=0.02).

Dietary Patterns

With prudent diet scores above the first quintile, there was a nonsignificant 28% to 38% lower risk of VTE across quintiles 2 to 5, again suggestive of a threshold pattern effect but not a linear trend (P_{trend}=0.12) (Table 4). Participants in the highest quintile of Western diet score had a 60% higher risk of VTE than those in the bottom quintile (P_{trend}=0.04).

Other Analyses

Adjustment for additional standard cardiovascular risk factors, including smoking, physical activity, and alcohol intake for all participants and hormone replacement therapy for women, did not change the associations between dietary intake and risk of VTE.[23] Further adjustment for FVIIc, FVIIIc, and vWF in the models in Tables 2 to 4 only slightly attenuated associations (data not shown). Results were also similar after we excluded from analysis VTE events with obvious precipitants (eg, surgery, trauma, recent hospitalization, or severe immobility[14]) to isolate idiopathic VTE (n=111) (data not shown).

Discussion

In this prospective study of black and white middle-aged adults, consumption of ≥4 servings of fruit and vegetables per day or at least 1 serving of fish per week was associated with lower incidence of VTE. In a comparison of the highest quintile of intake with the lowest, red and processed meat and a Western diet pattern were positively associated with incident VTE. To support these food findings, nutrient intakes of vitamin B_6, folate, and ω-3 fatty acids were inversely related to VTE, although the shape of the relation for folate and ω-3 fatty acids was that of a threshold pattern, whereas a dose-response relation was observed for vitamin B_6. Vitamin B_{12} and saturated fatty acids were not related to VTE risk. HRs were only slightly attenuated after adjustment for FVIIc, FVIIIc, and vWF.

TABLE 3. Hazard Ratios of VTE Across Quintiles of Fruit and Vegetable, Whole Grain, Fish, and Meat Intake Among ARIC Study Participants, 1987–2001 (N=14 962)

	Quintiles of Daily Food Intake					
	1	2	3	4	5	P_{trend}
Fruit and vegetables, servings/d						
Quintile ranges	<2.5	2.5–3.5	3.5–4.5	4.5–5.8	>5.8	
No. of cases	56	41	35	28	37	
HR (95% CI)	1.0	0.73 (0.48–1.11)	0.57 (0.37–0.90)	0.47 (0.29–0.77)	0.59 (0.36–0.99)	0.03
Whole grain, servings/d						
Quintile ranges	<0.4	0.4–0.8	0.8–1.25	1.25–2.0	>2.0	
No. of cases	37	46	33	48	33	
HR (95% CI)	1.0	1.13 (0.73–1.75)	0.87 (0.54–1.41)	1.23 (0.79–1.93)	0.89 (0.54–1.46)	0.69
Fish, servings/d						
Quintile ranges	<0.1	0.1–0.14	0.15–0.25	0.25–0.43	>0.43	
No. of cases	57	32	38	31	39	
HR (95% CI)	1.0	0.58 (0.37–0.90)	0.60 (0.39–0.92)	0.55 (0.35–0.88)	0.70 (0.44–1.10)	0.30
Red and processed meat, servings/d						
Quintile ranges	<0.5	0.5–0.75	0.75–1.0	1.0–1.5	>1.5	
No. of cases	33	41	39	34	50	
HR (95% CI)	1.0	1.24 (0.78–1.98)	1.21 (0.74–1.98)	1.09 (0.64–1.87)	2.01 (1.15–3.53)	0.02

Adjusted for age, race, gender, field center, energy intake, vitamin supplement use, BMI, diabetes, and the other food groups in the table.

HR indicates hazard ratio.

Because we are not aware of studies of dietary intake and VTE risk, we draw on "Virchow's triad"[24] to explain our study results. In 1856, Virchow hypothesized that venous thrombosis was the result of an increase in blood coagulability, stasis, and damage to the wall of the vein.[24] Although genetics may play a particular role in coagulation, all 3 factors may also be influenced by environment, such as dietary intake. We address the role of diet in coagulation and venous stasis, but not vessel wall injury, because few published data are available.

Most attention on nutrient factors and VTE has related to homocysteine as a risk factor.[1,25,26] Our findings of lower VTE risk with increasing dietary intake of vitamin B_6, folate, and foods rich in these nutrients are consistent with homocysteine as a risk factor for VTE.[26,27] Surprisingly, whole grain foods, good sources of folate and vitamin B_6, were not related to VTE risk. Homocysteinemia may result from low levels of folic acid, vitamin B_6, and vitamin B_{12}.[4–6,26,28–30] In a case-control study in which plasma nutrients were measured after DVT and compared with controls, folate, and pyridoxal-5′-phosphate, the coenzyme form of vitamin B_6, were significantly and inversely associated with DVT.[27] The relation between folate and DVT was attenuated when homocysteine was added to the model; pyridoxal-5′-phosphate, however, remained inversely associated with risk of DVT independent of homocysteine and folate.[27] In clinical trials, levels of homocysteine among healthy adults[4–6,30] and VTE pa-

TABLE 4. Hazard Ratios of VTE Across Quintiles of Prudent and Western Dietary Pattern Scores Among ARIC Study Participants, 1987–2001 (N=14 962)

	Quintiles of Diet Pattern Score					
	1	2	3	4	5	P_{trend}
Prudent Diet Pattern Score						
Quintile ranges	<−0.7	−0.7– −0.3	−0.3–0.03	0.03–0.5	>0.5	
No. of cases	49	37	39	35	37	
HR (95% CI)	1.0	0.72 (0.47–1.11)	0.69 (0.45–1.07)	0.62 (0.39–0.97)	0.69 (0.44–1.09)	0.12
Western Diet Pattern Score						
Quartile ranges	<−0.8	−0.8–−0.4	−0.4– −0.1	0.1–0.7	>0.7	
No. of cases	40	35	36	37	49	
HR (95% CI)	1.0	0.84 (0.53–1.33)	0.93 (0.59–1.48)	1.00 (0.62–1.62)	1.60 (0.97–2.66)	0.04

Adjusted for age, race, gender, field center, energy intake, vitamin supplement use, BMI, and diabetes.

HR indicates hazard ratio.

tients[30] declined with vitamin supplementation of folate alone, folate in combination with vitamins B_6 and B_{12}, or foods rich in these nutrients. Randomized clinical trials using supplementation with folic acid or folic acid in combination with vitamins B_6 and B_{12} also reduced plasma D-dimer,[31] a strong risk marker for incident VTE.[10] However, in a recent randomized trial, vitamin supplementation of folate with vitamins B_6 and B_{12} was not effective in reducing the risk of recurrent VTE.[32] Unlike vitamin supplements as used in the trial,[32] consuming a dietary pattern of foods rich in folate and vitamin B_6, such as fish, chicken, whole grains, potatoes, carrots, legumes, and bananas, also provides other nutrients and food compounds that may promote vascular health and prevent the occurrence of VTE events. There likely is a synergistic effect among foods and their nutritive and nonnutritive components, in which the sum of the diet's constituent parts has greater health effects than the individual effects of single foods or nutrients.[33]

Elevated FVIIc, FVIIIc, and vWF, which are related to increased risk of VTE incidence,[3,34] and elevated FVIIIc, which is related to recurrence,[34] may be influenced by dietary intake.[7,8,35–40] In a randomized clinical trial comparing the effectiveness of a Mediterranean-type diet, a diet rich in olive oil, fish, and fruit and vegetables, with a high-saturated-fat diet in lowering hemostatic factors, levels of FVIIc and FVIIIc were reduced in men consuming the Mediterranean-type diet but not in those consuming the high-saturated-fat diet.[7] Plasma vWF was significantly reduced in men with atherosclerosis who consumed a lipid-lowering diet (low in total, saturated, and monounsaturated fat but high in polyunsaturated fat) compared with men who had been following their normal diet for 3 years.[8] Shahar et al[9] reported an inverse cross-sectional relation of ω-3 fatty acids and fish intake with blood levels of FVIIIc and vWF in ARIC. Links between dietary fat and coagulation factors tend to support our study findings that greater intakes of ω-3 fatty acids and fish are inversely related to incident VTE, and meat intake is positively related to VTE risk. However, because adjustment for FVIIc, FVIIIc, and vWF did not affect the association between diet and VTE, we could not confirm their role as intermediaries between dietary intake and VTE.

In addition to the B vitamins and ω-3 fatty acids found in foods, it is feasible that the biologically active nutrients and food compounds in fruit, vegetables, and fish act singularly or synergistically to enhance some aspects of health.[33] When we examined the relations of 2 diet patterns, representing combinations of foods, with risk of incident VTE, we found that a high score (quintile 5) on the Western diet pattern, characterized by high intake of red and processed meat, fast food, and refined grain and low intakes of fish, fruit, and vegetables, had a 60% greater risk of incident VTE than a lower score (quintile 1). Similarly, prudent diet pattern scores in quintiles 2 to 5 were associated with lower risk of VTE, suggestive of a threshold effect, even though the linear trend was not statistically significant.

An important limitation to consider when our results are interpreted is the use of a food frequency questionnaire containing only 66 items, thus restricting the number of food categories to characterize usual dietary intake, which likely results in underestimated energy intake. Dietary intake may be misclassified by this questionnaire, contributing to measurement error in the point estimates that may potentially result in large biases either toward or away from the null.[41] Furthermore, the completeness of reported food intake, and therefore energy intake, may differ according to level of BMI; however, the statistical models were adjusted for BMI. An additional limitation to our study was that homocysteine was not measured on the entire cohort. Finally, although our data support reduced risk with greater intakes of folate, vitamin B_6, ω-3 fatty acids, fruit and vegetables, and fish, the reader should interpret the shape of the relationships with caution because our study lacked precision to establish whether the relations have threshold or dose-response shapes.

A major strength of this investigation is that it is the first prospective study on diet and VTE. It had a large number of white and black men and women enrolled and 12.5 years of follow-up. Another strength is the second diet interview that updated dietary information in the regression models, because food choices and frequency may change over time.[21] The use of repeated measurements of diet may reduce measurement error due to intraindividual variation in dietary intake. We adjusted for several VTE risk factors, but it is possible that there was residual confounding by unaccounted for factors that are associated with both diet and VTE.

In conclusion, before the present study, there has been no study of food in relation to prevalent, incident, or recurrent VTE. One randomized clinical trial, currently reported only in abstract form,[32] found no association between B vitamin supplementation and recurrent VTE. Nevertheless, a causal relationship between diet and VTE is suggested by 2 separate ecological studies from Norway, one showing a lower rate of VTE occurrence during World War II,[12] the other showing that dietary patterns changed with food rationing during this same time period.[13] Our hypothesis of a relationship between diet and VTE is also consistent with results from several randomized clinical trials and feeding studies demonstrating lower levels of putative risk factors for VTE with dietary intervention.[5–8,35–40] Our findings provide evidence that a diet including abundant plant food and fish and little meat is associated with lower risk of incident VTE. Potential prevention strategies for VTE may include eating a healthy diet consistent with the US Department of Agriculture *Dietary Guidelines for Americans*.[42]

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Disclosures

None.

References

1. den Heijer M, Lewington S, Clarke R. Homocysteine, MTHFR and risk of venous thrombosis: a meta-analysis of published epidemiological studies. *J Thromb Haemost*. 2005;3:292–299.
2. Martinelli I. von Willebrand factor and factor VIII as risk factors for arterial and venous thrombosis. *Sem Hematol*. 2005;42:49–55.
3. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Tracy RP, Aleksic N. Folsom AR. Coagulation factors, inflammation markers, and venous thromboembolism: the Longitudinal Investigation of Thromboembolism Etiology (LITE). *Am J Med*. 2002;113:636–642.
4. Homocysteine Lowering Trialists' Collaboration. Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomized trials. *BMJ*. 1998;316:894–898.
5. Tucker KL, Olson B, Bakun P, Dallal GE, Selhub J, Rosenberg IH. Breakfast cereal fortified with folic acid, vitamin B-6, and vitamin B-12 increases vitamin concentrations and reduces homocysteine concentrations: a randomized trial. *Am J Clin Nutr*. 2004;79:805–811.
6. Jacques PF, Selhub J, Bostom AG, Wilson PW, Rosenberg IH. The effect of folic acid fortification on plasma folate and total homocysteine concentrations. *N Engl J Med*. 1999;340:1449–1454.
7. Mezzano D, Leighton F, Martinez C, Marshall G, Cuevas A, Castillo O, Panes O, Munoz B, Perez DD, Mizon C, Rozowski J, San Martin A, Pereira J. Complementary effects of Mediterranean diet and moderate red wine intake on haemostatic cardiovascular risk factors. *Eur J Clin Nutr*. 2001;55:444–451.
8. Blann AD, Jackson P, Bath PM, Watts GF. von Willebrand factor, a possible indicator of endothelial cell damage, decreases during long-term compliance with a lipid-lowering diet. *J Intern Med*. 1995; 237:557–561.
9. Shahar E, Folsom AR, Wu KK, Dennis BH, Shimakawa T, Conlan MG, Davis CE, Williams OD. Associations of fish intake and dietary n-3 polyunsaturated fatty acids with a hypocoagulable profile: the Atherosclerosis Risk in Communities (ARIC) Study. *Arterioscler Thromb*. 1993;13:1205–1212.
10. Cushman M, Folsom AR, Wang L, Aleksic N, Rosamond WD, Tracy RP, Heckbert SR. Fibrin fragment D-dimer and the risk of future venous thrombosis. *Blood*. 2003;101:1243–1248.
11. Mangoni AA, Arya R, Ford E, Asonganyi B, Sherwood RA, Ouldred E, Swift CG, Jackson SH. Effects of folic acid supplementation on inflammatory and thrombogenic markers in chronic smokers: a randomised controlled trial. *Thromb Res*. 2003;110:13–17.
12. Jensen RA. Postoperative thrombosis-emboli. *Acta Chir Scand*. 1952; 103:263–278.
13. Strom A. Examination into the diet of Norwegian families during the war-years 1942–45. *Acta Med Scand Suppl*. 1948;214:1–47.
14. Cushman M, Tsai AW, White RH, Heckbert SR, Rosamond WD, Enright P, Folsom AR. Deep vein thrombosis and pulmonary embolism in two cohorts: the Longitudinal Investigation of Thromboembolism Etiology. *Am J Med*. 2004;117:19–25.
15. ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) study: design and objectives. *Am J Epidemiol*. 1989;129: 687–702.
16. Folsom AR, Wu KK, Rosamond WD, Sharrett AR, Chambless LE. Prospective study of hemostatic factors and incidence of coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation*. 1997;96:1102–1108.
17. Alberti K, Zimmet P. Definition, diagnosis and classification of diabetes mellitus and its complications, part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998;15:539–553.
18. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH, Speizer FE. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol*. 1985;122: 51–65.
19. Jacobs DR, Meyer KA, Kushi LH, Folsom AR. Whole-grain intake may reduce the risk of ischemic heart disease death in postmenopausal women: the Iowa Women's Health Study. *Am J Clin Nutr*. 1998;68: 248–257.
20. Steffen LM, Jacobs DR, Stevens J, Shahar E, Carithers T, Folsom AR. Associations of whole grain, refined grain, and fruit and vegetable consumption with all-cause mortality, incident coronary heart disease and ischemic stroke: the ARIC study. *Am J Clin Nutr*. 2003;78: 383–390.
21. Hu FB, Stampfer MJ, Rimm E, Ascherio A, Rosner BA, Spiegelman D, Willett WC. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. *Am J Epidemiol*. 1999;149:531–540.
22. Dunteman GH. *Principal Components Analysis*. Newbury Park, Calif: Sage Publications; 1989.
23. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: the Longitudinal Investigation of Thromboembolism Etiology. *Arch Intern Med*. 2002;162:1182–1189.
24. Virchow R. Neuer fall von todlichen: emboli der lungenarterie. *Arch Pathol Anat*. 1856;10:225–228.
25. Tsai AW, Cushman M, Tsai MY, Heckbert SR, Rosamond WD, Aleksic N, Yanez ND, Psaty BM, Folsom AR. Serum homocysteine, thermolabile variant of methylene tetrahydrofolate reductase (MTHFR), and venous thromboembolism: Longitudinal Investigation of Thromboembolism Etiology (LITE). *Am J Hematol*. 2003;72: 192–200.
26. Gemmati D, Previati M, Serino ML, Moratelli S, Guerra S, Capitani S, Forini E, Ballerini G, Scapoli GL. Low folate levels and thermolabile methylenetetrahydrofolate reductase as primary determinant of mild hyperhomocystinemia in normal and thromboembolic subjects. *Arterioscler Thromb Vasc Biol*. 1999;19:1761–1767.
27. Cattaneo M, Lombardi R, Lecchi A, Bucciarelli P, Mannucci PM. Low plasma levels of vitamin B6 are independently associated with a heightened risk of deep-vein thrombosis. *Circulation*. 2001;104: 2442–2446.
28. Alfthan G, Laurinen MS, Valsta LM, Pastinen T, Aro A. Folate intake, plasma folate and homocysteine status in a random Finnish population. *Eur J Clin Nutr*. 2003;57:81–88.
29. Quinlivan EP, Gregory JF III. Effect of food fortification on folic acid intake in the United States. *Am J Clin Nutr*. 2003;77:221–225.
30. den Heijer M, Brouwer IA, Bos GM, Blom HJ, van der Put NM, Spaans AP, Rosendaal FR, Thomas CM, Haak HL, Wijermans PW, Gerrits WB. Vitamin supplementation reduces blood homocysteine levels: a controlled trial in patients with venous thrombosis and healthy volunteers. *Arterioscler Thromb Vasc Biol*. 1998;18:356–361.
31. Klerk M, Verhoef P, Verbruggen B, Schouten EG, Blom HJ, Bos GM, den Heijer M. Effect of homocysteine reduction by B-vitamin supplementation on markers of clotting activation. *Thromb Haemost*. 2002;88:230–235.
32. Bos GMJ, Heijer den M, Willems H, Blom H, Gerrits W, Cattaneo M, Eichinger S, Rosendaal F. Homocysteine lowering by B vitamins and the secondary prevention of deep-vein thrombosis and pulmonary embolism: a first randomised, placebo-controlled, double-blind trial. *Blood*. 2004;104:A489.
33. Jacobs DR, Steffen LM. Nutrients, foods, and dietary patterns as exposures in research: issues and challenges. *Am J Clin Nutr*. 2003; 78(suppl):508S–513S.
34. Kraaijenhagen RA, in't Anker PS, Koopman MM, Reitsma PH, Prins MH, van den Ende A, Buller HR. High plasma concentration of factor VIIIc is a major risk for venous thromboembolism. *Thromb Haemost*. 2000;83:5–9.
35. Sandstrom B, Marckmann P, Jespersen J. Fat consumption and factor VII coagulant activity. In: Somogyi JC, Biró GY, Hötzel D, eds. *Nutrition and Cardiovascular Risks: 29th Symposium of the Group of European Nutritionists, Balatonföldvár, April 24-26, 1991 (Forum of Nutrition/Bibliotheca Nutritio Et Dieta).* Basel, Switzerland: Karger; 1992:93–101.
36. Mitropoulos KA, Miller GJ, Martin JC, Reeves BEA, Cooper J. Dietary fat induces changes in factor VII coagulant activity through effects on plasma free stearic acid concentration. *Arterioscler Thromb*. 1994;14:214–222.
37. Miller GJ. Dietary fatty acids and the haemostatic system. *Atherosclerosis*. 2005;179:213–227.
38. Marckmann P, Sandstrom B, Jespersen J. Effects of total fat content and fatty acid composition in diet on factor VII coagulant activity and blood lipids. *Atherosclerosis*. 1990;80:227–233.

39. Miller GJ, Martin JC, Mitropoulos KA, Reeves BE, Thompson RL, Meade TW, Cooper JA, Cruickshank JK. Plasma factor VII is activated by postprandial triglyceridaemia, irrespective of dietary fat composition. *Atherosclerosis*. 1991;86:163–171.
40. Mennen LI, Witteman JC, den Breeijen JH, Schouten EG, de Jong PT, Hofman A, Grobbee DE. The association of dietary fat and fiber with coagulation factor VII in the elderly: the Rotterdam Study. *Am J Clin Nutr*. 1997;65:732–736.
41. Kipnis V, Subar AF, Midthune D, Freedman LS, Ballard-Barbash R, Troiano RP, Bingham S, Schoeller DA, Schatzkin A, Carroll RJ. Structure of dietary measurement error: results of the OPEN biomarker study. *Am J Epidemiol*. 2003;158:14–21.
42. US Department of Agriculture, Center for Nutrition Policy and Promotion. *2005 Dietary Guidelines for Americans*. 6th ed. Available at: http://www.usda.gov/cnpp/DG2005/index.html. Accessed May 16, 2006.

CLINICAL PERSPECTIVE

Little is known about the role of dietary intake on the development of deep vein thrombosis or pulmonary embolus (venous thromboembolism [VTE]). Suspicion of a role is raised because elevated homocysteine, factor VIII, and von Willebrand factor are risk factors for VTE and are influenced by dietary intake. In a prospective study of almost 15 000 middle-aged adults, we observed a 41% lower risk of incident VTE among those eating >5.5 servings of fruit and vegetables per day and a 30% to 45% lower risk with 1 or more servings per week of fish. Adults who ate >1.5 servings per day of red and processed meat had twice the risk of developing VTE of those who ate <0.5 serving per day. The dietary pattern associated with lower risk of VTE in this study is similar to that suggested for reduced arterial disease by the American Heart Association 2006 Diet Recommendations. Such a diet may reduce the risk of VTE.

Greater Fish, Fruit, and Vegetable Intakes Are Related to Lower Incidence of Venous Thromboembolism: The Longitudinal Investigation of Thromboembolism Etiology

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