

# 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  $\omega$ -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) ( $P_{\text{trend}}=0.03$ ). 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) ( $P_{\text{trend}}=0.02$ ). 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,<sup>1</sup> factor VIII coagulant activity (FVIIIc), and von Willebrand factor (vWF), putative risk factors for VTE,<sup>1-3</sup> are affected by dietary intake.<sup>4-9</sup> Supplemental folic acid, alone or in combination with vitamin B<sub>12</sub> and vitamin B<sub>6</sub>, as well as foods rich in these vitamins, including fruit, vegetables, and cereal, reduce homocysteine levels.<sup>4-6</sup> Levels of FVIIIc<sup>7</sup> and vWF,<sup>8</sup> coagulation factors that also relate to blood viscosity and vascular function, may be influenced by dietary intake.<sup>7-9</sup> Recently, plasma levels of coagulation factor VII (FVIIc)<sup>3</sup> and fibrin fragment D-dimer<sup>10</sup> have been suggested as risk factors for VTE and may be responsive to dietary fat<sup>7</sup> or vitamin B intake.<sup>11</sup>

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In Norway, the rate of postoperative thrombosis emboli decreased considerably during World War II (1940–1944), although the rate increased again after 1944.<sup>12</sup> During this same period, food rationing changed food consumption patterns.<sup>13</sup> 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  $\omega$ -3 fatty acids, vitamin B<sub>6</sub>, and folate.<sup>13</sup> 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<sub>6</sub> and B<sub>12</sub> reduce homocysteine levels and  $\omega$ -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<sub>6</sub> and B<sub>12</sub>, and  $\omega$ -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  $\omega$ -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.<sup>3,14</sup> 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.<sup>15</sup>

### 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.<sup>15</sup> 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.<sup>16</sup> 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  $\geq$ 126 mg/dL,<sup>17</sup> nonfasting glucose  $\geq$ 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).<sup>18</sup> 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  $\geq$ 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<sub>6</sub> and B<sub>12</sub>, fiber, and saturated and  $\omega$ -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.<sup>19,20</sup> 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.<sup>3,14</sup> 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.<sup>21</sup> 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.<sup>21</sup> From 32 food subgroups, principal components analysis was performed, which yielded scores for 2 diet patterns, which we labeled as prudent (healthy) and Western.<sup>22</sup> 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<sub>6</sub> and B<sub>12</sub>, and saturated and  $\omega$ -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<sub>6</sub>) 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)**

Characteristic	Quintiles of Fruit and Vegetable Intake					P
	1	2	3	4	5	
<b>Demographic factors</b>						
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
<b>Clinical characteristics*</b>						
BMI, kg/m <sup>2</sup>	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
FVIc, % standard	120.1 (0.53)	117.9 (0.53)	119.0 (0.53)	119.5 (0.53)	118.9 (0.53)	0.62
FVIIC, % 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
<b>Daily nutrient intake†</b>						
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 (0.10)	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 <sub>6</sub> , 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 <sub>12</sub> , μg	7.07 (0.07)	7.45 (0.07)	7.67 (0.07)	7.87 (0.07)	8.26 (0.07)	<0.001
<b>Food intake (servings per day)†</b>						
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 FVIc, FVIIC, 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<sub>6</sub> and B<sub>12</sub> 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					<i>P</i> <sub>trend</sub>
	1	2	3	4	5	
<b>Folate, <math>\mu\text{g}/\text{d}</math></b>						
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
<b>Vitamin B<sub>6</sub>, mg/d</b>						
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
<b><math>\omega</math>-3 Fatty acids, g/d</b>						
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
<b>Saturated fatty acids, g/d</b>						
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  $\mu\text{g}$  per day ( $P_{\text{trend}}=0.06$ ) (Table 2). There was a decreasing dose-response relation between vitamin B<sub>6</sub> and VTE incidence ( $P_{\text{trend}}=0.007$ ), with the hazard ratio for the highest versus lowest quintile being 0.37 (95% CI, 0.17 to 0.80). For  $\omega$ -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<sub>12</sub> (data not shown).

### Food Intake

Compared with eating <2.5 servings per day of fruit and vegetables, eating  $\geq 2.5$  servings per day was associated with a 27% to 53% lower risk of VTE ( $P_{\text{trend}}=0.03$ ) (Table 3). Eating  $\geq 0.1$  serving of fish per day (or  $\geq 1$  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 ( $P_{\text{trend}}=0.30$ ). 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 ( $P_{\text{trend}}=0.02$ ).

### 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 ( $P_{\text{trend}}=0.12$ ) (Table 4). Participants in the

highest quintile of Western diet score had a 60% higher risk of VTE than those in the bottom quintile ( $P_{\text{trend}}=0.04$ ).

### 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.<sup>23</sup> 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<sup>14</sup>) to isolate idiopathic VTE (n=111) (data not shown).

### Discussion

In this prospective study of black and white middle-aged adults, consumption of  $\geq 4$  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<sub>6</sub>, folate, and  $\omega$ -3 fatty acids were inversely related to VTE, although the shape of the relation for folate and  $\omega$ -3 fatty acids was that of a threshold pattern, whereas a dose-response relation was observed for vitamin B<sub>6</sub>. Vitamin B<sub>12</sub> 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					<i>P</i> <sub>trend</sub>
	1	2	3	4	5	
<b>Fruit and vegetables, servings/d</b>						
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
<b>Whole grain, servings/d</b>						
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
<b>Fish, servings/d</b>						
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
<b>Red and processed meat, servings/d</b>						
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”<sup>24</sup> 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.<sup>24</sup> 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.<sup>1,25,26</sup> Our findings of lower VTE risk with increasing dietary intake of vitamin B<sub>6</sub>, folate, and foods rich in these nutrients are consistent

with homocysteine as a risk factor for VTE.<sup>26,27</sup> Surprisingly, whole grain foods, good sources of folate and vitamin B<sub>6</sub>, were not related to VTE risk. Homocysteinemia may result from low levels of folic acid, vitamin B<sub>6</sub>, and vitamin B<sub>12</sub>.<sup>4–6,26,28–30</sup> 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<sub>6</sub>, were significantly and inversely associated with DVT.<sup>27</sup> 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.<sup>27</sup> In clinical trials, levels of homocysteine among healthy adults<sup>4–6,30</sup> 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					<i>P</i> <sub>trend</sub>
	1	2	3	4	5	
<b>Prudent Diet Pattern Score</b>						
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
<b>Western Diet Pattern Score</b>						
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<sup>30</sup> declined with vitamin supplementation of folate alone, folate in combination with vitamins B<sub>6</sub> and B<sub>12</sub>, or foods rich in these nutrients. Randomized clinical trials using supplementation with folic acid or folic acid in combination with vitamins B<sub>6</sub> and B<sub>12</sub> also reduced plasma D-dimer,<sup>31</sup> a strong risk marker for incident VTE.<sup>10</sup> However, in a recent randomized trial, vitamin supplementation of folate with vitamins B<sub>6</sub> and B<sub>12</sub> was not effective in reducing the risk of recurrent VTE.<sup>32</sup> Unlike vitamin supplements as used in the trial,<sup>32</sup> consuming a dietary pattern of foods rich in folate and vitamin B<sub>6</sub>, 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.<sup>33</sup>

Elevated FVIIc, FVIIIc, and vWF, which are related to increased risk of VTE incidence,<sup>3,34</sup> and elevated FVIIIc, which is related to recurrence,<sup>34</sup> may be influenced by dietary intake.<sup>7,8,35–40</sup> 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.<sup>7</sup> 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.<sup>8</sup> Shahar et al<sup>9</sup> reported an inverse cross-sectional relation of  $\omega$ -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  $\omega$ -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  $\omega$ -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.<sup>33</sup> 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.<sup>41</sup> 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<sub>6</sub>,  $\omega$ -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.<sup>21</sup> 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,<sup>32</sup> 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,<sup>12</sup> the other showing that dietary patterns changed with food rationing during this same time period.<sup>13</sup> 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.<sup>5–8,35–40</sup> 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*.<sup>42</sup>

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## Disclosures

None.

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### 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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