Colloquium: Homocyst(e)ine, Vitamins and Arterial Occlusive Diseases

Relationship between Plasma Homocysteine, Vitamin Status and Extracranial Carotid-Artery Stenosis in the Framingham Study Population[1,2]

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ABSTRACT Recent studies demonstrated associations between occlusive vascular disease and hyperhomocysteinemia of both genetic and nutritional origin. In the present study we analyzed plasma samples from the 20th biannual examination of the Framingham Heart Study cohort to determine distribution of plasma homocysteine concentrations with emphasis on relationships to B vitamins and prevalence of carotid artery stenosis. Results showed that homocysteine exhibited strong inverse association with plasma folate and weaker associations with plasma vitamin B-12 and pyridoxal-5'-phosphate (PLP). Homocysteine was also inversely associated with intakes of folate and vitamin B-6, but not vitamin B-12. Prevalence of high homocysteine (>14 μmol/l) was 29.3% in this cohort, and inadequate plasma concentrations of one or more B vitamins appear to contribute to 67% of the cases of high homocysteine. Prevalence of stenosis ≥25% was 43% in men and 34% in women with an odds ratio of 2.0 for individuals in the highest homocysteine quartile (≥14.4 μmol/l) compared with those in the lowest quartile (≤9.1 μmol/l), after adjustment for sex, age, high density lipoprotein cholesterol, systolic blood pressure and cigarette smoking ($P_{trend} < 0.001$). Plasma concentrations of folate and pyridoxal-5'-phosphate and folate intake were inversely associated with extracranial carotid stenosis after adjustment for age, sex and other risk factors. J. Nutr. 126: 1258S–1265S, 1996.

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• *homocysteine* • *folic acid* • *pyridoxal phosphate* • *vitamin B-6* • *vitamin B-12* • *arteriosclerosis*

Almost 25 years ago McCully (1969) reported that a child dying of homocystinuria, cystathionuria and methylmalonic aciduria, secondary to abnormality of cobalamin metabolism, exhibited arterial lesions that were strikingly similar to those seen in patients with cystathionine beta synthase deficiency. These observations led to the proposal that the markedly elevated plasma homocysteine concentrations found in persons with homocystinuria were responsible for the development of premature occlusive vascular disease. In recent years this association between plasma homocysteine concentration and atherosclerosis has become the subject of a number of studies with growing clinical inter-

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est (for reviews see Mudd et al. 1989, Ueland and Refsum 1989, Ueland et al. 1992). A literature survey by Ueland et al. (1992) identified a total of 21 studies involving over 1500 patients with occlusive (cardiovascular, peripheral and cerebrovascular) vascular disease and over 1500 respective controls. Sixteen of these studies reported significantly higher mean plasma homocysteine concentrations in patients than in respective controls ($P < 0.05$ to <0.001). The mean patient: control homocysteine ratio according to this survey was 1.31, which indicates that the elevation of homocysteine in these patients is mild and certainly not as severe as that seen in homocystinuric patients.

Clarke et al. (1991), who relied on the methionine loading test to discriminate between (mildly) hyperhomocysteinemic and normal individuals, reported that the prevalence of hyperhomocysteinemia was 42% among patients with cerebral vascular disease, 28% among patients with peripheral vascular disease and 30% among patients with cardiovascular disease. They observed the risk of premature occlusive vascular disease to be about 30 times greater for people with hyperhomocysteinemia relative to normal controls. A recent prospective investigation of participants in the Physicians' Health Study showed that the risk of myocardial infarction within 5 years for individuals with no prior history of vascular disease was 3.4-fold greater for those with elevated plasma homocysteine concentrations than for those with normal plasma homocysteine levels (Stampfer et al. 1992). The association between homocysteine and vascular disease in this study and in earlier studies (Clarke et al. 1991, Genest et al. 1990) was independent of other known vascular disease risk factors, such as age, diabetes, hypertension, body mass index, total and high density lipoprotein (HDL) cholesterol. In addition, carotid ultrasound has previously been used to examine the association between homocysteine and arteriosclerosis. Obligate heterozygotes for cystathionine β-synthase deficiency were shown to have a greater prevalence of carotid arteriosclerosis than normal controls (Rubba et al. 1990), and postmethionine load plasma homocysteine levels were associated with asymptomatic carotid arteriosclerosis in a combined sample of obligate heterozygotes for cystathionine β-synthase deficiency and a similar number of controls (Clarke et al. 1992). A third study of asymptomatic individuals in a middle-aged, population-based cohort demonstrated that those with carotid artery wall thickness above the 90th percentile of the population distribution had significantly higher fasting plasma homocysteine levels than controls with carotid wall thickness below the 75th percentile (Malinow et al. 1993).

This paper is a summary of our studies (Selhub et al. 1993, Selhub et al. 1995) on the elderly survivors of the Framingham Study cohort. We examined, in this elderly population, the distribution of plasma homocysteine levels, the relationship between plasma homocysteine concentration and plasma and intake levels of folate, vitamin B-12 and vitamin B-6 and the relation between carotid stenosis and plasma concentrations of homocysteine, folate, vitamin B-12 and pyridoxal-5'-phosphate.

MATERIALS AND METHODS

Subjects. Participants were members of the original Framingham Heart Study cohort, a population-based sample of 5209 men and women originally examined in 1948–1952 (Dawber et al. 1957) and followed prospectively to the present to assess the occurrence of vascular disease. This study was based on 1401 survivors of the original cohort who participated in the 20th biennial examination (1989–1990). Homocysteine and carotid ultrasound measures were available for 1041 individuals (418 men and 623 women), aged 67–96 y old at the time of data collection. Informed consent was obtained from all participants. The protocols for this study were approved by the Human Investigations Review Committee at New England Medical Center and by the Institutional Review Board for Human Research at Boston University Medical Center.

Biochemical determinations. Blood was drawn nonfasting and plasma total cholesterol and HDL cholesterol were determined in the Framingham Heart Study laboratory using enzymatic methods (McNamara and Schaefer 1987, Warnick et al. 1982). Low density lipoprotein cholesterol was not determined because the blood samples were taken in a nonfasting state. Plasma samples stored frozen at −80°C were used for the determination of total homocysteine by the method of Araki and Sako (1987), plasma folate by a microbial assay using a 96-well plate and manganese supplementation as described by Tamura et al. (1990), vitamin B-12 using a (Magic) radioassay kit from Ciba-Corning (Medfield, MA) and pyridoxal-5'-phosphate by the tyrosine decarboxylase method as described by Camp et al. (1983). Because of insufficient plasma volume, vitamin measures were not available for all subjects.

Nutrient intake. Members of the Framingham cohort received a semiquantitative food frequency questionnaire (Willett et al. 1985) by mail when they were scheduled for their 20th biennial examination. Subjects returned the completed questionnaire at the time of their examination. Estimated folate and vitamin B-6 intakes corresponded well to the respective folate and PLP plasma concentrations. Vitamin B-12 intake was not, however, correlated to plasma vitamin B-12 (Jacques et al. 1993, Willet et al. 1985).

Measurement of carotid stenosis. At the 20th biennial examination, participants underwent a carotid doppler examination with Ultrasonix, high resolution, real-time scanner equipped with a 7.5-MHz imaging transducer, a 4-MHz pulse wave Doppler transducer

and a 4-MHz continuous wave transducer. For this report, we classified individuals into two categories based on the maximum percent diameter stenosis of the more diseased artery: 0–24% stenosis or 25–100% stenosis.

Statistical methods. To describe the associations between plasma homocysteine concentrations and the B vitamins, we grouped subjects into deciles of plasma vitamin concentration and vitamin intake. We calculated the geometric mean plasma homocysteine concentrations in each vitamin decile and plotted these values and their 95% confidence intervals (CI) at the median vitamin level within each decile. We adjusted mean homocysteine levels for age, sex and concentration or intake of the other B vitamins by analysis of covariance (Kleinbaum et al. 1988) with all covariates set to their respective sample means. We also adjusted all vitamin intakes for energy (Willett 1990).

To examine the association between the occurrence of high plasma homocysteine concentrations and these vitamins, we defined high homocysteine as concentrations >14.0 μmol/l (the 90th percentile for homocysteine among those subjects whose three plasma vitamins levels were above the 70th percentile). We developed a B vitamin index to describe the joint relationships of the three vitamins included in these analyses to homocysteine levels. The indices had five categories based on percentile values for each nutrient. We classified individuals with all three vitamins above the 70th percentile into the reference category (Category 1). Category 2 included individuals with all three vitamins above the 50th but at least one below the 70th percentiles; Category 3 included those with at least one vitamin above and one vitamin below the 50th percentile; Category 4 included those with all three vitamins below the 50th percentile but at least one above the 30th percentile; and Category 5 included individuals with all vitamins below the 30th percentile. We determined mean homocysteine concentration, the prevalence of high homocysteine, the prevalence rate ratio for high homocysteine and attributable proportion (attributable risk percent) (Rothman 1986) within each vitamin index category. We also estimated population attributable proportion, which represents the proportion of cases with high homocysteine in the population that can be attributed to low plasma vitamin concentrations or vitamin intake.

To graphically describe the relation of homocysteine to stenosis, we classified men and women into quartiles of homocysteine concentration. Within each quartile, we computed the prevalence of carotid stenosis ≥25% and plotted the prevalence estimates at the sex-specific median homocysteine concentration for that quartile. To adjust for other risk factors for carotid stenosis, logistic regression was used with stenosis ≥25% as the dependent variable. Homocysteine quartiles were modeled by using indicator variables to represent the three highest quartiles, and relative risk of stenosis for each quartile compared with the lowest quartile was estimated as the odds ratio derived as the antilogarithm of the logistic regression coefficients. To examine the association between the nutritional determinants of plasma homocysteine and stenosis, we also divided subjects into quartiles for each vitamin measure and represented them in the regression models as indicator variables using the highest plasma vitamin quartile as the reference category to estimate the relative risk of lower nutrient levels. If not otherwise noted, statistical significance refers to $P < 0.05$.

RESULTS

Homocysteine distribution and prevalence of high homocysteine concentrations

The mean homocysteine concentration for all subjects was 11.9 μmol/l (median = 11.6 μmol/l). Values ranged from 3.5 to 66.9 μmol/l. Homocysteine concentration was higher in men than in women and increased with age (**Table 1**). The increase with age remained highly significant ($P < 0.001$) for men and women after adjustment for plasma vitamin concentrations, but the difference between men and women was no longer statistically significant.

We defined high homocysteine as concentrations greater than the 90th percentile among subjects with all plasma vitamin levels greater than the 70th percentile (14.0 μmol/l). Prevalence of high homocysteine was 29.3% for the entire cohort and over 40% for individuals aged 80 years and older.

Mean homocysteine concentration by vitamin status and intake

Folate. Mean plasma homocysteine concentrations for subjects in the two lowest deciles of plasma folate (below 4.8 nmol/l) were 15.6 and 13.7 μmol/l. These were significantly greater than the mean for subjects in the highest decile, which was 11.0 μmol/l ($P < 0.01$) (**Fig. 1a**). Mean homocysteine concentrations for subjects in the three lowest deciles of folate intake (<253 μg/d) were 13.7, 12.9 and 13.2 μmol/l, respectively, and were significantly greater than the mean for subjects in the highest intake decile, which was 10.4 μmol/l ($P < 0.01$) (**Fig. 2a**).

Vitamin B-12. Mean homocysteine concentrations were significantly elevated for subjects in the lowest decile for vitamin B-12 relative to subjects in the highest decile ($P < 0.01$). Mean homocysteine concentrations were 15.4 and 10.9 μmol/l for subjects in the lowest and highest vitamin B-12 deciles (Fig. 1b). Subjects in the lowest vitamin B-12 decile had vitamin B-12 concentrations below 139 pmol/l. Vitamin B-12 intake appeared unrelated to mean homocysteine concentration even though subjects in the fifth decile had

TABLE 1

Mean homocysteine and B vitamin status and intake by age and sex

Sex	Age	n	Homocysteine	Homocysteine	Plasma concentrations			Nutrient intake/ 4200 kJ		
					Folate	Vitamin B-12	PLP	Folate	Vitamin B-12	Vitamin B-6
	y		*μmol/l*	*% elevated*	*nmol/l*	*pmol/l*	*nmol/l*	*μg*	*μg*	*mg*
Men	67–74	239	11.8	25.3	9.3	265	52.6	174	3.7	1.4
	75–79	110	11.9	26.7	9.5	260	49.6	180	3.8	1.3
	80+	108	14.1	48.3	10.0	255	47.6	204	4.8	1.4
P (for trend by age)		—	<0.001	<0.001	0.41	0.62	0.36	0.02	0.02	0.81
Women	67–74	310	10.7	19.5	10.4	302	59.9	214	4.0	1.6
	75–79	204	11.9	28.9	10.2	289	52.2	220	4.4	1.5
	80+	189	13.2	41.4	9.7	290	52.1	199	4.9	1.5
P (for trend by age)			<0.001	<0.001	0.60	0.47	0.13	0.23	0.03	0.55
P (sex)	—		<0.003	<0.09	0.19	0.001	0.08	<0.001	0.07	0.02

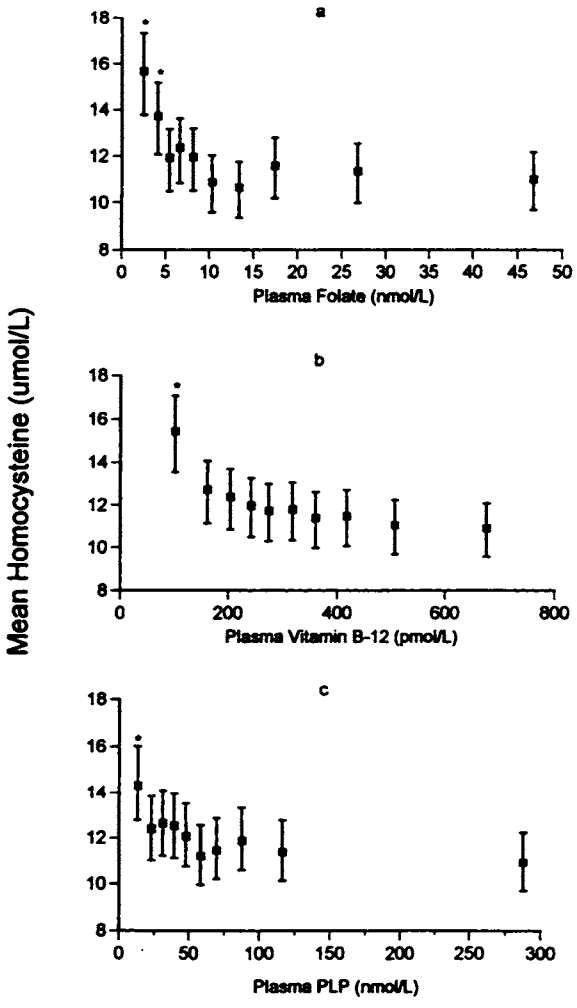

FIGURE 1 Mean plasma homocysteine concentrations (and 95% CI) by deciles of plasma folate (*a*), vitamin B-12 (*b*) and PLP (*c*) concentrations. Means are adjusted for age, sex and other plasma vitamins. *Significantly different from mean in the highest decile, $P < 0.01$.

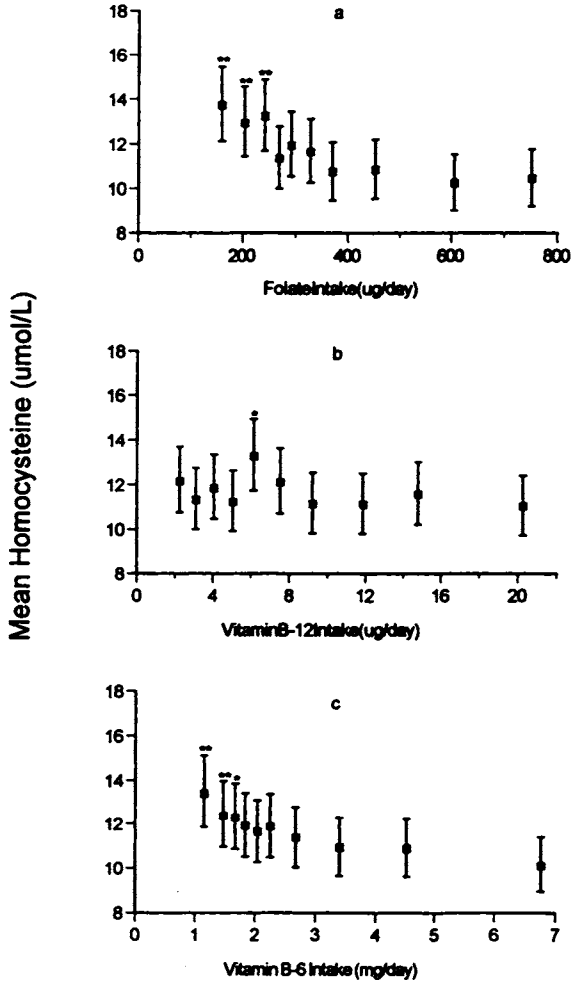

FIGURE 2 Mean plasma homocysteine concentrations (and 95% CI) by deciles of intake of folate (*a*), vitamin B-6 (*b*) and vitamin B-12 (*c*). Means are adjusted for age, sex and other vitamin intakes. *Significantly different from mean in the highest decile, $P < 0.05$; **significantly different from mean in the highest decile, $P < 0.01$.

TABLE 2

Elevated homocysteine concentrations by B vitamin status

B vitamin index[1]		*n*	Mean homocysteine	Prevalence	Prevalence rate ratio	Attributable	Population attributable
			μmol/l	%		%	%
Highest	1	89	9.4	10.1	1	0.0	0.0
	2	128	9.8	12.5	1.2	19.2	1.0
	3	534	11.9*	28.7*	2.8	64.8	33.7
	4	144	14.9*	52.1*	5.2	80.6	20.6
Lowest	5	70	16.5*	58.6*	5.8	82.8	11.6
						(total)	66.9

[1] Index combines plasma folate, vitamin B-12 and pyridoxal-5'-phosphate (PLP) concentrations: High (1) = all three B vitamins > 70th percentile; 2 = all vitamins > 50th, at least 1 < 70th percentile; 3 = vitamins above and below the 50th percentile; 4 = all vitamins < 50th percentile, at least 1 > 30th percentile; low (5) = all three vitamins < 30th percentile.

* Significantly different from Category 1, $P < 0.01$.

significantly higher homocysteine concentrations than subjects in the highest decile ($P < 0.05$) (Fig. 2b).

Vitamin B-6. Mean homocysteine concentrations were significantly elevated for subjects in the lowest decile for PLP relative to subjects in the highest decile for this vitamin ($P < 0.01$). Mean homocysteine concentrations were 14.3 and 10.9 μmol/l for subjects in the lowest and highest PLP deciles (Fig. 1c). Subjects in the lowest decile had PLP concentrations below 18.1 nmol/l. For vitamin B-6 intake, mean homocysteine concentrations were significantly elevated in the lowest two deciles ($P < 0.01$) and the third decile ($P < 0.05$). Mean homocysteine concentrations were 13.4, 12.4 and 12.3 μmol/l for subjects in the lowest three deciles; the mean in the highest decile was 10.1 μmol/l (Fig. 2c). Subjects in the lowest three intake deciles reported consuming less than 1.75 mg/d.

Homocysteine concentrations by overall vitamin status

Mean homocysteine and the prevalence of high homocysteine increased dramatically across categories of the B vitamin index (**Table 2**). Mean homocysteine concentration was 75 and 55% greater in the lowest relative to the highest index category for the plasma index. The prevalence of high homocysteine was almost sixfold greater among subjects in the lowest index category compared with subjects in the highest category for plasma index. Sixty-seven percent of the cases of high homocysteine in this cohort of older subjects were associated with at least one vitamin concentration below the 70th percentile. Although the prevalence of high homocysteine was substantially greater in lower vitamin categories (4 and 5) than in the middle category, this latter category contributed the largest share of cases of high homocysteine for the index because it included the largest proportion of the cohort.

Relationship between plasma homocysteine and prevalence of extracranial stenosis

The prevalence of extracranial carotid stenosis ≥25% was approximately 43 and 34% in men and women, respectively. **Figure 3** shows the age-adjusted prevalence of stenosis across quartiles of plasma homocysteine levels. In men, the prevalence of stenosis ≥25% was 27% (95% CI: 17–38%) in the lowest homocysteine quartile and 58% (95% CI: 49–67%) in the highest quartiles ($P_{trend} < 0.001$). The relation in women was not as striking as that in men; prevalence of stenosis ≥25% ranged from 31% (95% CI: 24–38%) to 39% (95% CI: 31–47%) across homocysteine quartiles ($P_{trend} = 0.03$). Although the risk of stenosis appeared to increase in the second homocysteine quartile (9.1–11.3 μmol/l) among men, it did not appear

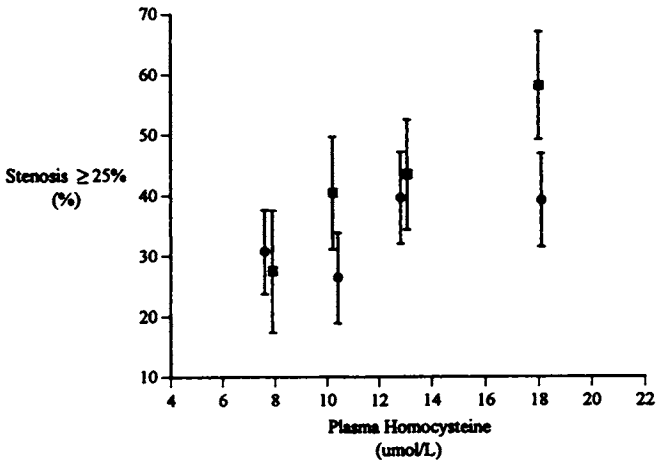

FIGURE 3 Age-adjusted prevalence and 95% CI of maximum extracranial carotid artery diameter stenosis ≥25% by quartile of plasma homocysteine concentration in men (■) and women (●). Homocysteine quartile cutoff values were 9.1, 11.3 and 14.3 μmol/l. Test for linear trend: $P < 0.001$ for men; $P = 0.03$ for women.

TABLE 3

Odds ratio of maximal extracranial carotid artery diameter stenosis ≥25% by quartile of plasma homocysteine concentration

Homocysteine quartile	Age and sex adjusted			Multiple risk factor adjustment[1]		
	Odds ratio	95% CI[2]	*P* value	Odds ratio	95% CI	*P* value
μmol/l						
≤9.1	1.0			1.0		
9.2–11.3	1.1	0.8, 1.6	0.60	1.1	0.8, 1.6	0.58
11.4–14.3	1.6	1.1, 2.4	0.009	1.6	1.1, 2.3	0.02
≥14.4	2.1	1.5, 3.0	<0.001	2.0	1.4, 2.9	<0.001
P_{trend}			<0.001			<0.001

[1] Adjusted for sex, age, total:HDL cholesterol ratio, smoking status and systolic blood pressure for 1041 individuals.
[2] CI = confidence interval.

to increase until the third homocysteine quartile (11.4–14.3 μmol/l) among women. Although the prevalence of stenosis appeared somewhat greater among men than women in the upper quartiles of homocysteine, a test of interaction between sex and homocysteine indicated that the trends for prevalence of stenosis ≥25% were not significantly different for men and women ($P = 0.07$).

The age and sex adjusted odds ratios for men and women combined were significantly increased in the third (odds ratio = 1.6; 95% confidence interval: 1.1–2.4) and fourth (odds ratio = 2.1; 95% confidence interval: 1.5–3.0) quartiles of homocysteine (≥14.4 μmol/l) relative to the lowest quartile (≤9.1 μmol/l) (**Table 3**). Adjustment for other risk factors had little effect on the odds ratios.

The associations between carotid stenosis and the plasma vitamins are shown in **Table 4.** The prevalence of stenosis ≥25% was inversely associated with both folate ($P_{trend} < 0.001$) and pyridoxal-5′-phosphate ($P_{trend} = 0.03$) after adjustment for age, sex and other risk factors. The odds ratio for stenosis was 1.9 (95% CI: 1.3–2.7) in the lowest folate quartile and 1.6 (95% confidence interval: 1.1–2.4) in the lowest pyridoxal-5′-phosphate quartile. Plasma vitamin B-12 exhibited a weak association with stenosis ($P_{trend} = 0.11$). The odds

TABLE 4

Odds ratios of maximal extracranial carotid artery diameter stenosis ≥25% by quartile of plasma vitamins

Vitamin	*n*	Multiple risk factor adjustment[1]			Multiple risk factor adjustment plus homocysteine		
		Odds ratio	95% CI[2]	*P* value	Odds ratio	95% CI	*P* value
Folate, *μg/l*[3]	1027						
<2.51		1.9	1.3, 2.7	0.001	1.5	1.0, 2.3	0.04
2.51–4.31		1.4	1.0, 2.0	0.08	1.3	0.9, 1.9	0.24
4.32–7.92		1.2	0.8, 1.8	0.28	1.2	0.8, 1.8	0.35
≥7.93		1.0			1.0		
P_{trend}				<0.001			0.05
Vitamin B-12, *ng/l*[3]	881						
<290		1.4	0.9, 2.1	0.11	1.2	0.8, 1.8	0.41
290–405		1.4	0.9, 2.0	0.14	1.2	0.8, 1.8	0.36
406–572		1.3	0.9, 2.0	0.16	1.3	0.9, 1.9	0.24
≥573		1.0			1.0		
P_{trend}				0.11			0.47
Pyridoxal-5′-phosphate, *nmol/l*	967						
<31.91		1.6	1.1, 2.4	0.02	1.3	0.9, 2.0	0.15
31.91–52.19		1.1	0.7, 1.6	0.67	1.0	0.6, 1.4	0.80
52.20–89.80		1.2	0.8, 1.7	0.48	1.1	0.7, 1.6	0.71
≥89.81		1.0			1.0		
P_{trend}				0.03			0.23

[1] Adjusted for sex, age, total:HDL cholesterol ratio, smoking status, and systolic blood pressure.
[2] CI = confidence interval.
[3] To convert to SI units, multiply folate values by 2.266 to get values in nmol/l and vitamin B-12 values by 0.7378 to get values in pmol/l.

ratio for stenosis was 1.4 (95% confidence interval: 0.9–2.1) in the lowest vitamin B-12 quartile compared with the highest quartile. Adjustment for homocysteine diminished the strength of plasma vitamin associations, but the elevated prevalence of stenosis in the lowest plasma folate quartile remained evident (odds ratio: 1.5; 95% CI: 1.0–2.3).

DISCUSSION

These data suggest an important role for nutritional status in homocysteine metabolism. We have demonstrated strong, nonlinear, inverse associations between homocysteine concentrations and plasma concentrations of folate, vitamin B-12 and vitamin B-6. We observed that individuals with low levels of each of these vitamins had high plasma homocysteine concentrations, whereas those with moderate vitamin levels had dramatically lower homocysteine concentrations. Homocysteine levels did not differ substantially between individuals with moderate and high vitamin concentrations.

The results for folate and vitamin B-6 intake data are consistent with those for the plasma vitamins. Although it is risky to attribute discrete quantitative values based on this method of dietary assessment (Willett et al. 1985), it still may be worth noting that homocysteine concentrations were elevated among individuals with folate intakes up to 280 μg/d, which is higher than the current RDA of 200 and 180 μg/d for adult men and women, and vitamin B-6 intakes as high as 1.92 mg/d, which is less than the RDA of 2.0 mg/d for men but greater than the RDA of 1.6 mg/d for women.

Adequate levels of all three vitamins may be needed to obtain an optimal homocysteine concentration. Using the index based on levels of all three vitamins, we estimated that approximately two thirds of the cases of elevated homocysteine concentration in this cohort were associated with low or moderate plasma levels of one or more of the three vitamins.

Our data also provide evidence that plasma homocysteine levels are associated with extracranial carotid stenosis in a population-based, elderly cohort. We observed that risk of stenosis ≥25% was increased at homocysteine concentrations previously believed to be normal based on levels of homocysteine among normative samples. As in our previous analysis, we defined elevated plasma homocysteine as concentrations >14 μmol/l (90th percentile among individuals with apparently adequate folate, vitamin B-12 and vitamin B-6 status). Stampfer et al. (1992) defined elevated homocysteine as concentrations >15.8 μmol/l (95th percentile among nondiseased control subjects). Joosten et al. (1993) defined elevated homocysteine as concentrations >13.9 μmol/l (mean plus 2 SD among healthy young controls). Genest and co-workers (1990) reported 90th and 95th percentile values of 15.0 and 19.0 μmol/l among their normal controls. In the present study we observed that risk of stenosis was elevated at levels of homocysteine between 11.4 and 14.3 μmol/l. These data will require us to reconsider the current beliefs regarding standards for elevated homocysteine.

We have also examined the relations between specific nutritional determinants of hyperhomocysteinemia and stenosis in this elderly cohort. We further demonstrated that folate and pyridoxal-5′-phosphate were linked to stenosis, in large part, because of their regulation of plasma homocysteine levels as indicated by the diminished odds ratios between stenosis and these vitamins after adjustment for homocysteine levels. Although there was some residual association between plasma folate and stenosis after adjustment for homocysteine, the likelihood ratio test statistic would suggest that addition of folate to a model containing homocysteine did not add any significant contribution. It is likely that measurement error and biological variability in both folate and homocysteine might explain the residual folate association.

We demonstrated that the majority of these elderly individuals with elevated homocysteine concentrations have insufficient status of folate, vitamin B-12 or vitamin B-6, and others have demonstrated that innocuous vitamin supplementation regimens (including folate, vitamin B-12 and vitamin B-6) effectively lower moderately elevated plasma homocysteine levels to the normal range (Brattsrom et al. 1988, Brattstrom et al. 1990, Dudman et al. 1993, Franken et al. 1994, Glueck et al. 1995, Lindgren et al. 1995, Ubbink et al. 1993, Ubbink et al. 1994). Results of our present study provide the rationale for a randomized, controlled trial of the effect of homocysteine lowering vitamin therapy on vascular disease morbidity and mortality in hyperhomocysteinemic, elderly individuals.

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