Vitamin Status and Intake as Primary Determinants of Homocysteinemia in an Elderly Population

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Objective.—To describe the distribution of plasma homocysteine concentrations in an elderly population and to analyze the relationship between homocysteine level and intake of vitamins and serum levels of vitamins that serve as coenzymes in homocysteine metabolism.

Design.—Cross-sectional analysis of homocysteine levels and vitamin blood levels and intake in elderly participants in the Framingham Study.

Setting.—Population-based cohort in Framingham, Mass.

Participants.—A total of 1160 adult survivors, aged 67 to 96 years, from the original Framingham Heart Study cohort.

Main Outcome Measures.—Plasma homocysteine concentration correlated with plasma folate, vitamin B₁₂, pyridoxal-5'-phosphate (PLP), and oral intakes of these vitamins, and the contribution of these vitamins to the prevalence of elevated homocysteine levels.

Results.—Homocysteine levels were positively correlated with age after controlling for vitamin concentrations. After controlling for age, sex, and levels of other vitamins, homocysteine exhibited a strong inverse association with plasma folate. When subjects were grouped by deciles of plasma folate, mean homocysteine was significantly higher in the lowest two folate deciles (15.6 and 13.7 μmol/L, respectively) than in the highest decile (11.0 μmol/L). Homocysteine demonstrated weaker, inverse associations with plasma vitamin B₁₂ and PLP. Similar inverse associations were demonstrated between homocysteine and intakes of folate and vitamin B₁₂, but not vitamin B₆. Prevalence of high homocysteine (>14 μmol/L) was 67% of the cases of high homocysteine in this cohort, and was greatest among subjects with low folate status. Inadequate plasma concentrations of one or more B vitamins appear to contribute to 67% of the cases of high homocysteine.

Conclusions.—These results indicate a strong association between homocysteine concentration and folate, vitamin B₁₂, and vitamin B₆ status, as well as age. It is possible that a substantial majority of the cases of high homocysteine in this older population can be attributed to vitamin status.

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ALMOST 25 years ago McCully¹ reported that a child dying of homocystinuria, cystathioninuria, and methylmalonic aciduria, secondary to abnormal cobalamin metabolism, exhibited arterial lesions that were strikingly similar to those seen in patients with cystathionine β-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 interest. A literature survey by Ueland et al² identified a total of 21 studies involving over 1500 patients with occlusive vascular disease (cardiovascular, peripheral, and cerebrovascular) and over 1500 respective controls. Sixteen of these studies reported significantly higher mean plasma homocysteine concentrations in patients than in respective controls (P<.05 to <.001). The mean patient-control homocysteine ratio according to this survey was 1.31, which indicates that the elevation of homocysteine in these patients was mild and certainly not as severe as that seen in homocystinuric patients.

For editorial comment see p 2726.

Clarke et al,³ 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.⁴ The association between homocysteine and vascular disease in this study, and in earlier studies,⁵ was independent of other known vascular disease risk factors such as age, diabetes, hypertension, body...
mass index, and total and high-density lipoprotein cholesterol. Despite our lack of understanding of the mechanism that underlies the relationship between hyperhomocysteinemia and atherosclerosis, the data support McCully's hypothesis1 that homocysteine or one of its metabolites is responsible for the development of some forms of occlusive vascular disease.

Most studies of moderate homocysteinemia have been conducted among subjects representing restricted segments of the population, such as those with occlusive vascular disease or known deficiencies of certain vitamins.24,26 While some of these studies employed age- and sex-matched normal controls, little is known about plasma homocysteine status in the general population. Furthermore, the extent to which elevated plasma homocysteine concentrations are associated with intake or plasma concentrations of the nutritional cofactors for homocysteine metabolism remains to be addressed in the general population.

In the present study, we used data from 1160 elderly survivors of the Framingham Study cohort to describe the distribution of plasma homocysteine in a representative sample of older adults and to study the relationship between plasma homocysteine concentration and plasma and intake levels of folate, vitamin B12, and vitamin B6.

METHODS

Subjects

The Framingham Study, an epidemiological study of heart disease, was established in Framingham, Mass., during the period 1948 through 1950. The original cohort consisted of 5209 men and women aged 30 to 62 years. The surviving members of this cohort have been examined every 2 years, and in 1988 and 1989, 1402 survivors participated in the 20th examination.

Sample Collection and Storage

Nonfasting blood samples were collected in ethylene diamine tetraacetic acid-containing tubes over a period of 2.5 years and were promptly centrifuged following collection. Plasma was stored at -70°C.

Laboratory Methods

Total homocysteine concentration in plasma was determined by the method of Araki and Sako.7 Vitamin B12 level was determined using a (Magic) radioassay kit from Ciba-Corning (Medfield, Mass). Plasma pyridoxal-5'-phosphate (PLP) level was determined by the tyrosine decarboxylase method as described by Camp et al.10 Plasma folate level was determined by a microbial assay using a 96-well plate and manganese supplementation as described by Tamura et al.11 We also determined plasma folate concentrations on a subset (n=385) of this cohort using the radioassay kit from Ciba-Corning for comparisons with the microbial assay method. The two methods were weakly correlated (r=0.38) at folate concentrations below 13.4 nmol/L. Both methods exhibited a significant correlation with folate intake, but the correlation with the microbial assay was stronger (r=0.56) than the correlation with the radioassay (r=0.43). Interassay coefficients of variation were 9% for homocysteine, 7% for vitamin B12, 15% for PLP, and 13% for folate.

Nutrient Intake

Members of the Framingham cohort received a semiquantitative food-frequency questionnaire12 by mail when they were scheduled for their 20th biennial examination. Subjects returned the completed questionnaire at the time of their examination. This questionnaire was designed to assess total nutrient intakes from both foods and nutrient supplements, and all analyses were performed using combined intakes from foods and supplements. Although it permits the estimation of nutrient intake for ranking or categorizing subjects, the food-frequency questionnaire does not provide precise quantitative measures of nutrient intake. Folate intake estimated by this questionnaire corresponded well with plasma folate concentrations (r=0.53) and vitamin B12 intake as estimated by diet records (r=0.55). Vitamin B12 and vitamin B12 intake and plasma PLP and vitamin B12 were 51 and 13, respectively. The correlation between plasma and intake measures of folate was described above. The weaker correlation for vitamin B12 in the present elderly population might be explained by weaknesses of this food-frequency questionnaire, but it is equally plausible that the discordance between vitamin B12 intake and circulating B12 levels is the result of diminished vitamin B12 absorption from foods associated with the age-related increase in incidence of atrophic gastritis.13

Statistical Analyses

Of the population of 1160 individuals for whom we had plasma homocysteine values, the plasma vitamin analyses were confined to a subset of 965 subjects who had a complete set of vitamin values, and analyses of vitamin intake were performed on 887 individuals with complete food-frequency questionnaires. Six hundred ninety-two individuals had complete vitamin data for both plasma and intake.

All plasma and intake measures were positively skewed, and we used logarithmic transformations to normalize their distributions. We therefore present geometric means (antilogarithms of the transformed means) for homocysteine concentration and all vitamins (both plasma and intake). Confidence intervals for the geometric means were calculated using the transformed values, and we display these intervals as the antilogarithm of the transformed values.

We calculated mean plasma homocysteine concentration and mean vitamin levels (plasma and intake) for men and women stratified into three age groups: 67 to 74, 75 to 79, and 80 years or older. We used polynomial contrasts to test for trend across age groups.14 We assessed the age-adjusted differences between men and women with analysis of covariance.15

To describe the associations between plasma homocysteine concentration and the B vitamins, we grouped subjects into deciles of plasma vitamin concentration and vitamin intake (Table 1). Each plasma vitamin category defined in this manner contained about 9% sub-
jests (range, 93 to 99) and each vitamin intake category contained about 89 subjects (range, 85 to 92). We calculated the geometric mean plasma homocysteine concentrations in each vitamin decile and age group and plotted these values and their 95% confidence intervals at the median vitamin intake level within each decile. We identified the vitamin deciles in which mean homocysteine concentrations were significantly different from those in the highest vitamin decile using Tukey's multiple comparison procedure. We adjusted mean homocysteine levels for age, sex, and concentration or intake of the other B vitamins by analysis of covariance with all covariates set to their respective sample means. We also adjusted all vitamin intakes for total energy intake. For each homocysteine-vitamin association, we examined the interactions with age, sex, and other B vitamins, but none was statistically significant. We elected to categorize the vitamin data rather than analyze them as continuous data so that we could apply a uniform approach to the analyses for all nutrients. Because many of the relationships considered did not adequately fit either linear or quadratic models, a variety of mathematical models would be required to describe these associations if we employed continuous vitamin data.

To examine the association between the occurrence of high plasma homocysteine concentrations and these vitamins, we defined high homocysteine as concentrations higher than 14.0 μmol/L (the 90th percentile for homocysteine among subjects whose three vitamin levels were above the 70th percentile). The 90th percentile for plasma homocysteine, when defined in this manner, was the same for both plasma vitamin concentration and vitamin intake. We determined the odds ratio of high homocysteine concentration among subjects in vitamin decile 1 through 9 relative to subjects in decile 10. These odds ratios were adjusted for age, sex, and the other B vitamins using logistic regression. The odds ratios for B vitamin intake were also adjusted for energy intake. An elevated odds ratio indicates that the prevalence of high homocysteine concentrations in that decile was significantly greater than the prevalence in the highest decile. However, the odds ratios cannot be interpreted as a prevalence rate ratio because of the excessive prevalence of high homocysteine.

We developed two B vitamin indexes, one using plasma concentrations and one using intakes, to describe the joint relationships of the three vitamins included in these analyses to high homocysteine levels. The indexes had five categories based on percentiles 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 percentile but at least one below the 70th; category 3, those with at least one vitamin above and one vitamin below the 50th percentile; category 4, those with all three vitamins below the 50th percentile but at least one above the 30th percentile; and category 5, 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) 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.

We used SPSS statistical software for these analyses. If not otherwise noted, statistical significance refers to P<.05.

Table 2 displays mean plasma folate, vitamin B6, and PLP concentrations by age and sex for the 391 men and 574 women with complete plasma vitamin data. Folate levels were similar in men and women and were not significantly associated with age. No age differences were found for vitamin B12, but women had higher vitamin B12 levels at all ages. Women had marginally higher PLP concentrations than men.

Table 2 also displays mean folate, vitamin B6, and vitamin B12 intakes (per 4200 kJ) by age and sex for the 343 men and 544 women with complete vitamin intake data. Folate and vitamin B6 intakes were significantly higher in women than in men. Vitamin B12 intakes were also higher in women, but the difference was only marginally significant.

### RESULTS

We had complete plasma homocysteine and either plasma vitamin or vitamin intake data for 1160 subjects. The mean (median) ages of the 457 men and 703 women were 75.6 (74.0) and 76.5 (75.0) years, respectively. Participants ranged in age from 67 to 96 years.

### Homocysteine Distribution

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 2). The increase with age remained significant (P<.001) for men and women after adjustment for plasma vitamin concentrations, but the difference between men and women was no longer statistically significant.

### Vitamin Status and Intake by Age and Sex

Table 2 displays mean plasma folate, vitamin B6, and PLP concentrations by age and sex for the 391 men and 574 women with complete plasma vitamin data. Folate levels were similar in men and women and were not significantly associated with age. No age differences were found for vitamin B12, but women had higher vitamin B12 levels at all ages. Women had marginally higher PLP concentrations than men.

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Mean Homocysteine Concentration by Vitamin Status and Intake

Folate.—Mean plasma homocysteine concentrations for subjects in the two lowest deciles of plasma folate (<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 < .01) (Fig 1, top). 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 < .01) (Fig 2, top).

Vitamin B₁₂.—Mean homocysteine concentrations were significantly elevated for subjects in the lowest decile for vitamin B₁₂ relative to subjects in the highest decile (P < .01). Mean homocysteine concentrations were 15.4 and 10.9 μmol/L for subjects in the lowest and highest vitamin B₁₂ deciles, respectively (Fig 1, center). Subjects in the lowest vitamin B₁₂ decile had vitamin B₁₂ concentrations below 130 pmol/L. Vitamin B₁₂ intake appeared unrelated to mean homocysteine concentration, even though subjects in the fifth decile had significantly higher homocysteine concentrations than subjects in the highest decile (P < .05) (Fig 2, center).

Vitamin B₆.—Mean homocysteine concentrations were significantly elevated among subjects in the lowest decile for PLP relative to subjects in the highest decile for this vitamin (P < .01). Mean homocysteine concentrations were 14.3 and 10.9 μmol/L for subjects in the lowest and highest PLP deciles (Fig 1, bottom). Subjects in the lowest decile had PLP concentrations below 18.1 nmol/L. For vitamin B₆ intake, mean homocysteine concentrations were significantly elevated in the lowest two deciles (P < .01) and the third decile (P < .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 2, bottom). Subjects in the lowest three intake deciles reported consuming less than 1.75 mg/d.

Prevalence of High Homocysteine Concentrations

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

High Homocysteine Concentration by Vitamin Status and Intake

Folate.—The odds ratio for high homocysteine were significantly elevated for subjects in the lowest five plasma folate deciles relative to subjects in the highest decile (Table 3). The odds ratios were 11.9 and 7.3 in the first and second deciles and decreased to 3.8 in the fifth decile. Subjects in these deciles constituted 50% of this cohort and had plasma folate concentrations below 3.2 nmol/L. For folate intake, the prevalence of high homocysteine was significantly greater among subjects in the lowest four deciles. Subjects in these deciles represented 40% of this cohort; they had reported folate intakes of less than 279 μg/d.

Vitamin B₁₂.—The prevalence of high homocysteine was significantly greater in the lowest two plasma deciles relative to the highest decile (P < .01); the odds ratios for the lowest two deciles were 3.4 and 2.1 (Table 3). Subjects in these two deciles had plasma vitamin B₁₂ levels below 181 pmol/L. Vitamin B₁₂ intake was unrelated to prevalence of high homocysteine (Table 4). The prevalence of high homocysteine among subjects in the lowest four deciles relative to subjects in the highest decile of intake. The reported intakes for subjects in these deciles, who constituted 40% of the sample, were less than 1.92 mg/d.

Homocysteinemia and B Vitamin Relationships—Selhub et al
Table 3.—Adjusted Odds Ratios of Elevated Homocysteine by Vitamin Deciles

<table>
<thead>
<tr>
<th>Decile</th>
<th>Plasma Concentration</th>
<th>Nutrient Intake</th>
</tr>
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<tr>
<td></td>
<td>Folate</td>
<td>Vitamin B_{12}</td>
</tr>
<tr>
<td>1</td>
<td>11.9†</td>
<td>3.4†</td>
</tr>
<tr>
<td></td>
<td>(4.9-29.7)</td>
<td>(1.7-7.2)</td>
</tr>
<tr>
<td>2</td>
<td>7.3†</td>
<td>2.1†</td>
</tr>
<tr>
<td></td>
<td>(3.0-17.8)</td>
<td>(1.0-4.4)</td>
</tr>
<tr>
<td>3</td>
<td>3.2†</td>
<td>1.2†</td>
</tr>
<tr>
<td></td>
<td>(1.3-7.8)</td>
<td>(0.6-2.5)</td>
</tr>
<tr>
<td>4</td>
<td>3.2†</td>
<td>1.6†</td>
</tr>
<tr>
<td></td>
<td>(1.3-7.8)</td>
<td>(0.8-3.4)</td>
</tr>
<tr>
<td>5</td>
<td>3.8†</td>
<td>1.5†</td>
</tr>
<tr>
<td></td>
<td>(1.6-9.3)</td>
<td>(0.8-3.4)</td>
</tr>
<tr>
<td>6-9‡</td>
<td>1.8†</td>
<td>1.1†</td>
</tr>
<tr>
<td></td>
<td>(0.8-4.0)</td>
<td>(0.8-2.1)</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>1</td>
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</tbody>
</table>

*Relative to vitamin decile 10; adjusted for age, sex, and other B vitamins.
†Significantly different from the highest decile (P<.01).
‡Significantly different from the highest decile (P<.05).
§Average odds ratios and confidence intervals for deciles 6 through 9. None of the individual odds ratios in these deciles were significantly different from one.

Table 4.—Elevated Homocysteine Concentrations by B Vitamin Status and Intake

<table>
<thead>
<tr>
<th>Vitamin Index*</th>
<th>n</th>
<th>Mean Homocysteine, μmol/L</th>
<th>Prevalence, %</th>
<th>Prevalence Rate Ratio</th>
<th>Attributable Percent†</th>
<th>Population Attributable Percent‡</th>
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<tbody>
<tr>
<td>Plasma</td>
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<tr>
<td>Highest</td>
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<td>0</td>
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<tr>
<td>2</td>
<td>128</td>
<td>9.8</td>
<td>12.5</td>
<td>1.2</td>
<td>19.2</td>
<td>1.0</td>
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<td></td>
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<td>4</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Lowest</td>
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<td></td>
<td></td>
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<tr>
<td>Intake</td>
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<tr>
<td>Highest</td>
<td>138</td>
<td>10.4</td>
<td>15.6</td>
<td>1.7</td>
<td>39.7</td>
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<td>369</td>
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</table>

* (Highest) indicates three B vitamins > 70th percentile; 2, all vitamins > 50th, at least 1 < 70th percentile; 3, vitamins both > 50th and < 50th percentile; 4, all vitamins < 50th percentile, at least 1 > 30th percentile; and 5 (lowest), all three vitamins < 30th percentile.
†Attributable percent is calculated using the equations AP = P \_i - P \_t / P \_t ; PAP = P \_i - P \_t / P \_t \times C \_t , where i indicates categories 1 to 5 and t indicates the reference (highest) category and t indicates the entire cohort, where AP indicates attributable percent in category i; P\_i, prevalence of elevated homocysteine in category i; P\_t , population attributable percent in category i; and C\_t , number of cases of elevated homocysteine in category i.
‡Significantly different from category 1 (P<.01).

Subjects were associated with at least one vitamin concentration below the 70th percentile, and 64% with intake of at least one vitamin below the 70th percentile. Although the prevalence of high homocysteinemia 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 both the plasma and intake indexes because it included the largest proportion of the cohort.

COMMENT

In the present study, we have measured plasma homocysteine levels in 1160 surviving elderly members of the Framingham Study cohort along with their blood levels and dietary intakes of vitamins B_{12}, B_{9}, and folate. We observed that homocysteine concentrations increased with age and lower B vitamin status. The age association remained strong after adjustment for plasma B vitamin levels. This increase in homocysteine with age, which was independent of B vitamin status, may result from an age-related decline in cystathionine B-synthase and possibly other enzymes involved in homocysteine metabolism. Although we observed that men had higher homocysteine levels than women, this difference was due to lower plasma B vitamin levels in men.

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_{9}. We observed that individuals with low levels of each of these vitamins had high plasma homocysteine concentrations, while those with moderate vitamin levels had dramatically lower homocysteine concentrations. Homocysteine levels did not differ substantially between individuals with moderate and high vitamin concentrations.

Studies of homocysteine and vascular disease would suggest that a substantial proportion of our elderly population may be at elevated risk of vascular disease due to hyperhomocysteinemia. Mean total plasma homocysteine concentrations were 13.7 μmol/L in patients with premature cardiovascular disease vs 10.5 μmol/L in controls, and plasma concentrations of folate, vitamin B_{12}, and vitamin B_{9}. We observed that individuals with low levels of each of these vitamins had high plasma homocysteine concentrations, while those with moderate vitamin levels had dramatically lower homocysteine concentrations. Homocysteine levels did not differ substantially between individuals with moderate and high vitamin concentrations.

Studies of homocysteine and vascular disease would suggest that a substantial proportion of our elderly population may be at elevated risk of vascular disease due to hyperhomocysteinemia. Mean total plasma homocysteine concentrations were 13.7 μmol/L in patients with premature cardiovascular disease vs 10.5 μmol/L in controls, 13.1 μmol/L.
in patients with cerebral infarction vs 7.3 μmol/L in controls, and 18.7 μmol/L in patients with peripheral vascular disease vs 11.0 μmol/L in controls. In our population, individuals in the lowest deciles for each plasma vitamin had mean homocysteine concentrations greater than 14 μmol/L, which is similar to values among subjects with vascular disease in other studies. Furthermore, the mean homocysteine concentration was above 14 μmol/L for 22% of our population with low status of at least one vitamin.

There is no consensus definition for hyperhomocysteinemia. Previous studies have employed percentile values from control samples to identify elevated homocysteine levels in patients with vascular disease. Genest and coworkers reported 90th and 95th percentile values of 15.0 and 19.0 μmol/L among their normol cholesterol patients and Stampfer and colleagues reported 95th percentile values of 14.1 and 15.8 μmol/L for men free of diagnosed vascular disease. Moreover, Stampfer and colleagues demonstrated a 3.4-fold increased risk of myocardial infarction among men with homocysteine levels above 15.8 μmol/L relative to men with levels below 14.1 μmol/L.

Although we defined our normal percentiles based on nutritional status, not absence of disease, our 90th and 95th percentile values, 14.0 and 16.4 μmol/L, are similar to those reported by Stampfer et al. Approximately 29% of our population had homocysteine concentrations higher than 14.0 μmol/L and 19% had concentrations higher than 16.4 μmol/L. More than 50% of individuals with low status of at least one vitamin had homocysteine levels higher than 14.0 μmol/L and more than 40% of these individuals had levels higher than 16.4 μmol/L. Twenty-one percent of our population had homocysteine levels higher than 15.8 μmol/L, the level that Stampfer and coworkers related to a more than threefold elevation in risk of myocardial infarction.

Using 14.0 μmol/L to define hyperhomocysteinemia, we observed strong associations between elevated homocysteine concentrations and vitamin status. Our results suggest that the prevalence of high homocysteine concentration could be reduced through improved folate status, even for individuals with plasma folate levels as high as 9 μmol/L. Similarly, individuals with plasma vitamin B12 levels as high as 180 μmol/L and PLP levels of 18 μmol/L might benefit by increasing vitamin B12 and vitamin B6 status, respectively. Thus, current normative criteria for plasma folate and vitamin B12 concentrations may be too low. There are no commonly accepted normative levels for PLP.

The results for folate and vitamin B12 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, it may still be worth noting that homocysteine concentrations were elevated among individuals with folate intakes up to 280 μg/d, which is higher than the current recommended dietary allowances (RDAs) of 200 and 180 μg/d for adult men and women, respectively, and vitamin B12 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. Reporting mean PLP levels 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 levels of one or more of the three vitamins.

All of the associations between homocysteine and vitamins were adjusted for levels of the other vitamins. The crude associations were substantially stronger and tended to appear more linear than the adjusted associations. Assessing the relationship of an individual nutrient without consideration of the other associated nutrients will overestimate the strength and distort the nature of the association between that specific nutrient and plasma homocysteine.

In the absence of intervention studies, we cannot conclude that lowering plasma homocysteine by increasing vitamin intake will reduce the risk of vascular disease. However, a strong case can be made for prevention of the marginal or manifest vitamin deficiency states that may contribute substantially to this potentially important risk factor for vascular disease, the largest cause of mortality in elderly individuals. Efforts to prevent deficiencies of folate, vitamin B12, and vitamin B6 in the increasing number of our population over the age of 65 years now have added impetus.

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References