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Homocyst(e)ine, Diet, and Cardiovascular Diseases

A Statement for Healthcare Professionals From the Nutrition Committee, American Heart Association

M. René Malinow, MD; Andrew G. Bostom, MD; Ronald M. Krauss, MD

Homocysteine and Diet

Homocysteine is a sulfur-containing amino acid, rapidly oxidized in plasma to the disulfides homocystine and cysteine-homocystine (Figure 1). Plasma/serum total homocysteine, also termed homocyst(e)ine, is the sum of homocysteine in all 3 components. Figure 2 displays factors involved in the metabolism of homocysteine, including its metabolic relationship to methionine. Although dietary intake of total protein and methionine does not correlate significantly with blood homocyst(e)ine,¹ a single dose of oral methionine (100 mg/kg body weight) can elevate homocyst(e)ine levels, and as described further below, this has been used as a diagnostic test to detect disordered homocyst(e)ine metabolism. Because variable changes in homocyst(e)ine levels have been observed postprandially,² it is customary to obtain measurements in the fasting state. Normal levels of fasting plasma homocyst(e)ine are considered to be between 5 and 15 $\mu\text{mol/L}$. Moderate, intermediate, and severe hyperhomocyst(e)inemia refer to concentrations between 16 and 30, between 31 and 100, and >100 $\mu\text{mol/L}$, respectively.³

Several vitamins function as cofactors and substrates in the metabolism of methionine and homocysteine (Figure 2). Folic acid and cyanocobalamin (vitamin B₁₂) regulate metabolic pathways catalyzed by the enzymes methylenetetrahydrofolate reductase (MTHFR) and methionine synthase, respectively, whereas pyridoxine (vitamin B₆) is a cofactor for cystathionine β -synthase. A number of studies have shown inverse relationships of blood homocyst(e)ine concentrations with plasma/serum levels of folic acid, vitamin B₆, and vitamin B₁₂.⁴⁻⁶

Administration of supplemental folic acid in doses between 0.2 and 15 mg/d can lower plasma homocyst(e)ine levels without apparent toxicity.⁷⁻⁹ On the basis of meta-analysis of 12 clinical studies, all but 1 of which was a placebo-

controlled trial, it has been estimated that a 25% reduction in homocyst(e)ine concentration can be achieved with mean supplementation of 0.5 to 5.7 mg of folic acid per day; an additional 7% lowering has been observed after the addition of vitamin B₁₂ (0.02 to 1 mg/d; mean, 0.5 mg).¹⁰ A recent report of the Food and Nutrition Board of the Institute of Medicine has recommended an upper limit of 1 mg/d folic acid on the basis of the possibility that higher doses may mask signs of vitamin B₁₂ deficiency in some subjects.¹¹ In overt cobalamin deficiency with intermediate and severe hyperhomocyst(e)inemia, vitamin B₁₂ can normalize homocyst(e)ine concentration in $\approx 70\%$ of cases.¹² In an open-label, uncontrolled study, vitamin B₆ at ≤ 250 mg/d was without effect in reducing basal homocyst(e)ine levels, but doses of 50 to 250 mg/d reduced homocyst(e)ine levels after a methionine-loading test by $\approx 25\%$.¹³ Subsequently, a study that used a randomized, placebo-controlled, 2 \times 2 factorial design demonstrated that 50 mg of vitamin B₆ per day independently reduced the post-methionine-loading increase in homocyst(e)ine levels by 22%.¹⁴ In a placebo-controlled study,¹⁵ a combination of multiple agents including folic acid (0.65 mg/d), vitamin B₆ (10 mg/d), and vitamin B₁₂ (0.4 mg/d) was very effective in reducing homocyst(e)ine levels in patients with moderate or intermediate hyperhomocyst(e)inemia. It has been reported, however, that increased vitamin intake from food sources (1 mg of folic acid, 12.2 mg of pyridoxine, and 50 μg of cyanocobalamin per day) failed to maintain normal homocyst(e)ine levels attained previously by vitamin supplementation.¹⁶

Other vitamins may also influence plasma homocyst(e)ine levels. Daily food intake of 0.6 mg of riboflavin, a vitamin that can function as a cofactor for MTHFR,¹⁷ results in modest reductions in homocyst(e)ine (0.475 $\mu\text{mol/L}$),¹ and pharmacological doses of nicotinic acid (3000 mg/d) may cause significant elevations.¹⁸ Users of multivitamin supplements in observational studies have lower homocyst(e)ine levels than nonusers, as well as higher concentrations of plasma folic acid and vitamins B₆ and B₁₂.¹⁹ The daily intake of fortified cereals containing 499 and 650 μg of folic acid per serving and the recommended dietary amount (RDA) of other vitamins reduced homocyst(e)ine by 11% and 14%, respectively.²⁰

A relatively common prevalence of the heat-labile variant of MTHFR has been shown to result from a cytosine to thymine (C to T) mutation at nucleotide 677.^{21,22} Although an increased prevalence of thermolabile MTHFR and T/T homozygotes has been reported among patients with coronary artery disease (CAD),^{19,21-24} this has not been confirmed in several other studies.²⁵⁻²⁸ T/T homozygotes have been re-

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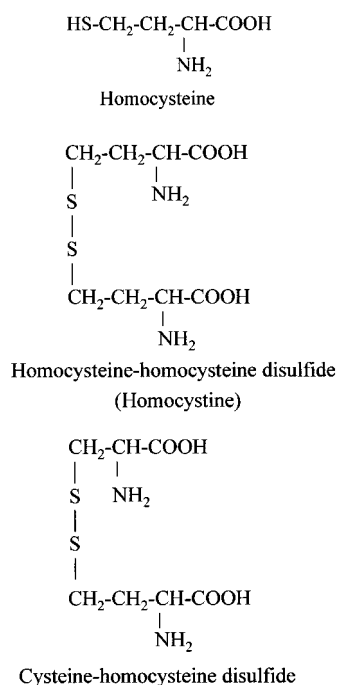


Figure 1. Molecular species of homocysteine.

ported to have higher geometric mean fasting homocyst(e)ine levels than C/T heterozygotes or C/C homozygotes when folate status was below the population median, but no differences in fasting homocyst(e)ine levels were detected between persons with different genotypes when plasma folate was at or above the population median.²⁹ The MTHFR genotype has been reported to influence the homocyst(e)ine response to folic acid. Reduction was greater in subjects with T/T than with C/C or C/T genotypes.¹⁹ Moreover, in 21 of 37 subjects with homocyst(e)ine $\geq 40 \mu\text{mol/L}$, in whom the frequency of the T/T genotype was 92%, homocyst(e)ine levels were normalized with supplemental intake of folic acid as low as 200 $\mu\text{g/d}$.⁸ It is likely but not proven that a

folate-rich diet ingested by subjects with the T/T genotype may be more effective in lowering homocyst(e)ine levels than a similar diet ingested by subjects with C/C or C/T genotypes.

Homocyst(e)ine and Coronary, Cerebral, and Peripheral Arterial Diseases

Homocystinuria is a rare autosomal recessive genetic disorder ($\approx 1:200\,000$ births) that usually results from defective activity of cystathionine β -synthase. Patients have severe hyperhomocyst(e)inemia and a variety of abnormalities, including a high incidence of vascular pathology that may result in early death from myocardial infarction, stroke, or pulmonary embolism.³⁰ Biochemical and pathological studies in homocystinuric children led McCully and Wilson³¹ to propose that elevated blood homocysteine may cause arteriosclerosis. Observations in ≈ 80 clinical and epidemiological studies have suggested that elevated homocyst(e)ine is a risk factor for atherosclerotic vascular disease and for arterial and venous thromboembolism.³² Moreover, moderate and intermediate hyperhomocyst(e)inemia is present in 12% to 47% of patients with coronary, cerebral, or peripheral arterial occlusive diseases³; these patients do not exhibit the systemic abnormalities characteristic of homocystinuria (see reviews in Reference 3 and References 33 to 38).

In a meta-analysis,³⁶ the odds ratio (OR) for CAD in subjects with hyperhomocyst(e)inemia was 1.7 in 15 studies (95% confidence interval [CI], 1.5 to 1.9). For stroke, the OR was 2.5 in 9 studies (95% CI, 2.0 to 3.0), and for peripheral vascular disease, the OR was 6.8 in 5 studies (95% CI, 2.9 to 15.8). Since this meta-analysis,³⁶ 22 reports involving 7800 subjects, including 9 cross-sectional³⁹⁻⁴⁷ and 13 case-controlled⁴⁸⁻⁶⁰ studies analyzed by Refsum et al,³² have provided further evidence for a relationship between homocyst(e)ine and coronary, cerebral, and peripheral atherosclerosis. In this period, only 2 cross-sectional^{61,62} and 2 case-control studies^{57,63} on 850 subjects failed to show an association between homocyst(e)ine and atherosclerosis; these studies included patients in the acute phase of myocardial infarction or stroke,

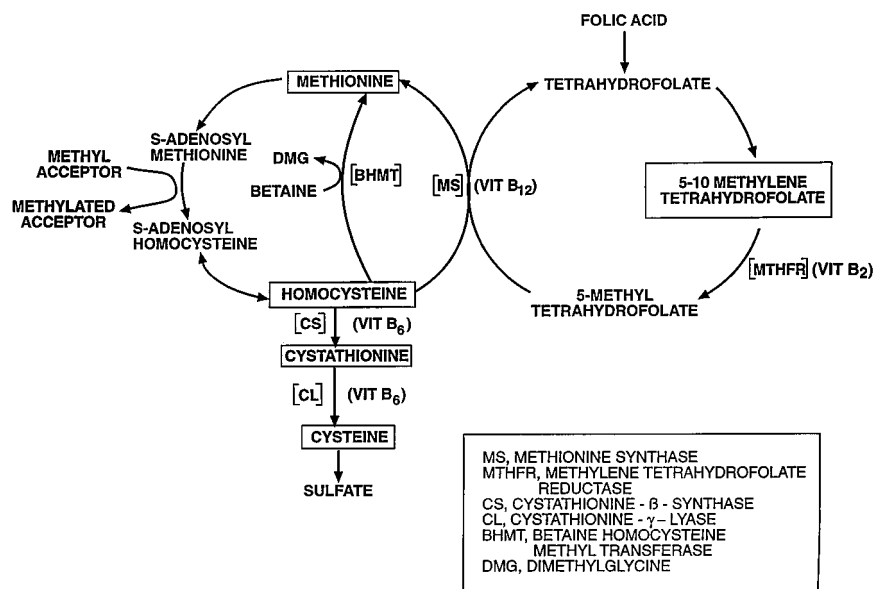


Figure 2. Simplified outline of methionine/homocysteine metabolism. Vitamin coenzymes and substrates: THF, tetrahydrofolate; B₂, riboflavin; B₆, vitamin B₆ as its biological active form, ie, pyridoxal 5'-phosphate; and B₁₂, methyl cobalamin. Intermediate metabolite: DMG, dimethylglycine.

in which homocyst(e)ine levels are decreased.^{64,65} The strongest evidence for a relationship between homocyst(e)ine and cardiovascular disease risk was provided by 6 prospective studies^{39,66–70} with follow-ups from 1.4 to 12.8 years on 830 cases and 1872 controls. However, 5 prospective studies^{28,71–74} on 995 cases and 1850 controls with follow-ups from 3.3 to 11 years failed to demonstrate such an association. For this reason, and in the absence of a controlled clinical intervention trial, it is premature to conclude that homocyst(e)ine levels are predictive of the development of cardiovascular disease.

Risk of CAD showed a dose-response effect across the entire distribution of basal^{36,39,57,59} and post-methionine-load⁵⁹ levels of homocyst(e)ine, and this effect was statistically independent of most conventional factors for atherosclerosis,^{32,39,59,75} although a multiplicative interaction with smoking and blood pressure has been reported.⁵⁹ Moreover, a recent study⁶⁸ demonstrated that the risk of death in 587 men and women with CAD was highly correlated with basal levels of homocyst(e)ine; after a median follow-up of 4.6 years, the mortality estimate for subjects with homocyst(e)ine ≥ 15.0 $\mu\text{mol/L}$ was 24.7% compared with 3.8% in subjects with homocyst(e)ine < 9.0 $\mu\text{mol/L}$. Finally, the more markedly elevated fasting homocyst(e)ine levels found in persons with dialysis-dependent, end-stage renal disease may also contribute independently to the excess incidence of fatal and nonfatal vascular disease outcomes in this patient population.⁶⁷

On the basis of these positive associations (excluding Reference 67), Omenn et al⁷⁶ provided a “best estimate” for the increased risk of CAD mortality associated with elevated plasma levels of homocyst(e)ine. The authors compared relative risks between homocyst(e)ine levels of >15 and <10 $\mu\text{mol/L}$ after adjustment for other cardiovascular risk factors and suggested that such risk difference is similar to that between total serum cholesterol levels of 7.1 and 4.9 mmol/L (275 and 189 mg/dL).

Vitamin Intake, Homocyst(e)ine, and Cardiovascular Disease

In the case-control study of arterial diseases described above,^{5,59} folate deficiency was more common in cases, and plasma vitamin B₆ below the lowest 20th percentile (<23.3 nmol/L) for control subjects was associated with increased risk for vascular disease, ie, OR = 1.84 (95% CI, 1.39 to 2.42). Of note, the relationship between vitamin B₆ and vascular disease was shown to be independent of homocyst(e)ine levels.⁵ Morrison et al⁷⁷ demonstrated in the prospective Nutrition Canada Survey that the risk of fatal CAD was associated with low serum folate in 165 CAD deaths in subjects among 5056 men and women monitored for 20 years.

In a subset of subjects from the Atherosclerosis Risk In Communities study,⁷⁸ carotid artery medial-intimal thickening was associated with high levels of homocyst(e)ine. Moreover, in a subset of subjects from the Framingham Heart Study,⁷⁹ the stenosis was inversely proportional to reported intakes of both folic acid and vitamin B₆. Another analysis from the Framingham Study⁸⁰ indicated that intake of fruits

and vegetables was inversely related to incidence of stroke over a 20-year follow-up. Although homocyst(e)ine levels were not measured, the authors discussed, among other factors, the potential role of dietary folic acid in lowering homocyst(e)ine as a plausible mechanism involved in the protective effects of diet.

Users of multivitamins have been reported to have a reduced prevalence of CAD compared with nonusers.⁵⁹ These findings have been extended in prospective observations conducted by Rimm et al⁸¹ in 80 082 women from the Nurses' Health Study. During a 14-year follow-up, the risk for fatal and nonfatal CAD was considerably lower among women who used multivitamins 4 to 7 times per week than among nonusers (risk ratio = 0.76; 95% CI, 0.65 to 0.90) after multivariate adjustments. Caution must be exercised in interpreting observational studies, however, because of the possible effects of differences in unmeasured behaviors or risk factors that may be associated with diet and vitamin intake. Moreover, the relationship of vitamin use to homocyst(e)ine levels was not evaluated in the study by Rimm et al.⁸¹

Dietary Guidance With Regard to Homocyst(e)ine and Cardiovascular Disease

Population Guidelines

On the basis of the apparent relationship of plasma homocyst(e)ine to cardiovascular disease risk and the estimated influence of folic acid on homocyst(e)ine levels, Boushey et al³⁶ suggested that a 350 $\mu\text{g/d}$ increase in folic acid intake in men and a 280 $\mu\text{g/d}$ increase in women could potentially prevent 30 500 and 19 000 vascular deaths annually in men and women, respectively. However, in the absence of prospective, placebo-controlled intervention trials of the effects of diet- or vitamin-mediated homocyst(e)ine reductions on incidence of cardiovascular disease, the clinical benefits of such interventions are unknown.

A recent report of the Food and Nutrition Board of the Academy of Sciences Institute of Medicine includes RDAs for folic acid, vitamin B₆, and vitamin B₁₂ of 400 μg , 1.7 mg, and 2.4 μg , respectively, for nonpregnant, nonlactating individuals.¹¹ Because a significant proportion of the population does not meet the current RDAs for folate intake,¹¹ a reasonable population approach is to recommend an increase in the intake of foods containing those vitamins, ie, ready-to-eat fortified cereals, leafy green vegetables, fruits, and legumes as sources of folate; ready-to-eat fortified cereals, noncitrus fruits, poultry, beef, and certain vegetables (eg, artichoke, asparagus, beans, and cabbage) as sources of vitamin B₆; and beef, poultry, fish, and ready-to-eat fortified cereals as sources of vitamin B₁₂ (see Reference 11 for more extensive information). These dietary modifications could result in elevated vitamin status and perhaps decreased homocyst(e)ine levels. However, because 10% to 30% of older people may malabsorb food-bound B₁₂, it is advisable for those older than 50 years to meet their RDA mainly by consuming food fortified with B₁₂ or a B₁₂-containing supplement.¹¹ Moreover, on the basis of relative differences in bioavailability, the RDA guidelines equate 100 μg of folic acid from unfortified foods to 60 μg from fortified food and

50 μg from supplements.¹¹ Because of methodological problems, food folate content in current databases may be significantly underestimated.⁸² Finally, prolonged heating or boiling, followed by discarding of water, or microwave heating may reduce folate content of food.⁸³

A complementary approach has been instituted as of January 1, 1998: the US Food and Drug Administration (FDA) has issued regulations requiring all "enriched" cereal grains to be fortified with folic acid at a concentration of 1.4 mg/kg grains to prevent neural tube birth defects. It has been estimated that this level of fortification would increase folic acid intake by 80 to 100 μg per day in women of childbearing potential and by 70 to 120 μg per day in adults older than 50 years.⁸⁴ Whether this level of fortification will lower homocyst(e)ine concentrations in CAD patients needs to be determined. However, as described above, cereal products have been shown recently to lower homocyst(e)ine in CAD patients when they were fortified with 4 to 5 times the levels of fortification mandated by the US FDA.²⁰

Detection and Management of Elevated Fasting Homocyst(e)ine

Levels of homocyst(e)ine have been remarkably similar between laboratories in studies conducted by different investigators using several methods,² perhaps because in the United States, determinations are routinely validated between laboratories as required by government regulations. With a method by which homocyst(e)ine was measured by high-performance chromatography with electrochemical detection, the within-assay precision showed a coefficient of variation of 1.1%, and the between-assay coefficient of variation was 2.1 to 11.4%,⁸⁵ whereas the coefficient of variation was 3.2% for within-pair quality-control specimens.⁶⁹ The cost of homocyst(e)ine analyses, coupled with the lack of definitive evidence for the clinical benefits of reducing homocyst(e)ine levels, precludes recommendations for population-wide screening at the present time. Thus, some researchers consider that a reasonable approach is to determine levels of fasting homocyst(e)ine in "high-risk patients," ie, in those with strong family history for premature atherosclerosis or with arterial occlusive diseases, particularly in the absence of other risk factors, as well as in members of their families, because hyperhomocyst(e)inemia in CAD seems to be transmitted, at least in part, through an autosomal dominant mechanism.⁸⁶ Other conditions that may be associated with high homocyst(e)ine are advanced age,³³ hypothyroidism,⁸⁷ impaired kidney function,⁸⁸ systemic lupus erythematosus,⁸⁹ and certain medications, eg, nicotinic acid,¹⁸ nitrous oxide exposure,⁹⁰ theophylline,⁹¹ methotrexate,⁹² and L-dopa.⁹³

After confirmation of high homocyst(e)ine concentration, it is important to check the vitamin status owing to the inverse relationships reported between homocyst(e)ine and blood levels of folate, B₆, and B₁₂.⁴⁻⁶ A useful algorithm for the diagnosis of vitamin B₁₂ deficiency, beyond the determination of blood levels of this vitamin, is described in Reference 11.

There is currently no firm basis for recommending specific therapeutic targets for homocyst(e)ine levels. Moreover, as reviewed above, the risk associated with homocyst(e)ine is continuous across the concentration distribution.^{36,39,57,59} Evi-

dence that vitamin supplementation favorably affects the evolution of atherosclerosis is limited to a single observation in 38 patients with homocyst(e)ine >14 $\mu\text{mol/L}$, in whom high doses of folic acid (2.5 and 5 mg/d) together with pyridoxine and vitamin B₁₂ resulted in reduced rate of progression of carotid plaque determined by ultrasonography after a mean follow-up of 4.4 \pm 1.5 years.⁹⁴ In the study of men and women younger than 60 years quoted above,⁵⁹ risk began to rise from the middle of the distribution (10.3 $\mu\text{mol/L}$). In a study contrasting survivors of myocardial infarction and noncoronary subjects,⁵⁷ the referent level (OR=1.0) was 9.8 $\mu\text{mol/L}$. Moreover, the referent value for risk of death associated with homocyst(e)ine was <9.0 $\mu\text{mol/L}$ ⁶⁸ or <10.0 $\mu\text{mol/L}$.⁷⁶ Thus, a basal homocyst(e)ine level <10 $\mu\text{mol/L}$ is a reasonable therapeutic goal for subjects at increased risk, rather than the definition of "normal" based on population statistical values of the mean \pm 2 SDs.

Accordingly, subjects with basal homocyst(e)ine \geq 10.0 $\mu\text{mol/L}$ should be advised to consume the diet indicated above. Chait et al⁹⁵ demonstrated that a folic acid-fortified diet reduced homocyst(e)ine in certain patients at high risk for cardiovascular disease, but other studies^{16,96} failed to show effectiveness of nonfortified, self-selected prescribed diets. Consequently, patients should repeat the homocyst(e)ine analysis after 1 month on the prescribed diet. If reduction in plasma homocyst(e)ine is not achieved, daily supplementation with a multivitamin containing *inter alia* 400 μg of folic acid, 2 mg of vitamin B₆, and 6 μg of vitamin B₁₂ or intake of "100% fortified" breakfast cereal also containing those amounts of vitamins per serving may be suggested, with repeat analysis at the end of 1 month. If such treatment is ineffective in lowering basal homocyst(e)ine in high-risk patients, a combination of folic acid (1 mg), vitamin B₆ (25 mg), and vitamin B₁₂ (0.5 mg) can be prescribed daily, after vitamin B₁₂ deficiency has been ruled out or adequately treated. If repeat analysis after 1 month shows ineffective homocyst(e)ine lowering, a trial of betaine (3 g BID) may be considered, although this remains investigational. Betaine, an intermediate metabolite from choline, is a methyl group donor for the enzymatic remethylation of homocysteine to methionine³⁰ (see Figure 2). Betaine has been found to be effective in reducing basal hyperhomocyst(e)inemia in subjects resistant to B vitamin therapy.⁹⁷

Methionine-Load Test

Homocyst(e)ine levels after a methionine-load test may be measured in high-risk patients with normal basal levels of homocyst(e)ine to identify those individuals with postload hyperhomocyst(e)inemia. The test measures homocyst(e)ine before and after the intake of 100 mg of methionine (dissolved in orange juice) per kilogram of body weight. Although multiple sampling strategies have been described, the 2-hour test has been validated extensively,⁹⁸ and it seems more practical than later blood sampling. This test may uncover 39% of subjects with homocyst(e)ine-related cardiovascular disease risk but with normal basal homocyst(e)ine levels.⁹⁹ The Table shows the 80th percentile of delta and absolute homocyst(e)ine levels in 2-hour post-methionine-load tests observed in 363 subjects free of clinically apparent vascular disease. The data, stratified by age and sex, con-

Post-Methionine-Load Test in 363 Subjects Without Clinically Apparent Vascular Disease

Age, y	Delta Homocyst(e)ine, $\mu\text{mol/L}^*$		Absolute PML, $\mu\text{mol/L}^\dagger$	
	Women	Men	Women	Men
	<50	20.3 (91)	15.1 (95)	28.0 (91)
≥ 50	23.9 (110)	15.0 (67)	34.7 (110)	25.5 (67)

PML indicates post-methionine-load test.

Values shown are 80th percentile distribution of 2-hour values. Number of subjects is shown in parentheses.

*Postload minus preload values.

†Absolute post-methionine-load values.

Adapted from Bostom AG, Selhub J, Jacques PF; unpublished data; 1998.

firmed that women have higher deltas and absolute post-methionine-load homocyst(e)ine levels than men; these values increase with age in women but not in men. Values equal to or above those indicated in the Table could be associated with enhanced risk for vascular disease.⁵⁹

As noted above, it has been reported that post-methionine-load delta homocyst(e)ine levels were reduced by an average of 22% with vitamin B₆ (50 mg/d)¹⁴ but not by folic acid supplementation up to 5 mg/d. Thus, it may not be possible to “normalize” the methionine-load response in all patients, and coupled with the lack of evidence for the benefit of a reduced response, the clinical value of this test remains uncertain. Moreover, when costs of the test and the need for adequate clinical facilities are considered, the methionine-load test may be reserved for research purposes.

Conclusions

Although there is considerable epidemiological evidence for a relationship between plasma homocyst(e)ine and cardiovascular disease, not all prospective studies have supported such

a relationship. Moreover, despite the potential for reducing homocyst(e)ine levels with increased intake of folic acid, it is not known whether reduction of plasma homocyst(e)ine by diet and/or vitamin therapy will reduce cardiovascular disease risk.^{100,101} Until results of controlled clinical trials become available, population-wide screening is not recommended, and emphasis should be placed on meeting current RDAs for folate, as well as vitamins B₆ and B₁₂, by intake of vegetables, fruits, legumes, meats, fish, and fortified grains and cereals. A high-risk strategy may include screening for fasting plasma homocyst(e)ine associated with augmented risk status, ie, $\geq 10.0 \mu\text{mol/L}$, in selected patients with personal or family history of premature cardiovascular disease, as well as in those with malnutrition, malabsorption syndromes, hypothyroidism, renal failure, or systemic lupus erythematosus; those taking certain medications, eg, nicotinic acid, theophylline, bile acid-binding resins, methotrexate, and L-dopa; or those with recent nitrous oxide exposure. In these patients, it may be advisable to increase their intake of vitamin-fortified foods and/or to suggest the daily use of supplemental vitamins, ie, 0.4 mg of folic acid, 2 mg of vitamin B₆, and 6 μg of vitamin B₁₂, with appropriate medical evaluation and monitoring. Treatment may include higher doses of those vitamins according to the response of homocyst(e)ine, as discussed in the text. However, such treatment is still considered experimental, pending results from intervention trials showing that homocyst(e)ine lowering favorably affects the evolution of arterial occlusive diseases.

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