

HOMOCYSTEINE

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Folate, vitamin B12, homocysteine status and chromosome damage rate in lymphocytes of older men.

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Deficient levels of folic acid and vitamin B12 are associated with elevated chromosome damage rate and high concentrations of homocysteine in the blood. We have therefore performed a study to determine the prevalence of folate deficiency, vitamin B12 deficiency and hyperhomocysteinemia in 64 healthy men aged between 50 and 70 years, and evaluate the relationship of these micronutrient levels in the blood with the micronucleus frequency in peripheral blood lymphocytes. We also performed a placebo-controlled, double-blind intervention study to determine whether supplementation of the diet with a daily dose of 0.7 mg (as a supplement in cereal) or 2.0 mg (in a tablet) over a period of 4 months resulted in a significant alteration of folate status, homocysteine status and the micronucleus index. Twenty-three per cent of the men were serum folate deficient (6.8 nmol/l), 16% were red blood cell folate deficient (317 nmol/l), 4.7% were vitamin B12 deficient (150 pmol/l) and 37% has plasma homocysteine levels 10 $\mu\text{mol/l}$. In total, 56% of the men had one or more abnormal blood values for folate, vitamin B12 or homocysteine. The micronucleus index of these men ($n = 34$) in cytokinesis-blocked binucleated cells (19.2 ± 1.1) was significantly elevated ($P = 0.02$) when compared to the micronucleus index of the rest of the men who had normal levels of folate, vitamin B12 and homocysteine (16.3 ± 1.3 , $n = 30$). Interestingly, the micronucleus index in men with normal folate and vitamin B12, but homocysteine levels $>10 \mu\text{mol/l}$ (19.4 ± 1.7 , $n = 15$) was also significantly higher ($P = 0.05$) when compared to those with normal folate, vitamin B12 and homocysteine. This novel result was also supported by the observation that the micronucleus index and plasma homocysteine were significantly ($P = 0.0086$) and positively correlated ($r(2) = 0.172$) in those subjects who were not deficient in folate or vitamin B12. The micronucleus index was not significantly correlated with folate indices, but there was a significant ($P = 0.013$) negative correlation with serum vitamin B12 ($r(2) = 0.099$). Daily supplementation of the diet with 0.7 mg free folic acid in cereal for 2 months followed by 2.0 mg free folic acid via a tablet produced a 4-fold increase in plasma folate, a 2.6-fold increase in red blood cell folate and a 11% reduction in plasma homocysteine; however, these changes were not accompanied by a reduction in the micronucleus index. In conclusion, it is apparent that elevated homocysteine status, in the absence of vitamin deficiency and low but not deficient, vitamin B12 status are important risk factors for increased chromosome damage in lymphocytes.

Relations of vitamin B-12, vitamin B-6, folate, and homocysteine to cognitive performance in the Normative Aging Study

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American Journal of Clinical Nutrition (USA) , 1996, 63/3 (306-314)

We investigated the relations between plasma concentrations of homocysteine and vitamins B-12 and B-6 and folate, and scores from a battery of cognitive tests for 70 male subjects, aged 54-81 y, in the Normative Aging Study. Lower concentrations of vitamin B-12 ($P = 0.04$) and folate ($P = 0.003$) and higher concentrations of homocysteine ($P = 0.0009$) were associated with poorer spatial copying skills. Plasma homocysteine was a stronger predictor of spatial copying performance than either vitamin B-12 or folate. The association of homocysteine with spatial copying performance was not explained by clinical diagnoses of vascular disease. Higher concentrations of vitamin B-6 were related to better performance on two measures of memory ($P = 0.03$ and $P = 0.05$). The results suggest that vitamins (and homocysteine) may have differential effects on cognitive abilities. Individual vitamins and homocysteine should be explored further as determinants of patterns of cognitive impairment.

Folate, vitamin B-12, and neuropsychiatric disorders.

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Nutr Rev 1996 Dec;54(12):382-390

Folate and vitamin B-12 are required both in the methylation of homocysteine to methionine and in the synthesis of S-adenosylmethionine. S-adenosylmethionine is involved in numerous methylation reactions involving proteins, phospholipids, DNA, and neurotransmitter metabolism. Both folate and vitamin B-12 deficiency may cause similar neurologic and psychiatric disturbances including depression, dementia, and a demyelinating myelopathy. A current theory proposes that a defect in methylation processes is central to the biochemical basis of the neuropsychiatry of these vitamin deficiencies. Folate deficiency may specifically affect central monoamine metabolism and aggravate depressive disorders. In addition, the neurotoxic effects of homocysteine may also play a role in the neurologic and psychiatric disturbances that are associated with folate and vitamin B-12 deficiency.

Lipid peroxidation induced in vivo by hyperhomocysteinaemia in pigs.

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Atherosclerosis 1997 Feb 28;129(1):67-71

Much attention has been focused recently on the relationship between homocysteinaemia and the development of premature atherosclerosis. Hyperhomocysteinaemia constitutes as strong a risk factor for the development of the disease as either hypercholesterolaemia or smoking. Although the mechanism involved is unclear homocysteine exhibits prooxidative activity in vitro. This finding suggests that it may be involved in the oxidative modification of low density lipoprotein (LDL). In the current study hyperhomocysteinaemia was induced in eight domestic pigs by intermittent exposure to nitrous oxide for 4 weeks. At necropsy, cardiac tissue was removed and malondialdehyde (MDA) and the unsaturated fatty acid content were measured and compared with values obtained from air-breathing control animals. Nitrous oxide treated animals had significantly higher tissue concentrations of MDA than the controls. There was also a reduction in the contribution of linoleic and linolenic acids to the total fatty acid content of heart. The hyperhomocysteinaemic animals also had a significantly higher iron concentration in the heart than controls. Hyperhomocysteinaemia was associated with elevations in tissue iron stores and increased in vivo lipid peroxidation.

Reduction of plasma homocyst(e)ine levels by breakfast cereal fortified with folic acid in patients with coronary heart disease.

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N Engl J Med 1998 Apr 9;338(15):1009-15

BACKGROUND: The Food and Drug Administration (FDA) has recommended that cereal-grain products be fortified with folic acid to prevent congenital neural-tube defects. Since folic acid supplementation reduces levels of plasma homocyst(e)ine, or plasma total homocysteine, which are frequently elevated in arterial occlusive disease, we hypothesized that folic acid fortification might reduce plasma homocyst(e)ine levels.

METHODS: To test this hypothesis, we assessed the effects of breakfast cereals fortified with three levels of folic acid, and also containing the recommended dietary allowances of vitamins B6 and B12, in a randomized, double-blind, placebo-controlled, crossover trial in 75 men and women with coronary artery disease.

RESULTS: Plasma folic acid increased and plasma homocyst(e)ine decreased proportionately with the folic acid content of the breakfast cereal. Cereal providing 127 microg of folic acid daily, approximating the increased daily intake that may result from the FDA's enrichment policy, increased plasma folic acid by 31 percent ($P=0.045$) but decreased plasma homocyst(e)ine by only 3.7 percent ($P=0.24$). However, cereals providing 499 and 665 microg of folic acid daily increased plasma folic acid by 64.8 percent ($P<0.001$) and 105.7 percent ($P=0.001$), respectively, and decreased plasma homocyst(e)ine by 11.0 percent ($P<0.001$) and 14.0 percent ($P=0.001$), respectively.

CONCLUSIONS: Cereal fortified with folic acid has the potential to increase plasma folic acid levels and reduce plasma homocyst(e)ine levels. Further clinical trials are required to determine whether folic acid fortification may prevent vascular disease. Until then, our results suggest that folic acid fortification at levels higher than that recommended by the FDA may be warranted.

Vitamin B-12, vitamin B-6, and folate nutritional status in men with hyperhomocysteinemia.

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Am J Clin Nutr 1993 Jan;57(1):47-53

We measured the vitamin B-6, vitamin B-12, and folic acid nutritional status in a group of apparently healthy men (n = 44) with moderate hyperhomocysteinemia (plasma homocysteine concentration > 16.3 $\mu\text{mol/L}$). Compared with control subjects (n = 274) with normal plasma homocysteine (< or = 16.3 $\mu\text{mol/L}$) concentrations, significantly lower plasma concentrations of pyridoxal-5'-phosphate (P < 0.001), cobalamin (P < 0.001), and folic acid (P = 0.004) were demonstrated in hyperhomocysteinemic men. The prevalence of suboptimal vitamin B-6, B-12, and folate status in men with hyperhomocysteinemia was 25.0%, 56.8%, and 59.1%, respectively. In a placebo-controlled follow-up study, a daily vitamin supplement (10 mg pyridoxal, 1.0 mg folic acid, 0.4 mg cyanocobalamin) normalized elevated plasma homocysteine concentrations within 6 wk. Because hyperhomocysteinemia is implicated as a risk factor for premature occlusive vascular disease, appropriate vitamin therapy may be both efficient and cost-effective to control elevated plasma homocysteine concentrations.

Hyperhomocysteinemia and low pyridoxal phosphate. Common and independent reversible risk factors for coronary artery disease.

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Circulation 1995 Nov 15;92(10):2825-30

BACKGROUND: High plasma homocysteine is associated with premature coronary artery disease in men, but the threshold concentration defining this risk and its importance in women and the elderly are unknown. Furthermore, although low B vitamin status increases homocysteine, the link between these vitamins and coronary disease is unclear.

METHODS AND RESULTS: We compared 304 patients with coronary disease with 231 control subjects. Risk factors and concentrations of plasma homocysteine, folate, vitamin B12, and pyridoxal 5'-phosphate were documented. A homocysteine concentration of 14 $\mu\text{mol/L}$ conferred an odds ratio of coronary disease of 4.8 (P < .001), and 5- $\mu\text{mol/L}$ increments across the range of homocysteine conferred an odds ratio of 2.4 (P < .001). Odds ratios of 3.5 in women and of 2.9 in those 65 years or older were seen (P < .05). Homocysteine correlated negatively with all vitamins. Low pyridoxal 5'-phosphate (< 20 nmol/L) was seen in 10% of patients but in only 2% of control subjects (P < .01), yielding an odds ratio of coronary disease adjusted for all risk factors, including high homocysteine, of 4.3 (P < .05).

CONCLUSIONS: Within the range currently considered to be normal, the risk for coronary disease rises with increasing plasma homocysteine regardless of age and sex, with no threshold effect. In addition to a link with homocysteine, low pyridoxal-5'-phosphate confers an independent risk for coronary artery disease.

Homocysteine metabolism and risk of myocardial infarction: relation with vitamins B6, B12, and folate.

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Am J Epidemiol 1996 May 1;143(9):845-59

Elevated plasma homocyst(e)ine levels are an independent risk factor for vascular disease. In a case-control study, the authors studied the associations of fasting plasma homocyst(e)ine and vitamins, which are important cofactors in homocysteine metabolism, with the risk of myocardial infarction. The cases were 130 Boston area patients hospitalized with a first myocardial infarction and 118 population controls, less than 76 years of age, enrolled in 1982 and 1983. Dietary intakes of vitamins B6, B12, and folate were estimated from a food frequency questionnaire. After adjusting for sex and age, the authors found that the geometric mean plasma homocyst(e)ine level was 11% higher in cases compared with controls (p = 0.006). There was no clear excess of cases with extremely elevated levels. The age- and sex-adjusted odds ratio for each 3- $\mu\text{mol/liter}$ (approximately 1

standard deviation) increase in plasma homocyst(e)ine was 1.35 (95% confidence interval 1.05-1.75; p trend = 0/007). After further control for several risk factors, the odds ratio was not affected, but the confidence interval was wider and the p value for trend was less significant. Dietary and plasma levels of vitamin B6 and folate were lower in cases than in controls, and these vitamins were inversely associated with the risk of myocardial infarction, independently of other potential risk factors. Vitamin B12 showed no clear association with myocardial infarction, although methylmalonic acid levels were significantly higher in cases. Comparing the mean levels of several homocysteine metabolites among cases and controls, the authors found that impairment of remethylation of homocyst(e)ine (dependent of folate and vitamin B12 rather than on vitamin B6-dependent transsulfuration) was the predominant cause of high homocyst(e)ine levels in cases. Accordingly, plasma folate and, to a lesser extent, plasma vitamin B12, but not vitamin B6, correlated inversely with plasma homocyst(e)ine, even for concentrations at the high end of normal values. These data provide further evidence that plasma homocyst(e)ine is an independent risk factor for myocardial infarction. In this population, folate was the most important determinant of plasma homocyst(e)ine, even in subjects with apparently adequate nutritional status of this vitamin.

Total serum homocysteine in senile dementia of Alzheimer type.

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Int J Geriatr Psychiatry 1998 Apr;13(4):235-9

OBJECTIVE: The main hypothesis was that subtle vitamin B12 deficiencies occur more commonly in senile dementia of Alzheimer type (SDAT) than in healthy elderly individuals, and may be revealed by elevated total serum homocysteine (tHcy). A subsidiary hypothesis was that such deficiencies would be nutritionally independent as determined by retinol binding protein (RBP).

DESIGN: A prospective case-controlled survey.

SETTING: A Welsh urban psychogeriatric assessment centre and local general practice.

PATIENTS: Thirty patients, aged 65 or over, seen consecutively in 1994 with features compatible with DSM-III-R criteria for primary degenerative dementia of Alzheimer type and 30 cognitively intact age-matched control subjects.

MEASURES: Diagnosis was assessed using the CAMDEX. Cognitive scores were evaluated with the CAMCOG scale for patients and MMSE scores for control subjects. tHcy was measured using high performance liquid chromatography (HPLC), and RBP assayed by a radial immunodiffusion method.

RESULTS: Patients had a highly significant elevation of tHcy compared with control ($p < 0.0001$). Multiple regression highlighted the interrelated effects of tHcy and total serum cobalamin on cognitive scores. RBP did not differ between groups. Macrocytosis was absent, and neutrophil hypersegmentation uncommon, in hyperhomocysteinaemic patients.

CONCLUSIONS: SDAT patients have significantly elevated tHcy. This is independent of RBP determined nutritional status. 'Classical' haematological changes of cobalamin or folate deficiency are poor predictors of tHcy in these patients. Aberrant cobalamin tissue delivery appears to contribute to SDAT cognitive decline. Relative contributions of other tHcy determinants require further investigation.

Abnormal amino acid metabolism in patients with early stage Alzheimer dementia.

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J Neural Transm 1998;105(2-3):287-94

Plasma levels of several amino acids were studied in 14 patients with early stage probable Alzheimer's disease (AD) and 17 age-matched controls. In the AD patients a possible relationship between amino acid levels and behavioural symptomatology was also investigated. We found significantly reduced levels of tryptophan and methionine in plasma samples from the AD patients compared to the control subjects. Moreover, plasma tyrosine/large neutral amino acids (LNAA) ratio and the ratio of plasma taurine and the product of the plasma levels of methionine and serine (TSM-ratio) were significantly increased in the AD patients in comparison with the controls. However, no difference was found in plasma tryptophan/LNAA ratio and in homocysteine levels between both groups. Concerning the behavioural symptomatology no significant correlation was found between the Reisberg

Behave AD scale and plasma amino acid levels or ratios. The reported findings suggest that abnormal amino acid metabolism is present in the early stages of AD. We hypothesize that this abnormality could play a role in the pathogenesis of behavioural changes occurring in later stages of AD.

Is metabolic evidence for vitamin B-12 and folate deficiency more frequent in elderly patients with Alzheimer's disease?

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J Gerontol A Biol Sci Med Sci 1997 Mar;52(2):M76-9

BACKGROUND: It is still unclear whether there is an association between Alzheimer's disease and vitamin B-12 or folate deficiency. This study was designed to investigate whether patients with Alzheimer's disease are particularly prone to metabolically significant cobalamin or folate deficiency as compared to nondemented hospitalized controls and healthy elderly controls living at home.

METHODS: Evaluation for the diagnosis of Alzheimer's disease, routine laboratory tests, serum folate and vitamin B-12, serum methylmalonic acid (MMA), total homocysteine (tHcy), and radiological tests was performed in 52 patients with Alzheimer's disease (AD), 50 nondemented hospitalized controls, and 49 healthy elderly subjects living at home.

RESULTS: Serum vitamin B-12 and folate levels are comparable between patients with AD, hospitalized control patients, and subjects living at home. Patients with AD have the highest serum MMA and tHcy levels. The MMA levels of patients with AD and hospitalized controls are not different, but the mean tHcy level is significantly higher in patients with AD as compared to nondemented patients or subjects living at home.

CONCLUSION: The interpretation of the vitamin B-12 and folate status in patients with AD depends largely on the methodology (i.e., serum vitamin vs metabolite levels) and the selection of the control group. Although patients with AD have the highest tHcy and MMA levels, metabolically significant vitamin B-12 and folate deficiency is also a substantial problem in nondemented elderly patients.

Decreased methionine adenosyltransferase activity in erythrocytes of patients with dementia disorders.

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Eur Neuropsychopharmacol 1995 Jun;5(2):107-14

ATP:1-methionine S-adenosyltransferase (EC 2.5.1.6, MAT) activity was analyzed in erythrocytes from nine patients with a clinical diagnosis of probable Alzheimer's disease (Pro.AD), four with possible Alzheimer's disease (Pos.AD), three with mild cognitive dysfunction (MCD) and two with dementia of vascular origin (VD), and 10 age-matched control subjects. Significantly lower kinetic parameters (V_{max} and K_m towards methionine) for MAT were observed in all the dementia cases. In the subgroup of Pro.AD patients who also had low plasma levels of vitamin B12 (B12), the reduction in MAT K_m was significantly correlated with an increase in the serum levels of homocysteine, while no such correlation was observed in all the other dementia groups. Treatment for 6 months of this subgroup of Pro.AD patients with B12 (1 mg x 7 days + 1 mg/week, i.m.), S-adenosylmethionine (SAM, 200 mg twice daily, p.o.) and folate (2.5 mg every 2 days, p.o.) caused a significant decrease in homocysteine in parallel with a significant increase in K_m for MAT. These findings support the hypothesis that aberrations in the B12 dependent transmethylation reactions might be involved in the pathogenesis of dementia, and suggest that the evaluation of erythrocyte MAT activity may be a useful marker for the detection of such an aberration.

Homocysteine and arterial occlusive disease: a concise review.

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Many cross-sectional and prospective studies have shown that raised serum/plasma levels of total homocysteine increase the risk of coronary, cerebral, and peripheral artery disease. The risk associated with hyperhomocysteinemia appears to be concentration-dependent and not attributable to traditional risk factors. The odds ratio for ischemic heart disease has been estimated to be 1.4 for every 5 $\mu\text{mol/l}$ increase of total plasma homocysteine. Median fasting total plasma homocysteine in adult males is approximately 10 $\mu\text{mol/l}$. Mild hyperhomocysteinemia is estimated to occur in 5-10% of the general population. Plasma concentrations are increased as a result of age, male gender, impaired renal function, low vitamin B intake, and genetically-determined defects of the enzymes involved in homocysteine metabolism. Folate supplements can reduce total homocysteine levels by approximately 25%. Studies in vitro and in vivo indicate that homocysteine can impair endothelial function. Despite increasing recognition of hyperhomocysteinemia as a risk factor for arterial occlusive disease, irrefutable proof that mild hyperhomocysteinemia contributes directly to the pathogenesis of atherothrombosis will come if interventions to lower total homocysteine reduce cardiovascular events. Family studies may also provide evidence of causality if genetic causes of hyperhomocysteinemia are found to segregate with disease.

Homocysteine and short-term risk of myocardial infarction and stroke in the elderly: the Rotterdam Study.

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Arch Intern Med 1999 Jan 11;159(1):38-44

BACKGROUND: Elevated homocysteine level increases vascular disease risk. Most data are based on subjects younger than 60 years; data for the elderly are more limited. We examined the relationship of homocysteine level to incident myocardial infarction and stroke among older subjects in a nested case-control study.

METHODS: Subjects were participants in the Rotterdam Study, a cohort study among 7983 subjects residing in the Ommoord district of Rotterdam, the Netherlands. Baseline examinations were performed from March 1, 1990, to July 31, 1993. The analysis is restricted to myocardial infarction and stroke that occurred before December 31, 1994. One hundred four patients with a myocardial infarction and 120 with a stroke were identified with complete data. Control subjects consisted of a sample of 533 subjects drawn from the study base, free of myocardial infarction and stroke. Nonfasting total homocysteine levels were measured.

RESULTS: Results were adjusted for age and sex. The risk of stroke and myocardial infarction increased directly with total homocysteine. The linear coefficient suggested a risk increase by 6% to 7% for every 1- $\mu\text{mol/L}$ increase in total homocysteine. The risk by quintiles of total homocysteine level was significantly increased only in the group with levels above 18.6 $\mu\text{mol/L}$ (upper quintile): odds ratios were 2.43 (95% confidence interval, 1.11-5.35) for myocardial infarction and 2.53 (95% confidence interval, 1.19-5.35) for stroke. Associations were more pronounced among those with hypertension.

CONCLUSIONS: The present study, based on a relatively short follow-up period, provides evidence that among elderly subjects an elevated homocysteine level is associated with an increased risk of cardiovascular disease.

Vitamin intake: a possible determinant of plasma homocyst(e)ine among middle-aged adults.

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Ann Epidemiol 1997 May;7(4):285-93

PURPOSE: Many epidemiologic studies have identified elevated plasma homocyst(e)ine as a risk factor for atherosclerosis and thromboembolic disease. To examine the relationship between vitamin intakes and plasma homocyst(e)ine, we analyzed dietary intake data from a case-control study of 322 middle-aged individuals with atherosclerosis in the carotid artery and 318 control subjects without evidence of this disease.

METHODS: All of these individuals were selected from a probability sample of 15,800 men and women who participated in the Atherosclerosis Risk in Communities (ARIC) Study.

RESULTS: Plasma homocyst(e)ine was inversely associated with intakes of folate, vitamin B6, and vitamin B12 (controls only for this vitamin)--the three key vitamins in homocyst(e)ine metabolism. Among nonusers of vitamin supplement products, on average

each tertile increase in intake of these vitamins was associated with 0.4 to 0.7 $\mu\text{mol/L}$ decrease in plasma homocyst(e)ine. An inverse association of plasma homocyst(e)ine was also found with thiamin, riboflavin, calcium, phosphorus, and iron. Methionine and protein intake did not show any significant association with plasma homocyst(e)ine.

CONCLUSIONS: In almost all analyses, cases and controls showed similar associations between dietary variables and plasma homocyst(e)ine. Plasma homocyst(e)ine among users of vitamin supplement products was 1.5 $\mu\text{mol/L}$ lower than that among nonusers. Further studies to examine possible causal relationships among vitamin intake, plasma homocyst(e)ine, and cardiovascular disease are needed.

Folic acid fortification of the food supply. Potential benefits and risks for the elderly population.

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JAMA 1996 Dec 18;276(23):1879-85

Published erratum appears in JAMA 1997 Mar 5;277(9):714

OBJECTIVE: To estimate the potential benefits and risks of food folic acid fortification for an elderly population. Benefits are expected through the improvement of folate and homocysteine status, but there is also a risk of masking or precipitating clinical manifestations related to vitamin B12 deficiency with increasing exposure to folic acid.

DESIGN: Cross-sectional analysis, with projected change at various levels of folic acid fortification.

SETTING: Participants in the Framingham Heart Study original cohort.

PARTICIPANTS: A total of 747 subjects aged 67 to 96 years who both completed usable food frequency questionnaires and had blood concentrations of B vitamins and homocysteine measured.

MAIN OUTCOME MEASURES: Projected blood folate and homocysteine concentrations and combined high folate intake and low plasma vitamin B12 concentration.

RESULTS: Percentages of this elderly population with folate intake below 400 $\mu\text{g/d}$ are projected to drop from 66% at baseline to 49% with 140 μg of folate per 100 g of cereal-grain product, to 32% with 280 μg , to 26% with 350 μg , and to 11% with 700 μg . Percentages with elevated homocysteine concentrations ($>14 \mu\text{mol/L}$) are projected to drop from 26% at baseline to 21% with 140 μg of folate per 100 g, to 17% with 280 μg , to 16% with 350 μg , and to 12% with 700 μg . Without fortification, the prevalence of combined high folate intake ($>1000 \mu\text{g/d}$) and low plasma vitamin B12 concentration ($<185 \text{ pmol/L}$ [$<250 \text{ pg/mL}$]) was 0.1%. This is projected to increase to 0.4% with folate fortification levels of 140 to 350 $\mu\text{g}/100 \text{ g}$ and to 3.4% with 700 μg .

CONCLUSION: The evidence suggests that, at the level of 140 $\mu\text{g}/100 \text{ g}$ of cereal-grain product mandated by the Food and Drug Administration, the benefits of folate fortification, through projected decreases in homocysteine level and heart disease risk, greatly outweigh the expected risks. However, quantification of the actual risks associated with vitamin B12 deficiency remains elusive. Before higher levels of folic acid fortification are implemented, further research is needed to better understand the clinical course of various forms of vitamin B12 deficiency, to measure the potential effect of high folate intake on this course, and to identify cost-effective approaches to the identification and treatment of all forms of vitamin B12 deficiency.

taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.