Benefits of Folic Acid and Vitamins B-12 and B-6: May Lower Risk of Heart Disease and Stroke

Prepared by Annette Dickinson, Ph.D.
Council for Responsible Nutrition
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A substantial body of scientific evidence suggests that generous intakes of three of the B vitamins may reduce the risk of two of the primary causes of death and disability in the United States—heart disease and stroke. The particular B vitamins are folic acid, vitamin B-6 and vitamin B-12.

More research is being done in this area, but many researchers believe it would make sense for people to begin supplementing their diets with these B vitamins to take early advantage of the potential benefits.

Key Scientific Findings

The effect of some of the B vitamins on heart disease was first recognized in people with a genetic abnormality called homocystinuria, in which an extremely high level of an amino acid called homocysteine builds up in the blood and spills over into the urine. People suffering from this disorder have a high risk of early death from the effects of vascular disease. (Kang 1992)

It is now recognized that in the general population even modestly elevated homocysteine levels in the blood are a risk factor for heart disease. Folic acid and some other B vitamins have been shown to reduce homocysteine levels. Homocysteine is produced in the body as a byproduct of methionine metabolism, in a set of reactions called the one-carbon cycle. Normally, homocysteine produced in cells is recycled through metabolic reactions involving folic acid, vitamin B-12, and vitamin B-6. When homocysteine builds up, additional amounts of these B vitamins can effectively metabolize or recycle it. Folic acid generally appears to be the most efficient nutrient for this purpose. Many researchers find the current evidence strong enough to justify public health action, even while additional scientific study continues.

In the third National Health and Nutrition Examination Survey (NHANES III), men and women with higher levels of homocysteine (more than 12 μmol/L) were more than twice as likely to report a history of a heart attack or stroke, compared to people with lower levels of homocysteine. There was an especially strong relation between higher

homocysteine levels and a history of a heart attack or stroke in *men under 60* (as compared to older men) and in *women over 60* (as compared to younger women). (Morris 2000)

There is evidence to suggest that folic acid may have a beneficial effect on cardiovascular health through several mechanisms, in addition to lowering homocysteine. For example, folates have a beneficial effect on endothelial function in blood vessels. Impaired endothelial function, which results in a decreased vasodilation response to various stimuli, "has been increasingly recognized as a surrogate end point for cardiovascular risk." One group of researchers recently concluded: "Overall, available data strongly suggest a benefit of folate supplementation in lowering cardiovascular risk," although additional study is needed. (Verhaar 2002)

In a prospective epidemiologic study involving more than 80,000 nurses, researchers at the Harvard School of Public Health found a 45 percent reduced risk of coronary heart disease (CHD) in women with high intakes of both folic acid and vitamin B-6. In the highest intake group, 95 percent of the women were users of multivitamins. Their intake of folic acid was greater than 0.4 mg, and their intake of B-6 was more than 3.0 mg. (Average folic acid intake in the top group was 0.7 mg, and average B-6 intake was 4.6 mg.) The researchers concluded that "intake of folate and vitamin B-6 above the current recommended dietary allowance may be important in the primary prevention of CHD among women." (Rimm 1998)

A meta-analysis of 28 studies on folic acid, homocysteine and vascular disease predicted that more than 56,000 deaths could be avoided annually if all Americans obtained adequate amounts of folic acid. Researchers from the University of Washington concluded that a strong case can be made for the likelihood that an increased folic acid intake will reduce the risk of heart disease and stroke. They recognized that randomized controlled trials would provide the most convincing proof, but noted that "such trials would require many years to show results." In the meantime, they say, "policies for increasing folic acid intake could have a considerable effect on the prevention of arteriosclerotic vascular disease." (Boushey 1995)

In the Physicians' Health Study, men who had a heart attack had higher levels of plasma homocysteine than matched controls who remained free of heart disease. After adjusting for other risk factors, high plasma homocysteine was associated with a greater than three-fold increase in risk of heart attack. The researchers pointed out that low intakes of vitamins B-6, B-12, and folic acid can lead to high levels of homocysteine, and that low intakes of these nutrients are not uncommon in the United States. In this study, high intakes of these three B vitamins were correlated with lower plasma homocysteine levels. (Stampfer 1992)

Another research group found that a substantial proportion of men with moderately high plasma homocysteine levels had suboptimal blood levels of vitamin B-6 (25 percent), vitamin B-12 (57 percent), and folate (59 percent). Treatment with a daily vitamin supplement normalized homocysteine levels within six weeks. The supplement contained

10 mg of vitamin B-6, 1 mg of folic acid, and 0.4 mg of vitamin B-12. The researchers concluded that adequate dietary intake of these vitamins may help reduce the risk of premature vascular disease. (Ubbink 1993)

In a study in Sweden, researchers found that high homocysteine levels were related to low or low-normal blood folate and serum B-12 levels. The authors suggested that "a large segment of the population with low normal concentrations of folate or vitamin B-12 have metabolically important deficiencies of these vitamins." Users of multivitamins had lower homocysteine levels than nonusers and had higher levels of blood folate and serum B-12. This indicates that "even regular intake of common multivitamins containing only 0.2–0.4 mg of folic acid effectively reduces the plasma homocysteine concentration." (Brattstrom 1994)

In a study in Norway, plasma homocysteine levels were a strong predictor of mortality from coronary artery disease. Homocysteine levels were higher in people with low levels of serum folate or vitamin B-12. (Nygard 1997)

In the European Concerted Action Project, people with high homocysteine levels were twice as likely to have vascular disease. *The increased cardiovascular risk related to homocysteine was equivalent to the increased risk related to high cholesterol levels or smoking.* The relatively small number of Europeans who used vitamin supplements had a 62 percent *reduced* risk of vascular disease. The authors state: "We believe it is time to consider whether existing recommended daily allowances of the vitamins that modulate homocysteine are adequate, and to undertake randomized controlled trials of the effects of folic acid and perhaps pyridoxine in the secondary prevention of cardiovascular disease." (Graham 1997)

Researchers from the USDA Human Nutrition Research Center on Aging at Tufts University examined carotid artery stenosis, homocysteine, and B vitamin levels in 1041 survivors of the original Framingham Heart Study subjects. In this cohort, 43 percent of the men and 34 percent of the women had 25 percent or greater narrowing of the carotid artery. Those with the highest homocysteine levels were twice as likely to have stenosis, compared to those with the lowest homocysteine levels. Those with stenosis tended to have lower plasma levels of folate and B-6 and lower dietary folate intake. (Selhub 1995)

In the Framingham Offspring cohort, homocysteine levels were lower in people who used B vitamin supplements than in those who did not. Homocysteine levels were lower in people with *higher plasma levels* of folate, B-12 and B-6, and in people with *higher intakes* of folate, B-6 and riboflavin. Homocysteine levels were increased in people who consumed higher amounts of alcohol or caffeine, who smoked more cigarettes, or who used antihypertensive medications. The Food and Drug Administration's folic acid fortification program for grain products was found to have increased plasma folate levels and decreased homocysteine levels substantially in this population, although not to the degree observed in those who had used supplements. (Jacques 1999, Jacques 2001)

In an editorial accompanying the above study, Dr. Meir Stampfer of Harvard Medical School and Dr. Rene Malinow of Oregon Health Sciences University suggest that it might not be necessary to wait for clinical trials before making recommendations about B vitamins. They note that the weight of the evidence for benefit is substantial, and folate supplementation is benign. Therefore, they say, "it may be possible to make broad preliminary recommendations based on trials of secondary prevention or disease progression (e.g., thickening of the carotid-artery wall) rather than wait for large, expensive, and prolonged trials of primary prevention." (Stampfer 1995)

In a study of 79 women less than 45 years of age diagnosed with myocardial infarction (MI) and 386 controls in Washington state, women with high plasma folate (over 8.4 nmol/L) had a 50 percent lower risk of MI, compared to women with low folate levels. (Schwartz 1997)

In the Nutrition Canada Survey, people with low serum folate levels were almost twice as likely to die from coronary heart disease than people with the highest levels. The increased risks "were not restricted to individuals with extremely low serum folate levels, but were observed for individuals with normal levels as well, suggesting that current definitions of appropriate serum folate levels be reassessed." The authors concluded that "low serum folate levels are associated with an increased risk of fatal CHD." They support efforts to encourage people to eat more vegetables and legumes, but recognize that "in spite of health promotion efforts, not all people will increase their dietary consumption of folate and the bioavailability of folate from foods is significantly less than that from folic acid supplements." (Morrison 1996)

In an editorial accompanying the above article, Dr. Meir Stampfer and Dr. Eric Rimm of Harvard Medical School and the Harvard School of Public Health make a plea for randomized clinical trials. They note that, if proven effective, lowering homocysteine levels "could prevent tens of thousands of cases of cardiovascular disease each year at very low cost and with few (if any) adverse effects." They call for government support of the trials: "Because there is little commercial interest and incentive to test such an inexpensive and nonpatentable intervention as folate (in contrast to cholesterol-lowering medication), the National Institutes of Health must step in to serve the public's interest to fund such trials. Further delays cannot be justified." (Stampfer 1996)

A study in Oregon "demonstrated that multivitamin users had lower baseline levels of [homocysteine] than nonusers." The multivitamin users also had higher baseline levels of plasma folate, vitamin B-6 and vitamin B-12. The effect of the multivitamins was so significant that Malinow suggests it may be advisable to exclude multivitamin users from clinical trials intended to test the effects of specific vitamins on homocysteine levels or related diseases. (Malinow 1997)

In a study involving about 200 patients who underwent coronary angioplasty, supplementation with 1 mg folic acid, 10 mg vitamin B-6 and 400 μg vitamin B-12 substantially reduced the risk of restenosis (recurrence of artery blockage) during the six months following angioplasty. The authors concluded: "This inexpensive treatment,

which has minimal side effects, should be considered as adjunctive therapy for patients undergoing coronary angioplasty." (Schnyder 2001)

Researchers in England studied the amount of folic acid that would most effectively reduce homocysteine levels in 151 patients with heart disease. Dosages used ranged from 0.2 to 1.0 mg of folic acid per day. There was a clear dose response, with increased levels of folic acid resulting in lower levels of homocysteine, up to 0.8 mg of folic acid daily. One milligram of folic acid was not more effective than 0.8 mg in this regard. The authors concluded that 0.8 mg of folic acid is needed in order to achieve maximum reduction in levels of homocysteine. They believe current folic acid fortification levels in the United States will achieve only a small fraction of the possible population benefit and suggest that it would be reasonable for physicians to advise patients with heart disease to take 0.8 mg of supplemental folic acid every day. (Wald 2001)

In an ongoing study of a group of elderly people in New Mexico, researchers found that about one-half of the population used supplements containing folic acid, B-6, and B-12. Supplement users had lower homocysteine levels than nonusers, and these levels were not further affected by increases in the amount of folate consumed from foods. In those who did not use supplements, higher levels of consumption of food folate resulted in lower levels of homocysteine. In terms of folate intake from foods, 85 percent of the participants obtained less than 400 μg per day (the Recommended Dietary Allowance for adults), and 62 percent obtained less than 320 μg per day (the Estimated Average Requirement for adults). Homocysteine levels were higher in people who consumed relatively higher amounts of coffee, tea, or alcohol, compared to people who consumed less. (Koehler 2001)

In a case-control study in Finland, high homocysteine levels were associated with an increased risk of a later heart attack in men who already had a history of heart disease but not in men who did not have heart disease at the beginning of the study. (Knekt 2001)

A population study in Norway followed a cohort of more than 4700 men and women over the age of 65 for about four years. Researchers found a strong association between higher levels of homocysteine and mortality from cardiovascular disease. Higher homocysteine levels were also associated with an increased risk of dying from cancer. (Vollset 2001)

Researchers at the USDA Human Nutrition Research Center on Aging at Tufts University studied whether a multivitamin/mineral supplement would further reduce homocysteine levels and increase plasma levels of folate, B-12, and B-6 in elderly adults who were *already consuming a diet containing grain products fortified with folic acid*. They found that the multivitamin increased plasma levels of these three B vitamins and decreased homocysteine levels by about 10 percent. (McKay 2000)

What Does the Food and Nutrition Board Recommend?

The Food and Nutrition Board of the Institute of Medicine issued new dietary recommendations for the B vitamins in 1998. The recommendations for adults for folic acid, vitamin B-6 and vitamin B-12 are shown in the table below.

GROUP	FOLIC ACID	B-6	B-12
Adults 19-30	400 μg	1.3 mg	2.4 μg
Adults 31-50	400 μg	1.3 mg	2.4 μg
Women over 50	400 μg	1.5 mg	2.4 μg
Men over 50	400 μg	1.7 mg	2.4 μg

For men and women over 50, the Food and Nutrition Board recommends that most of the B-12 intake "be obtained by consuming foods fortified with B-12 or a B-12-containing supplement." The reason for this is that a substantial percent of people over 50 have low stomach acid secretion, which decreases their absorption of vitamin B-12 from food but does not alter their absorption of crystalline vitamin B-12 from supplements or fortified foods. In addition, a supplemental source of folic acid is recommended for women of childbearing age (see chapter on folic acid and neural tube birth defects). The Food and Nutrition Board does not make a recommendation for supplemental B-6, but does cite dietary surveys showing that only about half of men and women over 50 get the recommended amount of B-6 from their diets.

On the specific issue of B vitamins and cardiovascular disease, the Food and Nutrition Board recognizes that it is "well established" that increasing folic acid intake will reduce homocysteine levels. However, the Food and Nutrition Board believes more evidence is needed before concluding that decreasing homocysteine levels will also decrease cardiovascular disease risk.

What Does the American Heart Association Recommend?

In a statement issued in 1999, the Nutrition Committee of the American Heart Association advised that the evidence on B vitamins, homocysteine levels, and cardiovascular disease is extensive, but not conclusive. More research was recommended. In the meantime, the American Heart Association urged people to consume RDA levels of folate and vitamins B-6 and B-12. Screening for high homocysteine levels was recommended in selected patients, including those with a personal or family history of premature cardiovascular disease. If homocysteine levels in these patients are above 10 micromoles per liter, then "it may be advisable to increase their intake of vitamin-fortified foods and/or to suggest the daily use of supplemental vitamins, i.e., 0.4 mg of folic acid, 2 mg of vitamin B-6 and 6 μg of vitamin B-12, with appropriate medical evaluation and monitoring." (Malinow 1999)

Why Do Some Researchers Think We Need More Evidence Before Making Recommendations?

While many researchers believe the evidence is strong enough to support a simple recommendation like taking a daily multivitamin in order to reduce the risk of cardiovascular disease, others believe more evidence is necessary. It is clear that folic acid (and to a lesser degree, vitamin B-6 and vitamin B-12) will lower homocysteine levels. It is also clear that people with lower homocysteine levels have a lower risk of cardiovascular disease. The missing link is a direct connection between the B vitamins and cardiovascular disease. The question is: In people who already have higher homocysteine levels, will lowering those levels also lower their risk of heart disease? Definitively answering this question will take one or more large clinical trials extending over several years. Described below are a number of trials already under way, with results expected in the next few years. Another focus of research concerns the mechanism(s) by which moderate increases in homocysteine could increase risk of cardiovascular disease. Some have suggested that elevated homocysteine levels may be a marker of existing disease rather than a predictor of future disease risk in otherwise healthy people. (Knekt 2001, Brattstrom 2000, Meleady 1999)

What New Clinical Trials Are Currently Under Way?

Nine new clinical trials are under way in several countries, involving over 40,000 patients with a history of heart disease or stroke. All nine will test the effects of folic acid as compared to a placebo, and some will also test the effects of vitamins B-6 and B-12. All of the trials started between 1997 and 1999 and are designed to continue for five or six years. The amount of folic acid being used ranges from a low of 0.2 mg (200 μg) to a maximum of 5 mg. Vitamin B-6 is supplemented at levels of 25 to 50 mg, and vitamin B-12 at levels of 0.06 mg (60 μg) to 1 mg (1000 μg). Two of the studies also include pharmaceutical treatments—simvistatin for cholesterol reduction in the Cambridge study and a blood pressure treatment in the Australian study. The names and locations of the studies are listed below. (Clarke and Collins 1998, Eikelboom 1999, Booth 2000)

1. Vitamin Intervention for Stroke Prevention (VISP), Wake Forest University, USA
2. Women's Antioxidant and Cardiovascular Disease Study (WACS), Harvard Medical School, USA
3. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH), University of Oxford, UK
4. Norwegian Study of Homocysteine Lowering with B-vitamins in Myocardial Infarction (NORVIT), University of Tromso, Norway
5. Bergen Vitamin Study, University of Bergen, Norway
6. Prevention with a Combined Inhibitor and Folate in Coronary Heart Disease (PACIFIC), University of Sydney, Australia
7. Cambridge Heart Antioxidant Study (CHAOS-2), University of Cambridge, UK
8. Heart Outcomes Prevention Evaluation Study (HOPE-2), McMaster University, Canada
9. Vitamins to Prevent Stroke Study (VITATOPS), Royal Perth Hospital, University of Western Australia, Australia

What Would Be the Costs and Potential Benefits of Providing These B Vitamins to the Populations?

Based on the assumption that supplementation with one or more B vitamins would be effective in reducing the risk of cardiovascular disease, researchers at the University of California in San Francisco used a mathematical model to predict the number of heart attacks and deaths that could be avoided and the medical costs that could be saved by folic acid fortification of grain products and by targeted supplementation with folic acid and vitamin B-12. One model predicted that *fortification with folic acid* would reduce heart attacks (myocardial infarctions) by 13 percent in men and by 8 percent in women over a 10-year period, with similar reductions in mortality from coronary heart disease. In addition, the model predicted that if all patients with heart disease were *supplemented with 1 mg of folic acid and 0.5 mg of vitamin B-12*, an additional 310,000 deaths from heart disease could be avoided over a 10-year period. Even counting the cost of the supplements, this intervention was predicted to save lives as well as a substantial amount of money among people with pre-existing heart disease. Finally, the model considered whether supplementation would save lives and money among adults *without* pre-existing heart disease. Assuming the intervention is effective in reducing the incidence of heart disease, the model suggests it would be cost-effective to routinely provide folic acid and B-12 supplements to men over 45 and women over 55. (Tice 2001)

Researchers at the University of Michigan Medical School examined the cost of providing men over 40 and women over 50 with daily supplementation of 400 μg folic acid and 500 μg of vitamin B-12. The cost of a "treat all" approach was compared to the cost of a "screen and treat" approach, in which people would be screened for homocysteine levels and only those with elevated levels (over 11 μmol/L) would be provided with supplements. The economic model predicted that either approach would save about nine life-years per 1000 men and about four life-years per 1000 women. The overall cost of the "screen and treat" strategy was just over $100 per person and was lower than the overall cost of the "treat all" strategy, which was near $300 per person. The researchers conclude that the screen and treat approach is more cost-effective, but that either of these strategies "could lead to substantial cardiovascular benefits at reasonable costs." (Nallamothu 2000)

Are There Other Potential Health Benefits of These B Vitamins?

There is clear and compelling evidence that folic acid supplementation can prevent a substantial fraction of neural tube birth defects, and educational programs are underway to spread this message to all women of childbearing age. See the chapter on folic acid and birth defects for a complete discussion.

Scientific studies also suggest the possibility that increased intakes of folic acid may reduce the risk of some cancers, and additional studies will be examining this association. (Choi 2000, Kim 1999, Shrubsole 2001)

Folate and vitamin B-12 also play a role in cognitive function, and it has been suggested that low intakes of one or both of these vitamins may increase the risk of Alzheimer's disease. (Snowdon 2000, Weir 2000, Wang 2001) "No other organ system in the body has a greater minute-to-minute dependence on its nutrient supply than the central nervous system." In turn, the central nervous system influences eating behavior and thus dietary intake. "Although severe vitamin deficiencies and congenital defects are rare, milder subclinical vitamin deficiencies are not uncommon in the elderly. Interest is increasing in learning the extent to which these mild, reversible deficiencies contribute to some decline in cognitive function in the later years of life." It is well established that deficiencies of the B vitamins involved in the single-carbon cycle have severe effects on brain function that can result in depression, dementia, and other disorders. Results of some studies "support the possibility that poor vitamin status is partially responsible for the cognitive decline seen in some elderly persons." (Selhub 2000) (See the chapter on antioxidants and eye, lung, and brain function for more information.)

The B vitamins generally serve as cofactors required for the function of numerous enzymes. Dr. Bruce Ames of the University of California at Berkeley has observed that there is natural variability in the functioning of many key enzymes, that this variability in some cases is due to genetic mutations, and that low enzyme activity in many instances can have serious health consequences. "About 50 human genetic diseases due to defective enzymes can be remedied or ameliorated by the administration of high doses of the vitamin component of the corresponding coenzyme, which at least partially restores enzymatic activity." Compensating for inadequate enzyme activity by providing high doses of vitamins could have an impact on numerous disease conditions including heart disease, cancer, and Alzheimer's disease. He concludes: "With the advent of genomics and individual polymorphism assessment, it will become possible to customize vitamin therapies to suit the genotypic, and thus more specific, needs of individuals, instead of treating the phenotype. For now, for many of the conditions discussed, high-dose B vitamin pills or high doses of individual vitamins are available to physicians as reasonably safe and potentially helpful therapies; however, the possibility of some accompanying side effects should not be discounted." (Ames 2002)

Bottom Line

A substantial volume of scientific evidence indicates that folic acid reduces blood levels of homocysteine, and that people with low levels of homocysteine have a decreased risk of heart attack and stroke. Other B vitamins, especially B-6 and B-12, also appear to play a beneficial role. Users of multivitamin supplements have lower homocysteine levels and lower risk of heart disease. While more research is needed, several experts suggest that it makes sense to increase folic acid intakes even while further investigation continues. Taking a multivitamin containing folic acid is an easy and economical way to accomplish this goal, and the multivitamin will also provide vitamin B-6 and B-12.

In a review on homocysteine, folic acid, and cardiovascular disease risk, Beresford and Boushey reiterate this advice: "On an individual basis, we recommend taking a dietary supplement of 400 μg/d folic acid to prevent vascular disease. This recommendation has particular potential benefit for middle aged and older people, both men and women." (Beresford and Boushey, 1997)

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