

NUTRITION

Folic Acid Fortification Is Safe, Effective, and Important from the Cradle to the Later Years

In 1998 the U.S. government mandated that cereal-grain products be fortified with folic acid. The fortification program has been successful in meeting its initial targets of improving the folate status of women of childbearing age and, thus, reducing the incidence of neural tube and other birth defects. To accurately assess the effects of the fortification program, blood levels of folate in a nationally representative sample of 7,300 participants in the National Health and Nutrition Examination Survey (NHANES) IV, part I (1999–2000) were compared with those from participants in NHANES III (1988–1994), which predated mandatory fortification (3,9). Compared with the NHANES III data, dietary, serum and erythrocyte folate concentrations increased in all gender and age groups, except in females over 60 years of age. The mean dietary total folate intake for the NHANES IV, part I, population increased by 76 µg/day (28%), from 275 to 351 µg/day. The increases in dietary folate translated into a greater than twofold increase in mean serum folate, from 11.4 to 26.9 nmol/L. The number of adults with low serum folate concentrations (<6.8 nmol/L) decreased from 16% before to 0.5% after fortification. Despite these dramatic gains, the authors (9) noted that further increases are still needed for women of childbearing age because less than 10% reached the recommended erythrocyte folate concentration of >906 nmol/L, the level associated with a significant reduction in neural tube defect risk.



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The study also measured whether folate intakes were too high in any population segment. There is concern that high folate levels could potentially mask vitamin B₁₂ deficiency. This is of special concern for older populations who are at risk for B₁₂ deficiency; B₁₂ deficiency could be masked by folate because of decreased ability to absorb B₁₂. In addition, diets consumed by elderly populations may deliver insufficient vitamin B₁₂ because natural dietary sources (meat and other animal products) may be too expensive or hard to chew. The analysis showed that in elderly persons, the prevalence of high serum folate concentrations (>45.3 nmol/L) increased from 7% before to 38% after fortification. The risk of folate masking vitamin B₁₂ deficiency, however, is low because only 3% of the elderly had marginally low serum vitamin B₁₂ concentrations (<148 pmol/L). Of interest for cereal chemists is the fact that cereal-based foods have become the most important dietary contributor of folate. Prior to fortification the largest contributors of folate were fruits and vegetables.

Other potential beneficial effects of folate were assessed by monitoring two coronary artery disease risk factors, plasma total homocysteine (tHcy) and methylmalonic acid (MMA). These markers were chosen because when folate status is inadequate, the conversion of methionine to cysteine is impaired, elevating tHcy and MMA in the bloodstream. In the NHANES IV, part I, population, 7% had elevated plasma MMA concentrations (>370 nmol/L), but 78% had plasma tHcy concentrations lower than 9 µmol/L. After analyzing the data, the authors concluded that "Every segment of the US population appears to benefit from folic acid fortification." Preliminary data from the Baltimore Longitudinal Study of Aging indicates that folate also may reduce the risk of developing Alzheimer's disease (AD) (2). In the 600 men and women over 60 years of age who participated in the study, those who, by self report, consumed at least 400 µg of folate each day had a 55% reduction in risk of AD. Most people in the study reached the RDA for folate by taking folic acid supplements. Of the vitamins studied, vitamins E, C, B₆, B₁₂, and folate, only folate was associated with a significantly decreased risk of AD. There are several ways in which folate is thought to impact the risk of developing AD. The primary means is through the lowering of tHcy levels. Recent animal studies suggest that high tHcy (and low folic acid) levels may make brain cells more vulnerable to damage from β-amyloid. There is also some evidence that homocysteine may cause direct toxicity of neuronal cells. The authors of the study stated that these associative data show promise, but urged further study, noting it is possible that other factors may be responsible for the reduction in risk. People with a high intake of one nutrient are likely to have a high intake of several nutrients and may generally have a healthy lifestyle.

One recent Dutch intervention study (4), while not looking specifically at AD, did show a positive effect of higher levels of folic acid on the maintenance of brain function in people aged 50–75 years. In this study, subjects (*n* = 818) with elevated levels of tHcy were either assigned to take 800 µg of folic acid a day or a placebo during the three years of the study. Blood folate levels for those in the supplement group increased fivefold, and tHcy concentrations decreased by around 25% by the end of the study. In several cognitive tests the folate-supplemented group performed significantly better than the placebo group. At the end of the study, those taking folic acid had scores on tests of memory comparable to people 5.5 years younger. On tests of cognitive speed, folic acid helped users perform as well as people 1.9 years younger.

Previous studies have shown that people with low folate levels have a higher risk of both heart disease and diminished cognitive function. Further study is needed to document the effect of folate intervention and to determine whether the effect is due to lowered tHcy, reduced inflammation, or altered expression of dementia-related genes or other potential mechanisms. One such trial sponsored by the U.S. National Institutes of Health is testing whether very high doses of folic acid and vitamins B₆ and B₁₂ can slow the rate of mental decline in people with AD. It is expected to be completed in 2006.

A study by Van Guelpen and coworkers (10) found that folate may also protect against hemorrhagic stroke independent of its role in lowering tHcy levels. High homocysteine levels have been associated with higher risk of stroke. Blood and dietary levels of folate and vitamin B₁₂ were measured in 62 patients who had a hemorrhagic stroke and 334 who had an ischemic stroke. Blood and dietary levels of folate were inversely associated with the risk of hemorrhagic stroke, even after accounting for homocysteine levels and other risk factors like high blood pressure. However, no association was seen between blood levels of vitamin B₁₂ and either type of stroke or between dietary folate and the risk of ischemic

stroke. The authors noted that grains in Sweden are not fortified with folate and intake of fruit and vegetables is relatively low, so levels of folate in the diet might have been too low to show a protective effect against ischemic stroke.

Whole-Grain Consumption and Atherosclerosis

A study of 229 women with a history of heart disease showed that those who ate six or more servings of whole grains per week had a slower progression of atherosclerosis (5). Dietary intake data taken from questionnaires were correlated with angiograms assessing changes over a 3-year period in the diameter of the subjects' coronary arteries. Researchers found that the progression of stenosis was slower in women who reported higher intakes of cereal fiber from whole-grain foods than those reporting lower intakes. The data suggest that following current dietary recommendations can slow the rate of heart disease progression. These data were robust after taking into account other dietary factors that affect vessel narrowing, including intake of fats, cholesterol, essential nutrients, and alcohol. Intakes of total, fruit, and vegetable fibers and number of servings of refined grains, fruits, or vegetables were not associated with progression of stenosis.

Low-Carb Versus High-Carb Diets for Weight Loss and Health

In an Australian study in which calories were carefully controlled, diets high in saturated fat and very low in carbohydrate were compared with diets high in unsaturated fat and traditional low-fat diets (8). Diets were very low fat (VLF) (70:10:20, carbohydrate/fat/protein; 3% saturated fat), high unsaturated fat (HUF) (50:30:20, carbohydrate/fat/protein; 6% saturated fat), or very low carbohydrate (VLC) (4:61:35, carbohydrate/fat/protein; 20% saturated fat). In this 8-week study with 83 middle-aged, overweight (average BMI 33 kg/m²), insulin-resistant subjects, all three diets resulted in the same amount of weight lost. However, there was greater loss of lean body tissue with the VLC and VLF diets compared with the HUF diet (32, 31, and 21%, respectively). The VLC diet, relative to the other two diets, caused a number of markers for coronary disease risk to improve, including increased HDL-C and decreased triglyceride. However, LDL rose by 7%, and plasma homocysteine increased 6.6% with the VLC diet. No such changes were seen with the other diets. The VLC diet also improved some markers of abnormal glucose tolerance. With the VLC diet the drop in fasting insulin was 33% compared with a 19% drop with the HUF diet. Fasting insulin was unchanged with the VLF diet. The VLC diet also promoted significantly lower postprandial glucose and insulin responses than the VLF and HUF diets. All diets decreased fasting glucose, blood pressure, and C-reactive peptide. This study shows that a VLC diet could be useful for those with insulin resistance, because it was more effective in improving triacylglycerols, HDL-C, and fasting and postprandial glucose and insulin concentrations. VLC diets may be useful in the short-term management of subjects with insulin resistance and hypertriglyceridemia.

This study agrees with many of the findings from a recent review published in the *International Journal of Obesity* (6) that compared weight loss diets with varying proportions of carbohydrate and fat. In the reviewed studies, there was more rapid weight loss after 3 and 6 months with low-carb diets compared with low-fat diets. After 1 year, however, weight losses were the same with both types of diets. Both types of diets improved risk factors for coronary heart disease. Low-carb diets, however, led to greater decreases in serum triglyceride and increases in HDL cholesterol compared with low-fat diets. Blood pressure, insulin sensitivity, and LDL cholesterol were improved to a similar degree by the two types of diets. The authors of the review suggested that there were several mechanisms for initial weight loss associated with low-carb diets. First, it is thought that the high protein content of the diet suppresses appetite. Second, they suggested that there is some satiety effect due to the ketogenic nature of the diet, with satiety signals for fat being

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active. Third, the authors speculated that through the absence of hunger-promoting carbohydrate components less food is eaten.

Several studies have looked at protein intake and its effect on dietary intake. A recent study kept carbohydrate constant and looked at the effect of increasing protein on appetite. In one study, 19 subjects first followed a weight-maintenance diet for 2 weeks, in which protein accounted for 15%, fat 35%, and carbohydrate 50% of calories (11). For the second 2 weeks, the subjects followed an isocaloric diet that was 30% protein, 20% fat, and 50% carbohydrate. Finally, for 12 weeks the subjects followed a diet in which there was no restriction on calories but the proportions were the same as the second phase (30% protein, 20% fat, and 50% carbohydrate). Appetite, caloric intake, body weight, and fat mass were measured throughout. After each phase of the study, blood levels of the hormones insulin, leptin (the hormone responsible for satiety), and ghrelin (the hormone responsible for hunger) were measured. During the short isocaloric phase with higher protein, subjects reported greater satiety although there were no measurable changes in satiety hormones. With the ad libitum high-protein diet, the participants' average spontaneous calorie intake decreased by between 376 and 504 cal per day, their body weight decreased by between 4.4 and 5.4 kg, and their fat mass decreased by between 3.3 and 4.1 kg. Leptin levels significantly decreased during this phase, and ghrelin increased. The authors concluded that since the carbohydrate was kept constant during the study, the effects appeared to be due to the high protein intake. (*Columnists' note:* This may be true but the protein to fat ratio also changed, and it is possible that micronutrient content changed.)

In the editorial accompanying the article, Danish obesity researcher Arne Astrup (1) argued the risk-benefit of additional protein. He cited the Institute of Medicine, which has found no potential adverse effects of a high-protein diet or any clear evidence that high protein intake increases the risk of renal stones, osteoporosis, cancer, or cardiovascular disease and sets the acceptable range of protein intake as between 10 and 35% of calories. He argues that there is a low risk from protein based on the backdrop of known risks of overweight, including the risk of developing chronic diseases such as cardiovascular disease, hypertension, and type II diabetes. The other aspect that needs to be considered in making such a recommendation is that many protein choices are high in saturated fats. Thus, proteins need to be selected from low-fat meats and dairy and fish and legumes.

Type of Breakfast and School Performance

Oatmeal was again ranked as an excellent choice for breakfast in a recent study conducted by Tufts and Quaker Oats on the effects of no breakfast, breakfast type, and learning activities (7). In this cross-over design study, elementary school children were tested with a variety of cognitive tests after eating one of two common breakfasts for 3 weeks. The two breakfasts were instant oatmeal and ready-to-eat (RTE) cereal, which were similar in energy, but differed in macronutrient composition, processing characteristics, effects on digestion and metabolism, and glycemic score. Results with 9–11 year olds replicated previous findings showing that breakfast intake enhances cognitive performance, particularly on tasks requiring processing of complex visual displays. The results extend previous findings by showing differential effects of breakfast type. Boys and girls showed enhanced spatial memory and girls showed improved short-term memory after consuming oatmeal. Results with 6–8 year olds also showed effects of breakfast type. Younger children had better spatial memory and better auditory attention and girls exhibited better short-term memory after consuming oatmeal. Based on compositional differences in protein and fiber content, glycemic scores, and rate of digestion, oatmeal may provide a slower and more sustained energy source and consequently result in cognitive enhancement compared with low-fiber, high-glycemic response RTE cereal. These results have important practical implications, suggesting the importance of what children consume for breakfast before school.

A meta-review (12) of what factors influence cancer risk affirms the percentages mentioned by Richard Doll more than 30 years ago, i.e., that dietary factors, including physical inactivity, may contribute to approximately one-third of all cancers. The meta-review shows there is relatively strong and consistent data from prospective epidemiologic studies that associate regular physical activity and minimal adult weight gain with lower risk of colorectal and breast cancer. Fruits, vegetables, and whole grains are the foods most strongly associated with reduced cancer risk. The review also assesses the strength of evidence from secondary prevention trials and observational prospective epidemiologic studies that shows the efficacy of a Mediterranean-type dietary pattern or DASH-type diet in decreasing the risk of both cancer and cardiovascular disease.

The authors recommended adopting dietary patterns emphasizing regular physical activity, fruits and vegetables, whole grains, legumes, nuts, seeds, and low-fat dairy products for those at risk for cancer and cardiovascular disease. There is nothing revolutionary about these findings, and in many ways, this is comforting. Science, after all, is evolutionary not revolutionary. One of the things the authors of this piece emphasized, which is sometimes omitted in nutrition studies, is that food recommendations may be easily incorporated into enjoyable cultural food patterns, as exemplified by Mediterranean-type diets. They further note that the preparation and enjoyment of meals in a convivial atmosphere is a vital component of healthy lifestyles that can help prevent chronic diseases such as cancer and certain cardiovascular diseases.

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