

Folic Acid References

A sample of existing research

Preterm and Low Birth Weight

Catov, JM et al. *Association of periconceptional multivitamin use and risk of preterm or small-for-gestational-age births*. Am J Epidemiol. 2007 Aug;166(3):296-303. Epub 2007 May 11. (6 months of use). Effect in non-obese women only. Reduced risk for preterm birth less than 34 weeks.

Bukowski R, et al. *Preconceptional folate supplementation and the risk of spontaneous preterm birth: a cohort study*. PLoS Med. 2009 May 5;6(5):e1000077. Pre-conception folate supplementation associated with 50-70% reduction in incidence of early spontaneous preterm birth between 20-28 wks. 50% decrease between 28-32 weeks. Lowest risk with folate supplementation for 1 year or longer.

Timmermans S. et al, *Periconception folic acid supplementation, fetal growth and the risks of low birth weight and preterm birth: the Generation Study*. Br J Nutr. 2009 Mar 30;101:1-9. Periconception folic acid supplementation is associated with increased fetal growth resulting in higher placental and birth weight, and decreased risks of low birth weight and SGA.

Placental Infarction or Abruption, Recurrent Pregnancy Loss, Pre-Eclampsia

Folic Acid and Homocysteine Metabolic Defects and the Risk of Placental Abruption, Pre-Eclampsia and Spontaneous Pregnancy Loss: A Systematic Review, Placenta, Volume 20, Issue 7, Pages 519-529, 1999. Possible relationship between these complications and folate deficiency.

Neural Tube Defects

Wolff T, et al. *Folic acid supplementation for the prevention of neural tube defects: an update of the evidence for the U.s. Preventive services Task Force*. Ann Intern Med. 2009 May 5; 150 (9): 632-0.

Cleft Lip and Cleft Palate

Wicox, A et al. *Folic acid supplements and the risk of facial clefts: A national population-based control study*, BMJ, 2007. 400 mcg/day reduced risk of isolated cleft lip with or without cleft palate by one third. No apparent effect on the risk of cleft palate alone.

Badovinac RL, et al. *Folic acid-containing supplement consumption during pregnancy and risk for oral clefts: a meta-analysis*. Birth Defects Res A Clin Mol Teratol. 2007 Jan;79(1): 8-15. Protective effect of folic acid containing supplement intake during pregnancy on oral clefts. Conclusion tempered by the potential for bias and uncontrolled confounding.

Other Health Issues

1. Cardiovascular disease

Forman JP, et al. *Folate intake and the risk of hypertension among US women*. JAMA 2005, Jan 19-29;320-9

Women ages 27-44 years taking 1000 mcg of folate x 8 years, 46% lower risk of developing hypertension than those consuming less than 200 mcg. 43-70 years, 18% lower risk

Lobo Arlene, et al. *Reduction of homocysteine levels in coronary artery disease by low-dose folic acid combined with vitamins B6 and B12*, American Journal of Cardiology. Vol 83, March 15, 1999. P 821-25. Daily dose of 400 mcg of folic acid combined with vitamins B6 (12.5 mg) and B12 (500 mcg) will normalize homocysteine levels in heart disease patients.

Rimm, Eric, B folate and vitamin B6 and cardiovascular disease. JAMA, vol 279. Feb. 4, 1998 p 392-93. Higher intake of folic acid (at least 545 mcg) and B6 (at least 5.9 mg) protects women against nonfatal heart attacks and fatal coronary heart disease. (American nurses study, Harvard School of PH)

McCully, Kilmer S. Homocysteine, folate, vitamin B6 and cardiovascular disease, JAMA, Vol. 29, Feb 4, 1998, p 392-93 (editorial)

2. Cancer

Yang et al. *Serum folate and cancer mortality among US Adults: findings from the Third National Health and Nutritional Examination Survey linked mortality file*, Cancer Epidemiol Biomarkers Prev 2009 May; 18(5): 1439-47.

May be a nonlinear relationship between folate status and risk of all-cancer mortality among persons with low, but not grossly deficient serum blood folate concentrations.

3. Cervical cancer

Pivathilake CJ, et al. *Lower risk of cervical intraepithelial neoplasia in women with high plasma folate and sufficient B12 in the post-folic fortification era*. Cancer Prev Res 9Phila PA. 2009 Jul;2(7): 658-64. Higher folate is associated with significantly lower risk of CIN, especially when B12 is sufficient, demonstrating the importance of B12 in the high-folate environment created by the folic acid fortification program.

Ghosh C, et al. Dietary intakes of selected nutrients and food groups and risk of cervical cancer. Nutri Cancer 2008;60(3):3331-41. Significant reductions in risk of approximately 40-60% were observed for women in the highest vs lowest tertiles of dietary fiber, vit C, E, A, alpha-carotene, betacarotene, lutein, folate and total fruit and vegetable intake. Diet rich in plant-based nutrients may be important in reducing risk of cervical cancer.

Piyathilake CJ, et al. *Folate is associated with the natural history of high-risk human papillomaviruses*. *Cancer Res.* 2004 Dec 1;64(23):8788-93. Independent protective role of higher folate status on several aspects of the natural history of high-risk HPV after controlling for known risk factors and other micronutrients. Improving folate status in subjects at risk of getting infected or already infected with high-risk HPV may have a beneficial impact in the prevention of cervical cancer.

Dementia and strokes

Elby, E. et al. *Folate status, vascular disease and cognition in elderly Canadians*. *Age and Aging*. Vol 27. July 1998. P 485-91. Subjects 65 years or older with low folate levels had a higher risk for ischemic stroke and were associated with increase in depression and dementia.

Reynolds, E.H. folic acid, ageing, depression and dementia. *BMJ*, vol 324. June 22, 2002. P 1512-15. Alzheimer's patients cognitive decline associated with elevated homocysteine levels.

Seshadri, Sudha, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's Disease. *NEJM*, vol 346. Feb 14, 2002 P 476-83. May be possible to substantially lower one's risk of AD by supplementing with folic acid, B6 and B 12.

4. Age-related macular degeneration

Christen, WG, et al. folic acid, pyridoxine, and cyanocobalamin combination treatment and age-related macular degeneration in women: the women's antioxidant and folic Acid Cardiovascular Study, *Arch Intern Med*. 2009 Feb 23;169 (4): 335-41 Daily use of the following nutrients may reduce risk of AMD. Folic acid 2.5 mg, B6 50 mg, B 12 1 mg