

# The Whitehall-Robins Supplement

## A Selection of Recent Findings in the Field of Nutrition

Sept 2008 - Volume 12, Number 3

### **Efficacy of folic acid supplementation in stroke prevention: a meta-analysis.**

Cardiovascular disease is the leading cause of death in the world. Raised blood concentrations of the amino acid homocysteine have been suggested as a modifiable, independent risk factor for coronary artery disease, stroke and deep venous thrombosis. Earlier epidemiological evidence from case-control studies, meta-analysis of prospective studies and genetic studies provided support that the association between high homocysteine and cardiovascular disease is causal. However, inconsistent results from randomized controlled trials raised doubt that lowering homocysteine concentrations with folic acid supplementation can reduce the risk of cardiovascular disease. Almost all the clinical trials should be considered as secondary and not primary prevention trials as they were conducted in patients with pre-existing cardiovascular disease. In addition, cardiovascular disease is a heterogeneous clinical condition and different cardiovascular events could respond differently to folic acid supplementation and this suggestion is supported by the results from some of the clinical trials. There is growing evidence that reducing the risk of stroke is one of the end points that could be achieved with folic acid supplementation. It was recently reported in a population-based study that there was a decline in stroke mortality between 1998-2002 in Canada and the USA since both countries implemented folic acid fortification of grain products in 1998. The aim of this meta-analysis is to evaluate the randomized trials and assess whether folic acid supplementation is efficacious in the prevention of stroke. This meta-analysis reported an overall significant reduction (18%) in the risk of stroke with folic acid supplementation. The risk reduction was greater when folic acid supplementation was used for more than 3 years (29%), more than 20% decrease in homocysteine concentration (23%), when grain is not fortified (25%), and in individuals with no history of stroke (25%). The authors conclude, "Our findings indicate that folic acid supplementation can effectively reduce the risk of stroke in primary prevention."

[Wang X, et al. *Lancet* 2007; 369:1876-1882]

### **Prenatal multivitamin supplementation and rates of pediatric cancers: A meta-analysis.**

In 2005, nearly 10,000 children in the United States under the age of 15 were diagnosed with cancer. The most common forms of cancer are leukemia, brain and spinal cord malignant tumors, and neuroblastoma. It is generally recommended that women of childbearing potential should supplement with folic acid pre-conceptionally and in early pregnancy to reduce the risk of neural tube defects (NTDs). There is growing evidence suggesting that consuming folic acid containing multivitamins may prevent congenital anomalies other than NTDs. Furthermore, several studies investigated the association between multivitamin use pre-conceptionally and in early pregnancy on rates of common tumors in children. This study conducted a systematic review and meta-analysis of this potential association. The findings from this meta-analysis suggested that prenatal supplementation with multivitamins containing folic acid is associated with 18% reduction in risk of brain tumors in children, 47% for neuroblastoma, and 36% for leukemia. The authors conclude "In conclusion, maternal ingestion of prenatal multivitamins is associated with a decreased risk of pediatric brain tumors, neuroblastoma, and leukemia. Presently, it is not known which constituent(s) among multivitamins confer this protective effect."

[Goh YI, et al. *Clin Pharmacol Therap* 2007; 81:685-691]

### **Serum 25-hydroxyvitamin D, ethnicity, and blood pressure in the Third National Health and Nutrition Examination Survey.**

It is recognized that alteration in calcium metabolism can influence the regulation of blood pressure (BP), hence the possibility that vitamin D may have a role in this regulation. Serum 25-hydroxyvitamin D (25 OHD) is increased in vitamin D deficiency. A recent US study reported a positive association between (25 OHD) and BP. The association between vitamin D and BP may explain some of the regional and ethnic variations in hypertension. It is well known that blood pressure is higher in British and American blacks compared with whites. This study analyzed a large sample of participants in an ongoing survey of the US population. The analyses comprised of 12,644 participants  $\geq 20$  years with measurements of BP and 25 OHD, and excluding those on hypertensive medication. The main aims of the study are to examine whether vitamin D status is inversely related to systolic and diastolic BP and whether ethnic differences in BP could be explained by ethnic differences in vitamin D status. In this study, adjusted mean serum 25 OHD was lowest in non-Hispanic blacks, intermediate in Mexican Americans, and highest in non-Hispanic whites. Systolic blood pressure and pulse pressure were inversely associated with serum 25 OHD. Although the vitamin D related BP differences reported in this article were small, this might still have public health significance. For example, a 2 to 3 mm Hg decrease in systolic BP could produce between 10%-15% decrease in cardiovascular mortality. The inverse association between 25 OHD and systolic BP was particularly strong in participants aged  $\geq 50$  years than younger participants. Ethnic differences in 25 OHD explained about half of the increased hypertension prevalence in non-Hispanic blacks compared with whites. The authors conclude, "Vitamin D status, which is amenable to intervention by safely increasing sun exposure or vitamin D supplementation, was associated inversely with BP in a large sample representative of the US population."

[Scragg R, et al. *Am J Hypertens* 2007; 20:713-719]

### **Folic acid improves vascular reactivity in humans: a meta-analysis of randomized controlled trials.**

There is a large body of epidemiologic evidence suggesting an association between high homocysteine levels and an increased risk of cardiovascular disease (CVD). Folic acid, vitamin B-6 and B-12 can lower high homocysteine concentrations. Endothelial function is a prognostic factor for CVD; however, the effect of folic acid on endothelial function is not well established. The objective of this study was to quantify

# The Whitehall-Robins Supplement

## A Selection of Recent Findings in the Field of Nutrition

the effect of folic acid on endothelial function which was measured with the use of flow-mediated dilatation (FMD). The investigators conducted a meta-analysis of randomized, double-blind, placebo-controlled folic acid trials and endothelial function. In the overall pooled estimate, supplementation with high doses of folic acid for 4 weeks improves FMD assessment of endothelial function. In this meta-analysis, folic acid dose significantly influenced the outcome with a suggestion of a dose-response effect on FMD (Folic acid doses ranged from 400 µg/d to 10,000 µg/d). Optimizing FMD may be crucial in the primary prevention of CVD. The authors conclude, "This study indicates that high doses of folic acid improve endothelial function, which could potentially reduce the risk of cardiovascular disease."

[De Bree A, et al. *Am J Clin Nutr* 2007; 86:610-617]

### **Suggested Readings**

#### **Micronutrients in HIV-positive persons receiving highly active antiretroviral therapy.**

[Drain PK, et al. *Am J Clin Nutr* 2007;85:333-345]

#### **Noninherited risk factors and congenital cardiovascular defects: current knowledge. A scientific statement from the American Heart Association Council cardiovascular disease in the young.**

[Jenkins KJ, et al. *Circulation* 2007; 115: 2995-3014]

#### **Use of calcium or calcium in combination with vitamin D supplementation to prevent fracture and bone loss in people aged 50 years and older: a meta-analysis.**

[Tang BMP, et al. *Lancet* 2007;370:657-666]

#### **Fish consumption, n-3 fatty acids, and subsequent 5-y cognitive decline in elderly men: The Zutphen Elderly Study.**

[van Gelder BM, et al. *Am J Clin Nutr* 2007; 85: 1142-1147]

#### **Vitamin D deficiency.**

[Holick MF. *N Engl J Med* 2007; 357:266-281]

#### **The association between betaine and choline intakes and the plasma concentrations of homocysteine in women.**

[Chiuve SE, et al. *Am J Clin Nutr* 2007;86:1073-1081]

#### **Older adults who use vitamin/mineral supplements differ from nonusers in nutrient intake adequacy and dietary attitudes.**

[Sebastian RS, et al. *J Am Diet Assoc* 2007; 107:1322-1332]

#### **How to select the doses of vitamin D in the management of osteoporosis. [Review]**

[Bischoff-Ferrari HA. *Osteoporos Int* 2007;18:401-407]

#### **Vitamin and mineral supplement use among US medical students: a longitudinal study.**

[Spencer EH, et al. *J Am Diet Assoc* 2006; 106: 1975-1983]

#### **Response of biomarkers of folate and riboflavin status to folate and riboflavin supplementation in healthy and colorectal polyp patients (The FAB2 Study).**

[Powers HJ, et al. *Cancer Epidemiol Biomarkers Prev* 2007; 16:2128-2135]

#### **Vitamin D supplementation and total mortality. A meta-analysis of randomized controlled trials.**

[Autier P, et al. *Arch Intern Med* 2007; 167:1730-1737]

#### **Plasma folate, vitamin B6, vitamin B12, and homocysteine and pancreatic cancer risk in four large cohorts.**

[Schernhammer E, et al. *Cancer Res* 2007; 67:5553-5560]