

# Health Benefits of Nutritional Supplements

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## Selected Abstracts

### Compiled by

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## Forward

The importance of nutrition for human health has long been recognized. Prior to 1960, interest in this field largely focused on the etiology and prevention of acute nutrient deficiency diseases such as scurvy, rickets, and pellagra. Some 50 essential nutrients (vitamins, minerals, antioxidants, cofactors, essential amino acids, essential fatty acids) were identified, and recommended daily intakes for those essential nutrients (e.g. Recommended Dietary Allowances or RDAs) were developed. These recommendations, in turn, proved to be valuable in eradicating acute nutrient deficiency diseases.

During the past 20-30 years, attention has shifted to the role of diet and nutrition in the pathogenesis of chronic degenerative diseases. Heart disease, some cancers, osteoporosis, type II diabetes, and macular degeneration are all known to have dietary risk factors, many of which involve chronic nutrient deficiencies. Importantly, these associations have been much more difficult to study, in large measure because of the time frames involved. Chronic degenerative diseases develop over decades (lifetimes), and it is extremely challenging to conduct research programs for such extended periods. Nevertheless, advances in epidemiological and clinical research have helped us learn a great deal about the impacts (positive and negative) of diet and essential nutrient intakes on long-term health.

During the past decade, the scientific and healthcare communities have paid increasing attention to the role of nutritional supplements (as components of diet) in preventing and treating chronic disease. Hundreds of scientific studies have been conducted and published. These studies span a broad range of health issues. They have employed a wide variety of methodologies. And they have produced both positive and negative results. In some areas (e.g. the role of calcium and vitamin D supplements in slowing the progression of osteoporosis, and the role of folic acid supplements in preventing certain birth defects), results have been consistent, and benefits have been well accepted. In other areas (e.g. the role of antioxidant supplementation in preventing heart disease), results have been less consistent, and conclusions remain controversial. In any event, research on the health benefits of nutritional supplements is progressing, and evidence continues to mount that nutritional supplements offer a convenient and cost effective means for promoting health, over both the short- and long-terms.

The following is a collection of abstracts from about 100 scientific papers describing research on the health benefits of nutritional supplements. This collection is not exhaustive. Papers were selected on the basis of scientific merit and relevance to the field. The majority describes positive results, but in some, negative results are reported. Our objective in compiling this list was to provide readers with a good cross section of the scientific literature so that they could develop a sense for the current state of research in this field and draw their own conclusions concerning the role of supplementation in healthcare. References for many more papers are given in our bibliography entitled *Health Benefits of Nutritional Supplements: Selected Readings* .

For convenience, the abstracts have been sorted by health issue; namely Cardiovascular Health, Cancer Prevention, Strong Bones, Healthy Pregnancies/Healthy Babies, Sound Metabolism, Robust Immune Function, Acute Vision, and Other.

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# Healthy Pregnancies / Healthy Babies

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## **Occurrence of congenital heart defects in relation to maternal multivitamin use.**

Botto LD, Mulinare J, Erickson JD. 2000.  
Am J Epidemiol 151(9):878-84

The purpose of this study was to assess the relation between maternal multivitamin use and risk for cardiac defects in the offspring, using a population-based approach. The Atlanta Birth Defects Case-Control study is a population-based case-control study of infants born between 1968 and 1980 to mothers residing in metropolitan Atlanta, Georgia. The 958 case infants with nonsyndromic cardiac defects were actively ascertained from multiple sources. The 3,029 infants without birth defects (control infants) were selected from birth certificates by stratified random sampling. Periconceptional multivitamin use, defined as reported regular use of multivitamins from 3 months before pregnancy through the first 3 months of pregnancy, was contrasted with no use during the same time period. Periconceptional multivitamin use was associated with a reduced risk for nonsyndromic cardiac defects in the offspring (odds ratio (OR) = 0.76; 95% confidence interval (CI): 0.60, 0.97). The risk reduction was strongest for outflow tract defects (OR = 0.46; 95% CI 0.24, 0.86) and ventricular septal defects (OR = 0.61; 95% CI: 0.38, 0.99). No risk reduction was evident when multivitamin use was begun after the first month of pregnancy. If these associations are causal, the results suggest that approximately one in four major cardiac defects could be prevented by periconceptional multivitamin use.

## **Effect of calcium supplementation on pregnancy-induced hypertension and preeclampsia: a meta-analysis of randomized controlled trials.**

Bucher HC, Guyatt GH, Cook RJ, Hatala R, Cook DJ, Lang JD, Hunt D. 1996.  
JAMA 276(17):1388

**OBJECTIVE:** To review the effect of calcium supplementation during pregnancy on blood pressure, preeclampsia, and adverse outcomes of pregnancy. **DATA SOURCE:** We searched MEDLINE and EMBASE for 1966 to May 1994. We contacted authors of eligible trials to ensure accuracy and completeness of data and to identify unpublished trials. **STUDY SELECTION:** Fourteen randomized trials involving 2459 women were eligible. **DATA EXTRACTION:** Reviewers working independently in pairs abstracted data and assessed validity according to six quality criteria. **DATA SYNTHESIS:** Each trial yielded differences in blood pressure change between calcium supplementation and control groups that we weighted by the inverse of the variance. The pooled analysis showed a reduction in systolic blood pressure of -5.40 mm Hg (95% confidence interval [CI], -7.81 to -3.00 mm Hg;  $P < .001$ ) and in diastolic blood pressure of -3.44 mm Hg (95% CI, -5.20 to -1.68 mm Hg;  $P < .001$ ). The odds ratio for preeclampsia in women with calcium supplementation compared with placebo was 0.38 (95% CI, 0.22 to 0.65). **CONCLUSIONS:** Calcium supplementation during pregnancy leads to an important reduction in systolic and diastolic blood pressure and preeclampsia. While pregnant women at risk of preeclampsia should consider taking calcium, many more patient events are needed to confirm calcium's impact on maternal and fetal morbidity.

## **Visual-acuity development in healthy preterm infants: effect of marine-oil supplementation.**

Carlson SE, Werkman SH, Rhodes PG, Tolley EA. 1993.  
Am J Clin Nutr 58(1):35-42

Docosahexaenoic acid (DHA; 22:6n-3) is important for normal visual development. We hypothesized that preterm infants fed formulas with marine oil as a source of DHA would have better visual acuity than infants fed formulas without marine oil, as measured by the Teller Acuity Card procedure. Marine oil ( $P < 0.001$ ) and age ( $P < 0.0001$ ) influenced visual acuity, by repeated-measures analysis of variance (ANOVA) corrected for the effect of subject. Marine-oil-supplemented infants had better visual acuity than those fed standard formulas at 2 and 4 mo of age, by Fishers' least-squares difference (LSD). Acuity of both dietary groups improved through 6.5 mo of age, then plateaued. Through 4 mo of age, acuity was inversely related to oxygen supplementation ( $\log_{10} h$ ) and positively related to DHA status, by general-linear-models (GLM) analysis. After 4 mo of age, birth weight and gestational age were the only variables consistently related to visual acuity by GLM. We conclude that marine-oil-supplemented formula improved visual acuity of preterm infants through 4 mo of age by improving DHA status.

## **Effect of antioxidants on the occurrence of pre-eclampsia in women at increased risk: a randomized trial.**

Chappell LC, Seed PT, Briley AL, Kelly FJ, Lee R, Hunt BJ, Parmar K, Bewley SJ, Shennan AH, Steer PJ, Poston L. 1999.  
Lancet 354(9181):810-6

**BACKGROUND:** Oxidative stress has been implicated in the pathophysiology of pre-eclampsia. This randomised controlled trial investigated the effect of supplementation with vitamins C and E in women at increased risk of the disorder on plasma markers of vascular endothelial activation and placental insufficiency and the occurrence of pre-eclampsia. **METHODS:** 283 women were identified as being at increased risk of pre-eclampsia by abnormal two-stage uterine-artery doppler analysis or a previous history of the disorder and were randomly assigned vitamin C (1000 mg/day) and vitamin E (400 IU/day) or placebo at 16-22 weeks' gestation. Plasma markers of endothelial activation (plasminogen-activator inhibitor 1 [PAI-1]) and placental dysfunction (PAI-2) were measured every month until delivery. Pre-eclampsia was assessed by the development of proteinuric hypertension. Analyses were done by intention to treat, and in the cohort who completed the study. **FINDINGS:** Supplementation with vitamins C and E was associated with a 21% decrease in the PAI-1/PAI-2 ratio during gestation (95% CI 4-35,  $p=0.015$ ). In the intention-to-treat cohort, pre-eclampsia occurred in 24 (17%) of 142 women in the placebo group and 11 (8%) of 141 in the vitamin group (adjusted odds ratio 0.39 [0.17-0.90],  $p=0.02$ ). In the cohort who completed the study (81 placebo group, 79 vitamin group), the odds ratio for pre-eclampsia was 0.24 (0.08-0.70,  $p=0.002$ ). **INTERPRETATION:** Supplementation with vitamins C and E may be beneficial in the prevention of pre-eclampsia in women at increased risk of the disease. Multicentre trials are needed to show whether vitamin supplementation affects the occurrence of pre-eclampsia in low-risk women and to confirm our results in larger groups of high-risk women from different populations.

## **Prevention of the first occurrence of neural-tube defects by periconceptual vitamin supplementation.**

Czeizel AE, Dudas I. 1992.  
N Engl J Med 327(26):1832-5

**BACKGROUND.** The risk of recurrent neural-tube defects is decreased in women who take folic acid or multivitamins containing such during the periconceptual period. The extent to which folic acid supplementation can reduce the first occurrence of defects is not known. **METHODS.** We conducted a randomized, controlled trial of periconceptual multivitamin supplementation to test the efficacy of this treatment in reducing the incidence of a first occurrence of neural-tube defects. Women planning a pregnancy (in most cases their first) were randomly assigned to receive a single tablet of a vitamin supplement (containing 12 vitamins, including 0.8 mg of folic acid; 4 minerals; and 3 trace elements) or a trace-element supplement (containing copper, manganese, zinc, and a very low dose of vitamin C) daily for at least one month before conception and until the date of the second missed menstrual period or later. **RESULTS.** Pregnancy was confirmed in 4753 women. The outcome of the pregnancy (whether the fetus or infant had a neural-tube defect or congenital malformation) was known in 2104 women who received the vitamin supplement and in 2052 who received the trace-element supplement. Congenital malformations were significantly more prevalent in the group receiving the trace-element supplement than in the vitamin-supplement group (22.9 per 1000 vs. 13.3 per 1000,  $P = 0.02$ ). There were six cases of neural-tube defects in the group receiving the trace-element supplement, as compared with none in the vitamin-supplement group ( $P = 0.029$ ). The prevalence of cleft lip with or without cleft palate was not reduced by periconceptual vitamin supplementation. **CONCLUSIONS.** Periconceptual vitamin use decreases the incidence of a first occurrence of neural-tube defects.

## **Folate levels and neural tube defects. Implications for prevention.**

Daly LE, Kirke PN, Molloy A, Weir DG, Scott JM. 1995.  
JAMA. 274(21):1698-702

Using data from a recent case-control study, a woman's risk of having a child with a neural tube defect (NTD) was found to be associated with early pregnancy red cell folate levels in a continuous dose-response relationship. These findings were used to calculate the reduction in NTD cases that would be expected under two different strategies to raise folate levels. Targeting high-risk individuals has a small effect on the population prevalence but can substantially change an individual's risk. Targeting the population produces a small change in individual risk but has a large effect on the population prevalence. Supplementation of high-risk women would be the most efficient method to implement the high-risk strategy, while food fortification would be preferable for the population approach. The current guidelines for the prevention of NTD are for an increased folic acid intake of 0.4 mg per day. This would result in a 48% reduction in NTDs, which may be near optimal. The two intervention strategies should be considered complementary in prevention of NTDs.

## **Effects of supplementation with omega 3 long-chain polyunsaturated fatty acids on retinal and cortical development in premature infants.**

Hoffman DR, Birch EE, Birch DG, Uauy RD. 1993.  
Am J Clin Nutr 57(5 Suppl):807S-812S

Deficiency of omega 3 long-chain polyunsaturated fatty acids (LCPUFAs) in vertebrates produces subtle adverse effects on visual and neural function. Preterm infants 1) are deprived of vital intrauterine fat accretion during late pregnancy, 2) must rely solely on formula for fatty acid supplies if not breastfed, and 3) may have limited postnatal desaturase activity. In a study to evaluate the necessity of dietary omega 3 LCPUFAs, preterm infants were fed human milk, corn-oil-based formula (omega 3 fatty acid deficient), soy-oil-based formula (rich in precursor fatty acids), or marine-oil-supplemented formula (containing docosahexaenoic acid). At 36 and 57 wk postconception, the LCPUFA profiles in red blood cell lipids were nearly equivalent in the human-milk and marine-oil groups whereas the corn-oil group had markedly lower values for omega 3 fatty acids. Rod photoreceptor function was significantly less mature in the corn-oil group compared with the human-milk and marine-oil-enriched groups in early postnatal development (36 wk). The corn-oil group also had impaired visual acuity at both 36 and 57 wk. The potential benefit of omega 3 LCPUFA-enriched full-term formula is discussed. The study supports a role for omega 3 LCPUFAs as required nutrients for the optimal maturation of visual and cortical function in preterm infants.

## **Multivitamin/folic acid supplementation in early pregnancy reduces the prevalence of neural tube defects.**

Milunsky A, Jick H, Jick SS, Bruell CL, MacLaughlin DS, Rothman KJ, Willett W. 1989.  
JAMA 262(20):2847-52

We examined the relation of multivitamin intake in general, and folic acid in particular, to the risk of neural tube defects in a cohort of 23,491 women undergoing maternal serum alpha-fetoprotein screening or amniocentesis around 16 weeks of gestation. Complete questionnaires and subsequent pregnancy outcome information was obtained in 22,776 pregnancies, 49 of which ended in a neural tube defect. The prevalence of neural tube defect was 3.5 per 1000 among women who never used multivitamins before or after conception or who used multivitamins before conception only. The prevalence of neural tube defects for women who used folic acid-containing multivitamins during the first 6 weeks of pregnancy was substantially lower--0.9 per 1000 (prevalence ratio, 0.27; 95% confidence interval, 0.12 to 0.59 compared with never users). For women who used multivitamins without folic acid during the first 6 weeks of pregnancy and women who used multivitamins containing folic acid beginning after 7 or more weeks of pregnancy, the prevalences were similar to that of the nonusers and the prevalence ratios were close to 1.0.

## **Prevention of neural tube defects: results of the Medical Research Council Vitamin Study.**

MRC Vitamin Study Research Group. 1991.  
Lancet 338(8760):131-7

A randomised double-blind prevention trial with a factorial design was conducted at 33 centres in seven countries to determine whether supplementation with folic acid (one of the vitamins in the B group) or a mixture of seven other vitamins (A,D,B1,B2,B6,C and nicotinamide) around the time of conception can prevent neural tube defects (anencephaly, spina bifida, encephalocele). A total of 1817 women at high risk of having a pregnancy with a neural tube defect, because of a previous affected pregnancy, were allocated at random to one of four groups--namely, folic acid, other vitamins, both, or neither. 1195 had a completed pregnancy in which the fetus or infant was known to have or not have a neural tube defect; 27 of these had a known neural tube defect, 6 in the folic acid groups and 21 in the two other groups, a 72% protective effect (relative risk 0.28, 95% confidence interval 0.12-0.71). The other vitamins showed no significant protective effect (relative risk 0.80, 95% CI 0.32-1.72). There was no demonstrable harm from the folic acid supplementation, though the ability of the study to detect rare or slight adverse effects was limited. Folic acid supplementation starting before pregnancy can now be firmly recommended for all women who have had an affected pregnancy, and public health measures should be taken to ensure that the diet of all women who may bear children contains an adequate amount of folic acid.

## **Periconceptual use of multivitamins and the occurrence of neural tube defects.**

Mulinare J, Cordero JF, Erickson JD, Berry RJ. 1988.  
JAMA 260(21):3141-5

We studied the association between multivitamin use during the periconceptual period and the occurrence of neural tube defects using data from the Atlanta Birth Defects Case-Control Study. There were 347 babies with neural tube defects who were live born or stillborn to residents of metropolitan Atlanta from 1968 through 1980. The 2829 control-babies born without birth defects were randomly selected through birth certificates. Periconceptual multivitamin use was defined as reported use for each of the three months before conception through the first three months of pregnancy. Mothers who reported not using multivitamins any time during the six-month period were defined as nonusers. Fourteen percent of mothers reported periconceptual multivitamin use and 40% reported nonuse. Multivitamin users were different from nonusers in a number of demographic, health-related, and life-style characteristics. We found an overall apparent protective effect of periconceptual multivitamin use on the occurrence of neural tube defects, with a crude estimated relative risk of 0.40 (95% confidence interval, 0.25 to 0.63). At this time, it is not possible to determine whether this apparently lower risk is the direct result of multivitamin use or the result of other characteristics of women who use multivitamins.

## **Use of multivitamin/mineral prenatal supplements: influence on the outcome of pregnancy.**

Scholl TO, Hediger ML, Bendich A, Schall JI, Smith WK, Krueger PM. 1997.  
Am J Epidemiol 146(2):134-41

The objective of this study was to examine the association of prenatal multivitamin/mineral supplement use during the first and second trimesters of pregnancy by low income, urban women in the Camden Study (1985-1995, n = 1,430) and preterm delivery (< 37 completed weeks) and infant low birth weight (< 2,500 g). Prenatal supplement use was corroborated by assay of circulating micronutrients at entry to care (no differences) and week 28 gestation (increased concentrations of folate and ferritin for supplement users). Compared with women who entered care during the first or second trimester but did not use prenatal supplements, supplement use starting in the first or second trimester was associated with approximately a twofold reduction in risk of preterm delivery. After controlling for potential confounding variables, risk of very preterm delivery (< 33 weeks' gestation) was reduced more than fourfold for first trimester users and approximately twofold when use dated from the second trimester. Infant low birth weight and very low birth weight (< 1,500 g) risks were also reduced. Risk of low birth weight was reduced approximately twofold with supplement use during the first and second trimester. Diminution in risk was greater for very low birth weight infants, amounting to a sevenfold reduction in risk of very low birth weight with first trimester supplementation and a greater than sixfold reduction when supplement use started in the second trimester. Thus, in low income, urban women, use of prenatal multivitamin/mineral supplements may have the potential to diminish infant morbidity and mortality.

## **Periconceptual folic acid exposure and risk of occurrent neural tube defects.**

Werler MM, Shapiro S, Mitchell AA. 1993.  
JAMA 269(10):1257-61

**OBJECTIVES--**A recent controlled trial has established that use of a 4-mg folic acid supplement before and during early pregnancy reduces the risk of recurrent neural tube defects (NTDs) by 72%. The present study was designed to determine whether folic acid also reduces the risk of first (occurent) NTDs. **DESIGN--**Case-control study. **SETTING--**Tertiary and birth hospitals in metropolitan areas of Boston, Mass, Philadelphia, Pa, and Toronto, Ontario. **PARTICIPANTS--** Mothers of 436 occurrent cases with NTDs and mothers of 2615 controls with other major malformations. **MAIN OUTCOME MEASURES--**The prevalence of use of multivitamins containing folic acid was compared between mothers of cases and controls. **RESULTS--**The mothers of 17% of cases and 3% of controls reported knowledge of the folic acid-NTD hypothesis and were excluded from further analysis. For daily use of a multivitamins containing folic acid in the periconceptual period (28 days before through 28 days after the last menstrual period), the relative risk (RR) (and 95% confidence interval) was 0.4 (0.2 to 0.6). The most commonly used dose of folic acid was 0.4 mg, and the RR estimate was 0.3 (95% confidence interval, 0.1 to 0.6). For dietary folate, there was a dose-related decline in risk according to the quintile of intake (P for trend = .02). **CONCLUSION--**These findings suggest that daily periconceptual intake of 0.4 mg of folic acid (the dose most commonly contained in over-the-counter multivitamin preparations) reduces the risk of occurrent NTDs by approximately 60%. A relatively high dietary intake of folate may also reduce the risk.