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# Lipotropic Adjunct



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## PEER REVIEWED STUDIES

### CELLULAR HEALTH

#### Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial

##### ABSTRACT

##### BACKGROUND:

Homocysteine is a risk factor for Alzheimer's disease. In the first report on the VITACOG trial, we showed that homocysteine-lowering treatment with B vitamins slows the rate of brain atrophy in mild cognitive impairment (MCI). Here we report the effect of B vitamins on cognitive and clinical decline (secondary outcomes) in the same study.

##### METHODS:

This was a double-blind, single-centre study, which included participants with MCI, aged  $\geq 70$  y, randomly assigned to receive a daily dose of 0.8 mg folic acid, 0.5 mg vitamin B(12) and 20 mg vitamin B(6) (133 participants) or placebo (133 participants) for 2 y. Changes in cognitive or clinical function were analysed by generalized linear models or mixed-effects models.

##### RESULTS:

The mean plasma total homocysteine was 30% lower in those treated with B vitamins relative to placebo. B vitamins stabilized executive function (CLOX) relative to placebo ( $P = 0.015$ ). There was significant benefit of B-vitamin treatment among participants with baseline homocysteine above the median ( $11.3 \mu\text{mol/L}$ ) in global cognition (Mini Mental State Examination,  $P < 0.001$ ), episodic memory (Hopkins Verbal Learning Test-delayed recall,  $P = 0.001$ ) and semantic memory (category fluency,  $P = 0.037$ ). Clinical benefit occurred in the B-vitamin group for those in the upper quartile of homocysteine at baseline in global clinical dementia rating score ( $P = 0.02$ ) and IQCODE score ( $P = 0.01$ ).

##### CONCLUSION:

In this small intervention trial, B vitamins appear to slow cognitive and clinical decline in people with MCI, in particular in those with elevated homocysteine. Further trials are needed to see if this treatment will

slow or prevent conversion from MCI to dementia.

Source

de Jager CA et al. Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial. *Int J Geriatr Psychiatry* [Epub ahead of print, July, 2011]

#### Select dietary flavonoids are associated with markers of inflammation and endothelial dysfunction in US women

##### ABSTRACT

Flavonoids show antiinflammatory effects in vitro and human intervention studies have suggested beneficial effects of flavonoid-rich foods on biomarkers of inflammation and endothelial function. In the present study, we assessed the relationship between flavonoid intake and biomarkers of inflammation and endothelial dysfunction in a cross-sectional study of participants from the Nurses' Health Study cohort. Intake of 6 flavonoid subclasses (flavonols, flavones, flavanones, flavan-3-ols, anthocyanidins, and polymeric flavonoids) was assessed using a FFQ administered in 1990. Also, the main food sources of these flavonoids were examined. Blood samples were collected in 1989–1990 and plasma C-reactive protein (CRP), IL-6, IL-18, soluble tumor necrosis factor receptor-2 (sTNF-R2), soluble intercellular adhesion molecule-1, soluble vascular adhesion molecule-1 (sVCAM-1), and E-selectin were measured in 1194–1598 women. The multivariate-adjusted geometric mean of plasma IL-8 were lower for women in the highest intake quintile of flavones, flavanones, and total flavonoids compared with those in the lowest quintiles by 9% (Q1: 264 ng/L, Q5: 241 ng/L;  $P$ -trend = 0.019), 11% (Q1: 273 ng/L, Q5: 244 ng/L;  $P$ -trend = 0.011), and 8% (Q1: 276 ng/L, Q5: 55 ng/L;  $P$ -trend = 0.034), respectively. The multivariate-adjusted geometric mean for women in the highest intake quintile of flavonol compared with those in the lowest quintile was 4% lower for sVCAM-1 (Q1: 578  $\mu\text{g/L}$ , Q5: 557  $\mu\text{g/L}$ ;  $P$ -trend = 0.012). Among flavonoid-rich foods, higher intake of grapefruit was significantly associated with

lower concentrations of CRP and sTNF-R2.

In summary, higher intakes of selected flavonoid subclasses were associated with modestly lower concentrations of inflammatory biomarkers. In particular, flavonoids typically found in citrus fruits were modestly associated with lower plasma IL-18 concentrations.

Source

Landberg R, et al. Select dietary flavonoids are associated with markers of inflammation and endothelial dysfunction in US women. *Journal of nutrition*, April 2011, doi: 10.3945/jn.101.133843

### CHILDREN'S HEALTH

#### Antenatal and Postnatal Iron Supplementation and Childhood Mortality in Rural Nepal: A Prospective Follow-up in a Randomized, controlled Community Trial

##### ABSTRACT

The long-term benefits of antenatal iron supplementation in child survival are not known. In 1999–2001, 4,926 pregnant women in rural Nepal participated in a cluster-randomized, double-masked, controlled trial involving 4 alternative combinations of micronutrient supplements, each containing vitamin A. The authors examined the impact on birth weight and early infant mortality in comparison with controls, who received vitamin A only. They followed the surviving offspring of these women at approximately age 7 years to study effects of in utero supplementation on survival. Of 4,130 livebirths, 209 infants died in the first 3 months and 8 were lost to follow-up. Of those remaining, 3,761 were followed, 150 died between ages 3 months and 7 years, and 152 were lost to follow-up. Mortality rates per 1,000 child-years from birth to age 7 years differed by maternal supplementation group, as follows: folic acid, 13.4; folic acid-iron, 10.3; folic acid-iron-zinc, 12.0; multiple micronutrients; 14.0; and controls, 15.2. Hazard ratios were 0.90 (95% confidence interval (CI): 0.65, 1.22), 0.69 (95% CI: 0.49, 0.99), 0.80 (95% CI: 0.58, 1.11), and 0.93

(95% CI: 0.66, 1.31), respectively, in the 4 supplementation groups. Maternal iron-folic acid supplementation reduced mortality among these children by 31% between birth and age 7 years. These results provide additional motivation for strengthening antenatal iron-folic acid programs.

#### Source

Christian P, et al. Antenatal and Postnatal Iron Supplementation and Childhood Mortality in Rural Nepal: A Prospective Follow-up in a Randomized, controlled Community Trial. *Am J of epid.* 2009 Sep;170 (9): 1127-1136.

### Lower maternal folate status in early pregnancy is associated with childhood hyperactivity and peer problems in offspring

#### ABSTRACT

##### BACKGROUND:

Maternal nutrition during pregnancy has been linked with fetal brain development and psychopathology in the offspring. We examined for associations of maternal folate status and dietary intake during pregnancy with brain growth and childhood behavioural difficulties in the offspring.

##### METHODS:

In a prospective cohort study, maternal red blood cell folate (RCF) was measured at 14 weeks of pregnancy and total folate intake (TFI) from food and supplements was assessed in early and late pregnancy. The offspring's head circumference and body weight were measured at birth and in infancy, and 100 mothers reported on children's behavioural difficulties at a mean age of 8.75 years using the Strengths and Difficulties Questionnaire.

##### RESULTS:

Lower maternal RCF and TFI in early pregnancy were associated with higher childhood hyperactivity (RCF:  $\beta = -.24$ ;  $p = .013$ ; TFI:  $\beta = -.24$ ;  $p = .022$ ) and peer problems scores (RCF:  $\beta = -.28$ ;  $p = .004$ ; TFI:  $\beta = -.28$ ;  $p = .009$ ) in the offspring. Maternal gestational RCF was positively associated with head circumference at birth (adjusted for gestational age), and mediation analyses

showed significant inverse indirect associations of RCF with hyperactivity/inattention and peer problems via fetal brain growth. Adjustment for mother's smoking and drinking alcohol during pregnancy did not change the results.

##### CONCLUSIONS:

Although the associations are small and residual confounding is possible, our data provide preliminary support for the hypothesis that lower folate status in early pregnancy might impair fetal brain development and affect hyperactivity/inattention and peer problems in childhood.

#### Source

Schlotz W, et al. Lower maternal folate status in early pregnancy is associated with childhood hyperactivity and peer problems in offspring. *J Child Psychol Psychiatry.* 2010 May;51(5):594-602.

### Periconception dietary intake of choline and betaine and neural tube defects in offspring

#### ABSTRACT

Periconceptional intake of folic acid prevents some neural tube defects (NTDs). Other nutrients may also contribute to NTD etiologies; a likely candidate is choline. Similar to folic acid, choline is involved in one-carbon metabolism for methylation of homocysteine to methionine. The authors investigated whether maternal periconceptional dietary intakes of choline and its metabolite betaine influence NTD risk. Data were derived from a case-control study of fetuses and infants with NTDs among 1989-1991 California births. In-person interviews were conducted with mothers of 424 NTD cases and with mothers of 440 nonmalformed controls. A standard 100-item food frequency questionnaire was used to assess nutrient intake. Dietary intakes of choline were associated with reduced NTD risks. Controlling for intake of supplemental folic acid, dietary folate, dietary methionine, and other covariates did not substantially influence risk estimates for choline. NTD risk estimates were lowest for women whose diets were rich in choline, betaine,

and methionine. That is, for women whose intake was above the 75th percentile compared with below the 25th percentile for all three nutrients, the odds ratio was 0.17 (95% confidence interval: 0.04, 0.76). Study findings for dietary components other than folic acid offer additional clues about the complex etiologies of NTDs.

#### Source

Shaw G et al. Periconception dietary intake of choline and betaine and neural tube defects in offspring. *Am J Epidemiol* 2004;160:102-109.

### COGNITIVE HEALTH

#### ABSTRACT

Obsessive-compulsive disorder (OCD) is a debilitating mental illness which has a significant impact on quality of life. First-line SSRI treatments for OCD typically are of limited benefit to only 40-60% of patients, and are associated with a range of adverse side effects. Current preclinical research investigating nutraceuticals (natural products) for OCD, reveals encouraging novel activity in modulating key pathways suggested to be involved in the pathogenesis of OCD (glutamatergic and serotonergic pathway dysregulation). Emerging clinical evidence also appears to tentatively support certain nutrients and plant-based interventions with known active constituents which modulate these pathways: N-acetylcysteine, myo-inositol, glycine, and milk thistle (*Silybum marianum*). The serotonin precursor tryptophan is unlikely to be of use in treating OCD while 5-HTP may possibly be a more effective precursor strategy. However, there is currently no clinical evidence to test the efficacy of either of these substances. Currently the balance of clinical evidence does not support the use of St. John's wort (*Hypericum perforatum*) in OCD. While clinical research in this area is in its infancy, further research into nutraceuticals is warranted in light of the promising preclinical data regarding their mechanisms of action and their favourable side effect profiles in comparison to current SSRI treatments. It is recommended that future clinical trials

of nutraceutical treatments for OCD utilize randomized placebo-controlled study designs and considerably larger sample sizes in order to properly test for efficacy.

#### Source

Camfield DA, Sarris J, Berk M. Nutraceuticals in the treatment of obsessive compulsive disorder (OCD): A review of mechanistic and clinical evidence. *Prog Neuro-Psychopharmacol Biol Psychiatry* (2011), doi:10.1016/j.pnpbp.2011.02.011

### Inositol—clinical applications for exogenous use

#### ABSTRACT

Recent advances in nutritional and biochemical research have documented inositol as an important dietary and cellular constituent. The processes involved in inositol metabolism and its derivatives in the tissues of mammals have been characterized in vivo as well as at the enzymatic level. Biochemical functions defined for phosphatidylinositol in biological membranes include the regulation of cellular responses to external stimuli and/or nerve transmission as well as the mediation of enzyme activity through interactions with various specific proteins. Altered production of inositol has been documented in patients with diabetes mellitus, chronic renal failure, galactosemia, and multiple sclerosis. Inositol has been reported to be effective in treating central nervous system disorders such as depression, Alzheimer's disease, panic disorder, and obsessive-compulsive disorder. It has documented benefit for use in pediatric respiratory depression syndrome. In addition, recent studies have evaluated its usefulness as an analgesic. Inositol has been studied extensively as potential treatment to alleviate some negative effects associated with lithium therapy. The use of inositol in pregnant women remains controversial. Although its benefit in preventing neural tube defects in embryonic mice is documented, the risk of inducing uterine contractions limits its usefulness in pregnancy.

#### Source

Colodny L, Hoffman RL. Inositol—clinical

applications for exogenous use. *Altern Med Rev* 1998;3(5):432-47.

### Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial

#### ABSTRACT

##### BACKGROUND:

Homocysteine is a risk factor for Alzheimer's disease. In the first report on the VITACOG trial, we showed that homocysteine-lowering treatment with B vitamins slows the rate of brain atrophy in mild cognitive impairment (MCI). Here we report the effect of B vitamins on cognitive and clinical decline (secondary outcomes) in the same study.

##### METHODS:

This was a double-blind, single-centre study, which included participants with MCI, aged  $\geq 70$  y, randomly assigned to receive a daily dose of 0.8 mg folic acid, 0.5 mg vitamin B(12) and 20 mg vitamin B(6) (133 participants) or placebo (133 participants) for 2 y. Changes in cognitive or clinical function were analysed by generalized linear models or mixed-effects models.

##### RESULTS:

The mean plasma total homocysteine was 30% lower in those treated with B vitamins relative to placebo. B vitamins stabilized executive function (CLOX) relative to placebo ( $P = 0.015$ ). There was significant benefit of B-vitamin treatment among participants with baseline homocysteine above the median ( $11.3 \mu\text{mol/L}$ ) in global cognition (Mini Mental State Examination,  $P < 0.001$ ), episodic memory (Hopkins Verbal Learning Test-delayed recall,  $P = 0.001$ ) and semantic memory (category fluency,  $P = 0.037$ ). Clinical benefit occurred in the B-vitamin group for those in the upper quartile of homocysteine at baseline in global clinical dementia rating score ( $P = 0.02$ ) and IQCODE score ( $P = 0.01$ ).

##### CONCLUSION:

In this small intervention trial, B vitamins appear to slow cognitive and clinical decline in people with MCI, in particular in those with elevated homocysteine. Further trials are needed to see if this treatment will

slow or prevent conversion from MCI to dementia.

#### Source

de Jager CA et al. Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial. *Int J Geriatr Psychiatry* [Epub ahead of print, July, 2011]

### Dietary choline and betaine intakes in relationship to concentrations of inflammatory markers in healthy adults: the ATTICA study

#### ABSTRACT

##### BACKGROUND:

Choline and betaine are found in a variety of plant and animal foods and were recently shown to be associated with decreased homocysteine concentrations.

##### OBJECTIVE:

The scope of this work was to investigate the associations between dietary choline and betaine consumption and various markers of low-grade systemic inflammation.

##### DESIGN:

Under the context of a cross-sectional survey that enrolled 1514 men (18-87 y of age) and 1528 women (18-89 y of age) with no history of cardiovascular disease (the ATTICA Study), fasting blood samples were collected and inflammatory markers were measured. Dietary habits were evaluated with a validated food-frequency questionnaire, and the intakes of choline and betaine were calculated from food-composition tables.

##### RESULTS:

Compared with the lowest tertile of choline intake ( $<250 \text{ mg/d}$ ), participants who consumed  $>310 \text{ mg/d}$  had, on average, 22% lower concentrations of C-reactive protein ( $P < 0.05$ ), 26% lower concentrations of interleukin-6 ( $P < 0.05$ ), and 6% lower concentrations of tumor necrosis factor-alpha ( $P < 0.01$ ). Similarly, participants who consumed  $>360 \text{ mg/d}$  of betaine had, on average, 10% lower concentrations of homocysteine ( $P <$

0.01), 19% lower concentrations of C-reactive protein ( $P < 0.1$ ), and 12% lower concentrations of tumor necrosis factor- $\alpha$  ( $P < 0.05$ ) than did those who consumed  $<260$  mg/d. These findings were independent of various sociodemographic, lifestyle, and clinical characteristics of the participants.

### CONCLUSIONS:

Our results support an association between choline and betaine intakes and the inflammation process in free-eating and apparently healthy adults. However, further studies are needed to confirm or refute our findings.

### Source

Detopoulou P et al. Dietary choline and betaine intakes in relationship to concentrations of inflammatory markers in healthy adults: the ATTICA study. *Am J Clin Nutr* 2008;87:424-430.

### Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment

### ABSTRACT

Is it possible to prevent atrophy of key brain regions related to cognitive decline and Alzheimer's disease (AD)? One approach is to modify nongenetic risk factors, for instance by lowering elevated plasma homocysteine using B vitamins. In an initial, randomized controlled study on elderly subjects with increased dementia risk (mild cognitive impairment according to 2004 Petersen criteria), we showed that high-dose B-vitamin treatment (folic acid 0.8 mg, vitamin B6 20 mg, vitamin B12 0.5 mg) slowed shrinkage of the whole brain volume over 2 y. Here, we go further by demonstrating that B-vitamin treatment reduces, by as much as seven fold, the cerebral atrophy in those gray matter (GM) regions specifically vulnerable to the AD process, including the medial temporal lobe. In the placebo group, higher homocysteine levels at baseline are associated with faster GM atrophy, but this deleterious effect is largely prevented by B-vitamin treatment. We additionally show that the beneficial effect of B vitamins is confined to

participants with high homocysteine (above the median, 11  $\mu\text{mol/L}$ ) and that, in these participants, a causal Bayesian network analysis indicates the following chain of events: B vitamins lower homocysteine, which directly leads to a decrease in GM atrophy, thereby slowing cognitive decline. Our results show that B-vitamin supplementation can slow the atrophy of specific brain regions that are a key component of the AD process and that are associated with cognitive decline. Further B-vitamin supplementation trials focusing on elderly subjects with high homocysteine levels are warranted to see if progression to dementia can be prevented.

### Source

Douaud G. et. al. Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment. *PNAS* 2013;119(23):9523-9528.

### Effects of high-dose B vitamin complex with vitamin C and minerals on subjective mood and performance in healthy males

### ABSTRACT

### RATIONALE:

A significant proportion of the general population report supplementing their diet with one or more vitamins or minerals, with common reasons for doing so being to combat stress and fatigue and to improve mental functioning. Few studies have assessed the relationship between supplementation with vitamins/minerals and psychological functioning in healthy cohorts of non-elderly adults.

### OBJECTIVES:

The present randomised, placebo-controlled, double-blind, parallel groups trial assessed the cognitive and mood effects of a high-dose B-complex vitamin and mineral supplement (Berocca®) in 215 males aged 30 to 55 years, who were in full-time employment.

### METHODS:

Participants attended the laboratory prior to and on the last day of a 33-day treatment period where they completed the Profile of Mood States (POMS), Perceived Stress Scale (PSS) and General

Health Questionnaire (GHQ-12). Cognitive performance and task-related modulation of mood/fatigue were assessed with the 60 min cognitive demand battery. On the final day, participants also completed the Stroop task for 40 min whilst engaged in inclined treadmill walking and subsequent executive function was assessed.

### RESULTS:

Vitamin/mineral supplementation led to significant improvements in ratings on the PSS, GHQ-12 and the 'vigour' subscale of the POMS. The vitamin/mineral group also performed better on the Serial 3s subtractions task and rated themselves as less 'mentally tired' both pre- and post-completion of the cognitive demand battery.

### CONCLUSIONS:

Healthy members of the general population may benefit from augmented levels of vitamins/minerals via direct dietary supplementation. Specifically, supplementation led to improved ratings of stress, mental health and vigour and improved cognitive performance during intense mental processing.

### Source

Kennedy DO et al. Effects of high-dose B vitamin complex with vitamin C and minerals on subjective mood and performance in healthy males. *Psychopharmacol* 211:55-68, 2010.

### Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: A randomized controlled trial

### ABSTRACT

### BACKGROUND:

An increased rate of brain atrophy is often observed in older subjects, in particular those who suffer from cognitive decline. Homocysteine is a risk factor for brain atrophy, cognitive impairment and dementia. Plasma concentrations of homocysteine can be lowered by dietary administration of B vitamins.

### OBJECTIVE:

To determine whether supplementation with B vitamins that lower levels of plasma

total homocysteine can slow the rate of brain atrophy in subjects with mild cognitive impairment in a randomised controlled trial (VITACOG, ISRCTN 94410159).

#### METHODS AND FINDINGS:

Single-center, randomized, double-blind controlled trial of high-dose folic acid, vitamins B(6) and B(12) in 271 individuals (of 646 screened) over 70 y old with mild cognitive impairment. A subset (187) volunteered to have cranial MRI scans at the start and finish of the study. Participants were randomly assigned to two groups of equal size, one treated with folic acid (0.8 mg/d), vitamin B(12) (0.5 mg/d) and vitamin B(6) (20 mg/d), the other with placebo; treatment was for 24 months. The main outcome measure was the change in the rate of atrophy of the whole brain assessed by serial volumetric MRI scans.

#### RESULTS:

A total of 168 participants (85 in active treatment group; 83 receiving placebo) completed the MRI section of the trial. The mean rate of brain atrophy per year was 0.76% [95% CI, 0.63-0.90] in the active treatment group and 1.08% [0.94-1.22] in the placebo group ( $P = 0.001$ ). The treatment response was related to baseline homocysteine levels: the rate of atrophy in participants with homocysteine  $>13 \mu\text{mol/L}$  was 53% lower in the active treatment group ( $P = 0.001$ ). A greater rate of atrophy was associated with a lower final cognitive test scores. There was no difference in serious adverse events according to treatment category.

#### CONCLUSIONS AND SIGNIFICANCE:

The accelerated rate of brain atrophy in elderly with mild cognitive impairment can be slowed by treatment with homocysteine-lowering B vitamins. Sixteen percent of those over 70 y old have mild cognitive impairment and half of these develop Alzheimer's disease. Since accelerated brain atrophy is a characteristic of subjects with mild cognitive impairment who convert to Alzheimer's disease, trials are needed to see if the same treatment will delay the development of Alzheimer's disease.

Source

Smith AD, et al. Homocysteine-lowering

by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: A randomized controlled trial. 2010;PloS ONE 5(9):e12244.

#### Vitamin B12, cognition, and brain MRI measures: A crosssectional examination

##### ABSTRACT

##### OBJECTIVE:

To investigate the interrelations of serum vitamin B12 markers with brain volumes, cerebral infarcts, and performance in different cognitive domains in a biracial population sample cross-sectionally.

##### METHODS:

In 121 community-dwelling participants of the Chicago Health and Aging Project, serum markers of vitamin B12 status were related to summary measures of neuropsychological tests of 5 cognitive domains and brain MRI measures obtained on average 4.6 years later among 121 older adults.

##### RESULTS:

Concentrations of all vitamin B12-related markers, but not serum vitamin B12 itself, were associated with global cognitive function and with total brain volume. Methylmalonate levels were associated with poorer episodic memory and perceptual speed, and cystathionine and 2-methylcitrate with poorer episodic and semantic memory. Homocysteine concentrations were associated with decreased total brain volume. The homocysteine-global cognition effect was modified and no longer statistically significant with adjustment for white matter volume or cerebral infarcts. The methylmalonate-global cognition effect was modified and no longer significant with adjustment for total brain volume.

##### CONCLUSIONS:

Methylmalonate, a specific marker of B12 deficiency, may affect cognition by reducing total brain volume whereas the effect of homocysteine (nonspecific to vitamin B12 deficiency) on cognitive performance may be mediated through increased white matter hyperintensity and cerebral infarcts. Vitamin B12 status may affect the brain through

multiple mechanisms.

Source

Tangney CC et al. Vitamin B12, cognition, and brain MRI measures: A crosssectional examination. *Neurol* 77:1276-82, 2011.

#### Neuroprotective effects of anthocyanins and their in vivo metabolites in SH-SY5Y cells

##### ABSTRACT

Recent in vivo studies have highlighted an important role for the neuroprotective actions of dietary anthocyanins. However, one consistent result of these studies is that the systemic bioavailability of anthocyanins, including cyanidin 3-O-glucopyranoside (Cy-3G), is very poor. Cy-3G has been demonstrated to be highly unstable at physiological pH, so its in vivo metabolites, such as the aglycon cyanidin (Cy) and protocatechuic acid (PA), may be responsible for both the antioxidant activity and the neuroprotective effects observed in vivo. Therefore, we investigated the protective effects of Cy-3G, Cy and PA against H(2)O(2)-induced oxidative stress in a human neuronal cell line (SH-SY5Y). We determined their ability to counteract reactive oxygen species (ROS) formation and to inhibit apoptosis in terms of mitochondrial functioning loss and DNA fragmentation induced by H(2)O(2). We demonstrated that pretreatment of SH-SY5Y cells with Cy-3G, Cy and PA inhibits H(2)O(2)-induced ROS formation at different cellular levels: Cy-3G at membrane level, PA at cytosolic level and Cy at both membrane and cytosolic levels. In addition, Cy showed a higher antioxidant activity at membrane and cytosolic level than Cy-3G and PA, respectively. Interestingly, both Cy and PA, but not Cy-3G, could inhibit H(2)O(2)-induced apoptotic events, such as mitochondrial functioning loss and DNA fragmentation. These results suggest that Cy and PA may be considered as neuroprotective molecules and may play an important role in brain health promotion. These in vitro findings should encourage further research in animal models of neurological diseases to explore the potential neuroprotective effects of

compounds generated during in vivo metabolism of anthocyanins.

#### Source

Tarozzi A, et al. Neuroprotective effects of anthocyanins and their in vivo metabolites in SH-SY5Y cells. *Journal of neuroscience letters*. 2007; 424(1):36-40. doi:10.1016/j.neulet.2007.07.017

## HEALTHY PREGNANCY

### **Antenatal and Postnatal Iron Supplementation and Childhood Mortality in Rural Nepal: A Prospective Follow-up in a Randomized, controlled Community Trial**

#### ABSTRACT

The long-term benefits of antenatal iron supplementation in child survival are not known. In 1999-2001, 4,926 pregnant women in rural Nepal participated in a cluster-randomized, double-masked, controlled trial involving 4 alternative combinations of micronutrient supplements, each containing vitamin A. The authors examined the impact on birth weight and early infant mortality in comparison with controls, who received vitamin A only. They followed the surviving offspring of these women at approximately age 7 years to study effects of in utero supplementation on survival. Of 4,130 livebirths, 209 infants died in the first 3 months and 8 were lost to follow-up. Of those remaining, 3,761 were followed, 150 died between ages 3 months and 7 years, and 152 were lost to follow-up. Mortality rates per 1,000 child-years from birth to age 7 years differed by maternal supplementation group, as follows: folic acid, 13.4; folic acid-iron, 10.3; folic acid-iron-zinc, 12.0; multiple micronutrients; 14.0; and controls, 15.2. Hazard ratios were 0.90 (95% confidence interval (CI): 0.65, 1.22), 0.69 (95% CI: 0.49, 0.99), 0.80 (95% CI: 0.58, 1.11), and 0.93 (95% CI: 0.66, 1.31), respectively, in the 4 supplementation groups. Maternal iron-folic acid supplementation reduced mortality among these children by 31% between birth and age 7 years. These results provide additional motivation for strengthening

antenatal iron-folic acid programs.

#### Source

Christian P, et al. Antenatal and Postnatal Iron Supplementation and Childhood Mortality in Rural Nepal: A Prospective Follow-up in a Randomized, controlled Community Trial. *am J of epid*. 2009 Sep;170 (9): 1127-1136.

### **Lower maternal folate status in early pregnancy is associated with childhood hyperactivity and peer problems in offspring**

#### ABSTRACT

##### **BACKGROUND:**

Maternal nutrition during pregnancy has been linked with fetal brain development and psychopathology in the offspring. We examined for associations of maternal folate status and dietary intake during pregnancy with brain growth and childhood behavioural difficulties in the offspring.

##### **METHODS:**

In a prospective cohort study, maternal red blood cell folate (RCF) was measured at 14 weeks of pregnancy and total folate intake (TFI) from food and supplements was assessed in early and late pregnancy. The offspring's head circumference and body weight were measured at birth and in infancy, and 100 mothers reported on children's behavioural difficulties at a mean age of 8.75 years using the Strengths and Difficulties Questionnaire.

##### **RESULTS:**

Lower maternal RCF and TFI in early pregnancy were associated with higher childhood hyperactivity (RCF: beta = -.24; p = .013; TFI: beta = -.24; p = .022) and peer problems scores (RCF: beta = -.28; p = .004; TFI: beta = -.28; p = .009) in the offspring. Maternal gestational RCF was positively associated with head circumference at birth (adjusted for gestational age), and mediation analyses showed significant inverse indirect associations of RCF with hyperactivity/inattention and peer problems via fetal brain growth. Adjustment for mother's smoking and drinking alcohol during pregnancy did not change the results.

## CONCLUSIONS:

Although the associations are small and residual confounding is possible, our data provide preliminary support for the hypothesis that lower folate status in early pregnancy might impair fetal brain development and affect hyperactivity/inattention and peer problems in childhood.

#### Source

Schlottz W, et al. Lower maternal folate status in early pregnancy is associated with childhood hyperactivity and peer problems in offspring. *J Child Psychol Psychiatry*. 2010 May;51(5):594-602.

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Periconceptional intake of folic acid prevents some neural tube defects (NTDs). Other nutrients may also contribute to NTD etiologies; a likely candidate is choline. Similar to folic acid, choline is involved in one-carbon metabolism for methylation of homocysteine to methionine. The authors investigated whether maternal periconceptional dietary intakes of choline and its metabolite betaine influence NTD risk. Data were derived from a case-control study of fetuses and infants with NTDs among 1989-1991 California births. In-person interviews were conducted with mothers of 424 NTD cases and with mothers of 440 nonmalformed controls. A standard 100-item food frequency questionnaire was used to assess nutrient intake. Dietary intakes of choline were associated with reduced NTD risks. Controlling for intake of supplemental folic acid, dietary folate, dietary methionine, and other covariates did not substantially influence risk estimates for choline. NTD risk estimates were lowest for women whose diets were rich in choline, betaine, and methionine. That is, for women whose intake was above the 75th percentile compared with below the 25th percentile for all three nutrients, the odds ratio was 0.17 (95% confidence interval: 0.04, 0.76). Study findings for dietary components other than folic acid offer additional clues about the

complex etiologies of NTDs.

Source

Shaw G et al. Periconception dietary intake of choline and betaine and neural tube defects in offspring. *Am J Epidemiol* 2004;160:102-109.

## HEART HEALTH

### Habitual intake of flavonoid subclasses and incident hypertension in adults

ABSTRACT

#### BACKGROUND:

Dietary flavonoids have beneficial effects on blood pressure in intervention settings, but there is limited information on habitual intake and risk of hypertension in population-based studies.

#### OBJECTIVE:

We examined the association between habitual flavonoid intake and incident hypertension in a prospective study in men and women.

Design: A total of 87,242 women from the Nurses' Health Study (NHS) II, 46,672 women from the NHS I, and 23,043 men from the Health Professionals Follow-Up Study (HPFS) participated in the study. Total flavonoid and subclass intakes were calculated from semiquantitative food-frequency questionnaires collected every 4 y by using an updated and extended US Department of Agriculture database.

#### RESULTS:

During 14 y of follow-up, 29,018 cases of hypertension in women and 5629 cases of hypertension in men were reported. In pooled multivariate-adjusted analyses, participants in the highest quintile of anthocyanin intake (predominantly from blueberries and strawberries) had an 8% reduction in risk of hypertension [relative risk (RR): 0.92; 95% CI: 0.86, 0.98;  $P < 0.03$ ] compared with that for participants in the lowest quintile of anthocyanin intake; the risk reduction was 12% (RR: 0.88; 95% CI: 0.84, 0.93;  $P < 0.001$ ) in participants  $\leq 60$  y of age and 0.96 (0.91, 1.02) in participants  $> 60$  y of age ( $P$  for age interaction = 0.02). Although intakes of other subclasses

were not associated with hypertension, pooled analyses for individual compounds suggested a 5% (95% CI: 0.91, 0.99;  $P = 0.005$ ) reduction in risk for the highest compared with the lowest quintiles of intake of the flavone apigenin. In participants  $\leq 60$  y of age, a 6% (95% CI: 0.88, 0.97;  $P = 0.002$ ) reduction in risk was observed for the flavan-3-ol catechin when the highest and the lowest quintiles were compared.

#### CONCLUSIONS:

Anthocyanins and some flavone and flavan-3-ol compounds may contribute to the prevention of hypertension. These vasodilatory properties may result from specific structural similarities (including the B-ring hydroxylation and methoxylation pattern).

Source

Cassidy A, et al. Habitual intake of flavonoid subclasses and incident hypertension in adults. *Am J Clin Nutr*. 2011 Feb; 93 (2): 338-347

### Dietary choline and betaine intakes in relationship to concentrations of inflammatory markers in healthy adults: the ATTICA study

ABSTRACT

#### BACKGROUND:

Choline and betaine are found in a variety of plant and animal foods and were recently shown to be associated with decreased homocysteine concentrations.

#### OBJECTIVE:

The scope of this work was to investigate the associations between dietary choline and betaine consumption and various markers of low-grade systemic inflammation.

#### DESIGN:

Under the context of a cross-sectional survey that enrolled 1514 men (18-87 y of age) and 1528 women (18-89 y of age) with no history of cardiovascular disease (the ATTICA Study), fasting blood samples were collected and inflammatory markers were measured. Dietary habits were evaluated with a validated food-frequency questionnaire, and the intakes of choline

and betaine were calculated from food-composition tables.

#### RESULTS:

Compared with the lowest tertile of choline intake ( $< 250$  mg/d), participants who consumed  $> 310$  mg/d had, on average, 22% lower concentrations of C-reactive protein ( $P < 0.05$ ), 26% lower concentrations of interleukin-6 ( $P < 0.05$ ), and 6% lower concentrations of tumor necrosis factor- $\alpha$  ( $P < 0.01$ ). Similarly, participants who consumed  $> 360$  mg/d of betaine had, on average, 10% lower concentrations of homocysteine ( $P < 0.01$ ), 19% lower concentrations of C-reactive protein ( $P < 0.1$ ), and 12% lower concentrations of tumor necrosis factor- $\alpha$  ( $P < 0.05$ ) than did those who consumed  $< 260$  mg/d. These findings were independent of various sociodemographic, lifestyle, and clinical characteristics of the participants.

#### CONCLUSIONS:

Our results support an association between choline and betaine intakes and the inflammation process in free-eating and apparently healthy adults. However, further studies are needed to confirm or refute our findings.

Source

Detopoulou P et al. Dietary choline and betaine intakes in relationship to concentrations of inflammatory markers in healthy adults: the ATTICA study. *Am J Clin Nutr* 2008;87:424-430.

### Select dietary flavonoids are associated with markers of inflammation and endothelial dysfunction in US women

ABSTRACT

Flavonoids show antiinflammatory effects in vitro and human intervention studies have suggested beneficial effects of flavonoid-rich foods on biomarkers of inflammation and endothelial function. In the present study, we assessed the relationship between flavonoid intake and biomarkers of inflammation and endothelial dysfunction in a cross-sectional study of participants from the Nurses' Health Study cohort. Intake of 6 flavonoid subclasses (flavonols, flavones,

flavanones, flavan-3-ols, anthocyanidins, and polymeric flavonoids) was assessed using a FFQ administered in 1990. Also, the main food sources of these flavonoids were examined. Blood samples were collected in 1989–1990 and plasma C-reactive protein (CRP), IL-6, IL-18, soluble tumor necrosis factor receptor-2 (sTNF-R2), soluble intercellular adhesion molecule-1, soluble vascular adhesion molecule-1 (sVCAM-1), and E-selectin were measured in 1194–1598 women. The multivariate-adjusted geometric mean of plasma IL-8 were lower for women in the highest intake quintile of flavones, flavanones, and total flavonoids compared with those in the lowest quintiles by 9% (Q1: 264 ng/L, Q5: 241 ng/L; P-trend = 0.019), 11% (Q1: 273 ng/L, Q5: 244 ng/L; P-trend = 0.011), and 8% (Q1: 276 ng/L, Q5: 55 ng/L; P-trend = 0.034), respectively. The multivariate-adjusted geometric mean for women in the highest intake quintile of flavonol compared with those in the lowest quintile was 4% lower for sVCAM-1 (Q1: 578 µg/L, Q5: 557 µg/L; P-trend = 0.012). Among flavonoid-rich foods, higher intake of grapefruit was significantly associated with lower concentrations of CRP and sTNF-R2. In summary, higher intakes of selected flavonoid subclasses were associated with modestly lower concentrations of inflammatory biomarkers. In particular, flavonoids typically found in citrus fruits were modestly associated with lower plasma IL-18 concentrations.

#### Source

Landberg R, et al. Select dietary flavonoids are associated with markers of inflammation and endothelial dysfunction in US women. *Journal of nutrition*, April 2011, doi: 10.3945/jn.101.133843

### Multivitamin use and the risk of myocardial infarction: a population-based cohort of Swedish women

#### ABSTRACT

##### BACKGROUND:

Dietary supplements are widely used in industrialized countries.

##### OBJECTIVE:

The objective was to examine the

association between multivitamin use and myocardial infarction (MI) in a prospective, population-based cohort of women.

##### DESIGN:

The study included 31,671 women with no history of cardiovascular disease (CVD) and 2262 women with a history of CVD aged 49–83 y from Sweden. Women completed a self-administered questionnaire in 1997 regarding dietary supplement use, diet, and lifestyle factors. Multivitamins were estimated to contain nutrients close to recommended daily allowances: vitamin A (0.9 mg), vitamin C (60 mg), vitamin D (5 µg), vitamin E (9 mg), thiamine (1.2 mg), riboflavin (1.4 mg), vitamin B-6 (1.8 mg), vitamin B-12 (3 µg), and folic acid (400 µg).

##### RESULTS:

During an average of 10.2 y of follow-up, 932 MI cases were identified in the CVD-free group and 269 cases in the CVD group. In the CVD-free group, use of multivitamins only, compared with no use of supplements, was associated with a multivariable-adjusted hazard ratio (HR) of 0.73 (95% CI: 0.57, 0.93). The HR for multivitamin use together with other supplements was 0.70 (95% CI: 0.57, 0.87). The HR for use of supplements other than multivitamins was 0.93 (95% CI: 0.81, 1.08). The use of multivitamins for ≥5 y was associated with an HR of 0.59 (95% CI: 0.44, 0.80). In the CVD group, use of multivitamins alone or together with other supplements was not associated with MI.

##### CONCLUSIONS:

The use of multivitamins was inversely associated with MI, especially long-term use among women with no CVD. Further prospective studies with detailed information on the content of preparations and the duration of use are needed to confirm or refute our findings.

#### Source

Rautiainen S et al. Multivitamin use and the risk of myocardial infarction: a population-based cohort of Swedish women. *Am J Clin Nutr*. 95:1251–6, 2010.

## IMMUNE HEALTH

### Update: effects of antioxidant and non-antioxidant vitamin supplementation on immune function

#### ABSTRACT

The purpose of this manuscript is to review the impact of supplementation with vitamins E and C, carotenoids, and the B vitamins on parameters of innate and adaptive immune function as reported from clinical trials in humans. There is evidence to support causal effects of supplementation with vitamins E and C and the carotenoids singly and in combination on selected aspects of immunity, including the functional capacity of innate immune cells, lymphocyte proliferation, and the delayed-type hypersensitivity (DTH) response. Controlled intervention trials of B vitamin-containing multivitamin supplements suggest beneficial effects on immune parameters and clinical outcomes in HIV-positive individuals.

#### Source

Webb AL, et al. Update: effects of antioxidant and non-antioxidant vitamin supplementation on immune function. *Nutr Rev*. 2007 May;65(5):181–217.

## SKIN HEALTH

### Discovering the link between nutrition and skin aging

#### ABSTRACT

Skin has been reported to reflect the general inner-health status and aging. Nutrition and its reflection on skin has always been an interesting topic for scientists and physicians throughout the centuries worldwide. Vitamins, carotenoids, tocopherols, flavonoids and a variety of plant extracts have been reported to possess potent antioxidant properties and have been widely used in the skin care industry either as topically applied agents or oral supplements in an attempt to prolong youthful skin appearance. This review will provide an overview of the current literature “linking” nutrition with skin aging.

## Source

Schagen S et al. Discovering the link between nutrition and skin aging. Review. *Dermato-Endocrinol* 4:298-307, 2012.

## SPORTS NUTRITION

### Update: effects of antioxidant and non-antioxidant vitamin supplementation on immune function

#### ABSTRACT

The purpose of this manuscript is to review the impact of supplementation with vitamins E and C, carotenoids, and the B vitamins on parameters of innate and adaptive immune function as reported from clinical trials in humans. There is evidence to support causal effects of supplementation with vitamins E and C and the carotenoids singly and in combination on selected aspects of immunity, including the functional capacity of innate immune cells, lymphocyte proliferation, and the delayed-type hypersensitivity (DTH) response. Controlled intervention trials of B vitamin-containing multivitamin supplements suggest beneficial effects on immune parameters and clinical outcomes in HIV-positive individuals.

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Webb AL, et al. Update: effects of antioxidant and non-antioxidant vitamin supplementation on immune function. *Nutr Rev*. 2007 May;65(5):181-217.

## WEIGHT MANAGEMENT

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##### BACKGROUND:

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The scope of this work was to investigate the associations

between dietary choline and betaine consumption and various markers of low-grade systemic inflammation.

##### DESIGN:

Under the context of a cross-sectional survey that enrolled 1514 men (18-87 y of age) and 1528 women (18-89 y of age) with no history of cardiovascular disease (the ATTICA Study), fasting blood samples were collected and inflammatory markers were measured. Dietary habits were evaluated with a validated food-frequency questionnaire, and the intakes of choline and betaine were calculated from food-composition tables.

##### RESULTS:

Compared with the lowest tertile of choline intake (<250 mg/d), participants who consumed >310 mg/d had, on average, 22% lower concentrations of C-reactive protein ( $P < 0.05$ ), 26% lower concentrations of interleukin-6 ( $P < 0.05$ ), and 6% lower concentrations of tumor necrosis factor- $\alpha$  ( $P < 0.01$ ). Similarly, participants who consumed >360 mg/d of betaine had, on average, 10% lower concentrations of homocysteine ( $P < 0.01$ ), 19% lower concentrations of C-reactive protein ( $P < 0.1$ ), and 12% lower concentrations of tumor necrosis factor- $\alpha$  ( $P < 0.05$ ) than did those who consumed <260 mg/d. These findings were independent of various sociodemographic, lifestyle, and clinical characteristics of the participants.

##### CONCLUSIONS:

Our results support an association between choline and betaine intakes and the inflammation process in free-eating and apparently healthy adults. However, further studies are needed to confirm or refute our findings.

#### Source

Detopoulou P et al. Dietary choline and betaine intakes in relationship to concentrations of inflammatory markers in healthy adults: the ATTICA study. *Am J Clin Nutr* 2008;87:424-430.

### Laboratory, epidemiological, and human intervention studies show that tea (*Camellia sinensis*) may be useful in the prevention of obesity

#### ABSTRACT

Tea (*Camellia sinensis*, Theaceae) and tea polyphenols have been studied for the prevention of chronic diseases, including obesity. Obesity currently affects >20% of adults in the United States and is a risk factor for chronic diseases such as type II diabetes, cardiovascular disease, and cancer. Given this increasing public health concern, the use of dietary agents for the prevention of obesity would be of tremendous benefit. Whereas many laboratory studies have demonstrated the potential efficacy of green or black tea for the prevention of obesity, the underlying mechanisms remain unclear. The results of human intervention studies are mixed and the role of caffeine has not been clearly established. Finally, there is emerging evidence that high doses of tea polyphenols may have adverse side effects. Given that the results of scientific studies on dietary components, including tea polyphenols, are often translated into dietary supplements, understanding the potential toxicities of the tea polyphenols is critical to understanding their potential usefulness in preventing obesity. In this review, we will critically evaluate the evidence for the prevention of obesity by tea, discuss the relevance of proposed mechanisms in light of tea polyphenol bioavailability, and review the reports concerning the toxic effects of high doses of tea polyphenols and the implication that this has for the potential use of tea for the prevention of obesity. We hope that this review will expose areas for further study and encourage research on this important public health issue.

#### Source

Grove KA and Lambert JD. Critical Review. Laboratory, epidemiological, and human intervention studies show that tea (*Camellia sinensis*) may be useful in the prevention of obesity. *J of Nutr* 140:446-53, 2010.