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# Threshold Controlled Super-B



Get the science behind Threshold Controlled Super-B with Peer Reviewed Studies that support ingredients found in this amazing product.



## 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]

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.

### 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),

### COGNITIVE HEALTH

Nutraceuticals in the treatment of obsessive compulsive disorder (OCD): A review of mechanistic and clinical evidence

#### 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

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##### 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 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.

## 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.

## 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.

## 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.

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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.

## HEART HEALTH

### 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.

#### 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  $\mu$ g), vitamin E (9 mg), thiamine (1.2 mg),

riboflavin (1.4 mg), vitamin B-6 (1.8 mg), vitamin B-12 (3  $\mu$ g), and folic acid (400  $\mu$ g).

#### 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  $\geq 5$  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 anti-oxidant 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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