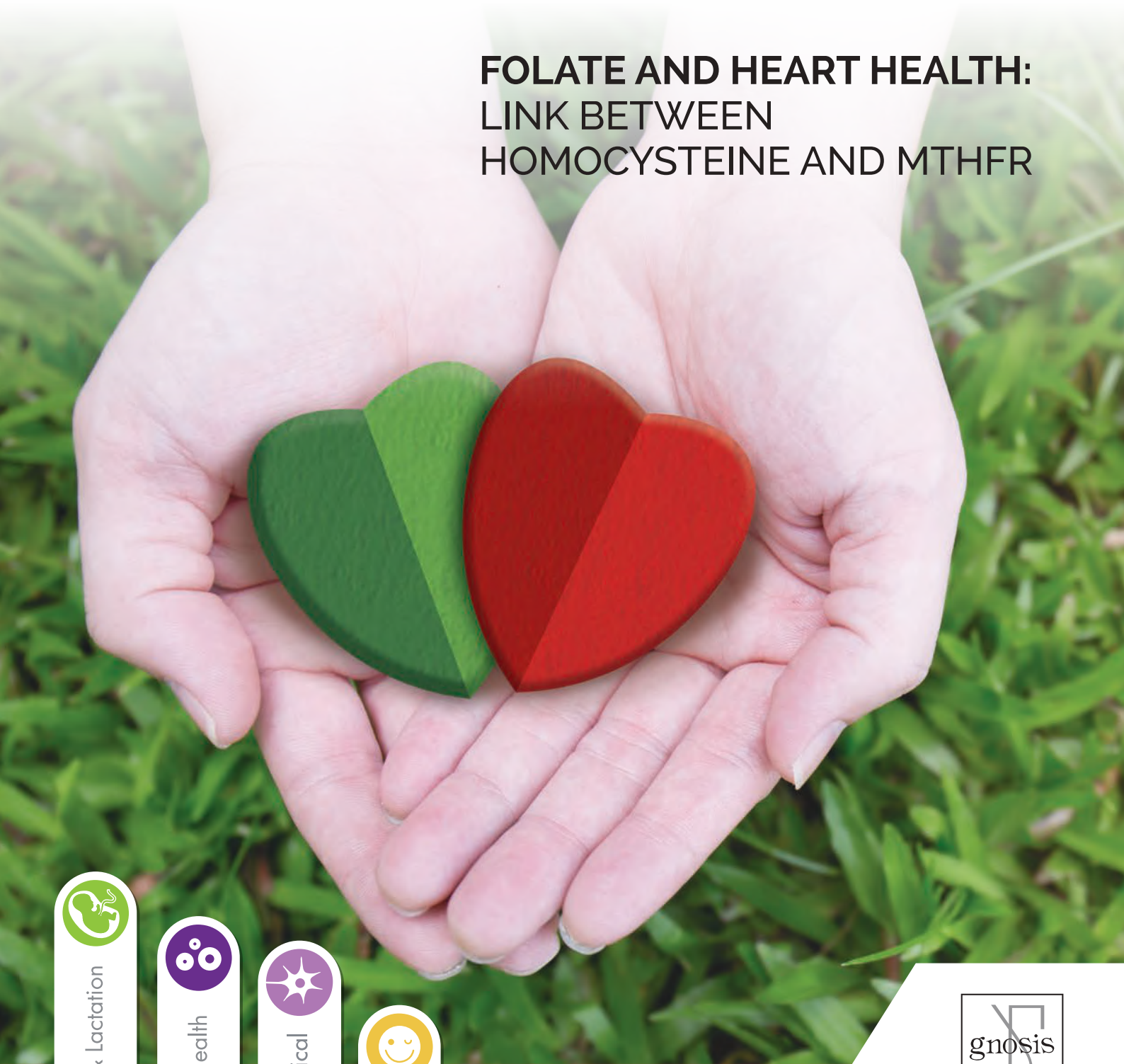
Quatrefolic®
The innovACTIVE folate!

News from Science

FOLATE AND HEART HEALTH: LINK BETWEEN HOMOCYSTEINE AND MTHFR



Prenatal & Lactation

Cellular Health

Neurological

Mood

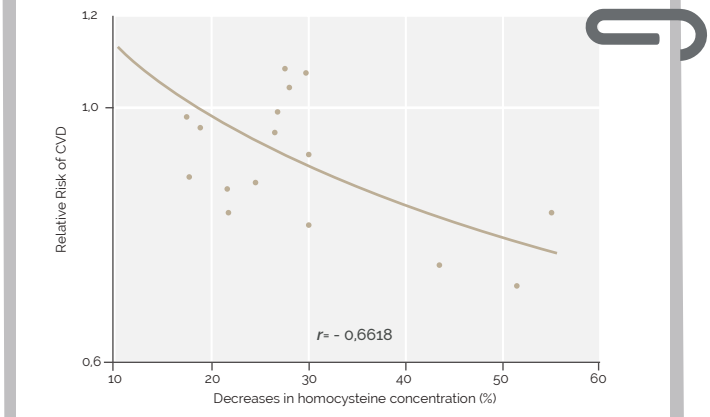
gnosis
by LESAFFRE

Quatrefolic® and heart-healthy life

Extensive researches are trying to identify strategies to promote heart health and prevent the related risk factors for cardiovascular disease (CVD). Of particular interest is the role of homocysteine (Hcy), a common amino acid found in the bloodstream and produced as a metabolite of methionine metabolism in the one carbon cycle.

THE CLASSIFICATION OF HOMOCYSTEINEMIA

THE RESULTS	DIAGNOSIS
Normal	5-15 mmol/l
Mild	15-30 mmol/l
Moderate	30-100 mmol/l
Severe	> 100 mmol/l



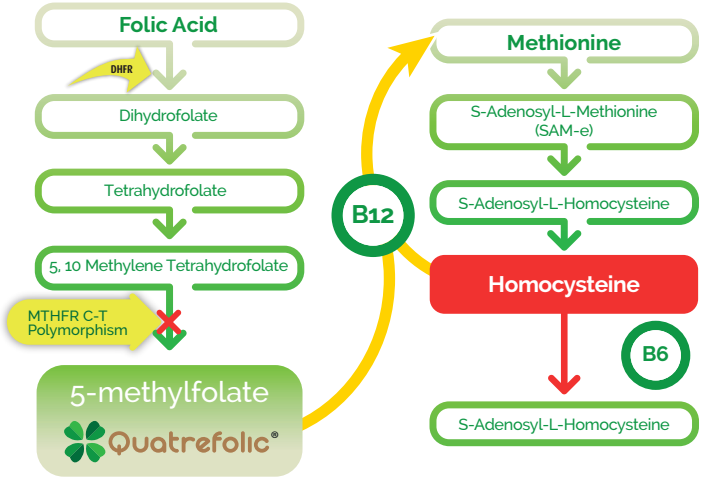
Relation between homocysteine reduction and relative risk of CVD (significant dose-response association)
Adapted from Li et al. 2016.

Folate is an important regulator of Hcy metabolism and helps to maintain normal plasma homocysteine concentrations. Clinical studies report evidence that folate supplementation can reduce cardiovascular disease risk by lowering homocysteine levels.

Li Y. et al. J Am Heart Assoc. 2016; Clarke R et al. Arch Intern Med. 2010;
Toole J.F. et al. JAMA 2004; Blom H.J. et al. Nat Rev Neurosci. 2006;
Wald D.S. et al. BMJ 2002; Homocysteine Studies Collaboration. JAMA 2002.

Increased plasmatic levels of Hcy are predictive for cardiovascular risk and determined by several factors (lifestyle, genetics and diet). The most common cause of genetic hyperhomocysteinemia (HHcy) is the 677CT polymorphism of methylenetetrahydrofolate reductase (MTHFR), gene involved in the folate metabolism, which impairs the conversion into L-methylfolate (5-MTHF), the biologically active form of folate.
5-MTHF works as a methyl donor for homocysteine remethylation in the one carbon metabolism cycle.

While folic acid must be first converted into 5-MTHF, Quatrefolic®, (6S)-5-methyltetrahydrofolate glucosamine salt, is the biologically active form of folate that completely bypasses the "damaged" MTHFR conversion step, overstepping the problem of people with polymorphisms in folate-related enzyme, and that can better guarantee heart health.



A reduction of homocysteine level is important for cardiovascular protection. Two meta-analyses concluded that ischemic heart disease risk could be reduced by 16% with a 3 µmol/L decrease in homocysteine levels and by 11% with a 25% decrease in homocysteine levels.

Behind the Hcy mechanism and heart health

CVD continues to be one of the main causes of mortality in the western world. Elevated plasma Hcy concentration is considered a risk factor for CVD and may also be associated with hypertension. Hcy is responsible for 10% of the total risk for atherothrombotic vascular disease; furthermore, a meta-analysis has highlighted that each increase of 5 µmol/L in homocysteine level raises the risk of Coronary Artery Disease (CHD) events by approximately 20%, independently of traditional CHD risk factors.
The mechanisms by which high levels of homocysteine exert disease effects may be either indirect or direct. In the first case, Hcy is a simple marker; in the second case, it is a true risk factor of cardiovascular disease.

MOLECULAR MECHANISMS OF HOMOCYSTEINE-INDUCED CELLULAR DYSFUNCTION

HYPERHOMOCYSTEINEMIA

INDIRECT MECHANISM

DNA hypomethylation

Lipid peroxidation

ATHEROSCLEROSIS

DIRECT MECHANISM

Production of free-reactive oxygen species that can directly injure the endothelium

- Oxidative stress
- Impairment of endothelial function
- Inflammation and increased inflammatory cytokine expression
- Promotion of oxidant injury to the vascular endothelium due to decrease of the antioxidant activity of superoxide dismutase on endothelial cell surfaces
- Inhibition of nitric oxide production
- Protein aggregation
- Increased platelets' aggregation
- Activation of apoptosis

Stanger O. et al. Clin Chem Lab Med. 2003; Boushey C.J. et al. J. Am Med Assoc. 1995; Ganguly P.et al. Nutr J. 2015;
Djuric D. et al. Indian J Chest Dis Allied Sci. 2008; Cacciapuoti F. Ann Vasc Med Res. 2017.

Hcy and the 677CT polymorphism of the MTHFR enzyme

It is estimated that with a 677TT homozygous mutation of MTHFR, up to 70% of the enzyme function is lost; and with a C677T heterozygous mutation, there is a 35% loss of enzymatic function. In these subjects the immediate use of the bioavailable form of folate 5-MTHF Quatrefolic® is a tangible benefit.

World variability of the prevalence of MTHFR polymorphism (homozygous 677TT genotype) among different ethnic groups and regions (the incidence is higher in Mediterranean countries, Latin Americans and lower in African-Americans)

Prevalence of 677TT in main Ethnic Groups

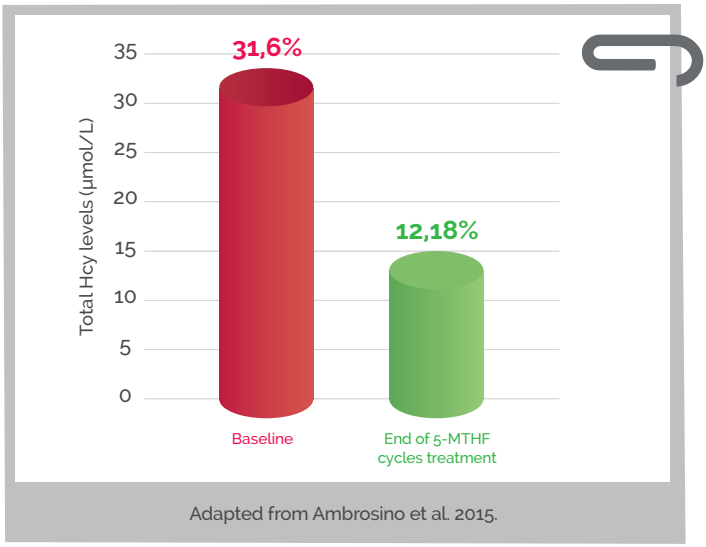
- 0-2% In Africans
- 12% in Whites
- 20% in Asians

Prevalence of 677TT in some Geographic Areas

- 11,5% Australia
- 20% Northern China
- 26% Southern Italy
- 32% Mexico

Kiseljaković E. et al. Bosn J Basic Med Sci. 2008; Wilcken D.E. J Cardiovasc Risk. 1998; Ambrosino et al. Nutr Res. 2015.

Subjects with homozygotes polymorphism have 25% higher homocysteine levels (about 2,5 µmol/l) due to the reduced enzyme activity. They need to have an increased dietary folate intake to maintain adequate enzyme function.
Ambrosino et al clearly shows that a cyclic schedule (1 month of therapy followed by 2 months of withdrawal) of 5-MTHF supplementation is able to significantly reduce tHcy levels in patients with mild/moderate HHcy.
During the entire study period, there was a reduction of tHcy levels from 31.6 to 12.18 µmol/L. The repeated folate cycles normalized levels in 86.8% of patients treated.



Adapted from Ambrosino et al. 2015.

Quatrefolic® and the right folate supplementation

Epidemiological data

Recently, a randomized study that included 20,702 adults without a history of stroke or myocardial infarction (MI) has revealed that the combined use of the hypertension medication enalapril and folic acid, compared with enalapril alone, significantly reduced the risk of first stroke among Chinese adults with hypertension. **Participants were stratified by variations in the polymorphism of the enzyme methylenetetrahydrofolate reductase (MTHFR) C677T gene (CC, CT, and TT genotypes) that affects folate levels.**

The protective effect of folic acid was not the same in the different genotypes. **In patients with polymorphism (TT homozygous mutation) the preventive effect of folic acid therapy was lost and the group had the highest stroke rates.**

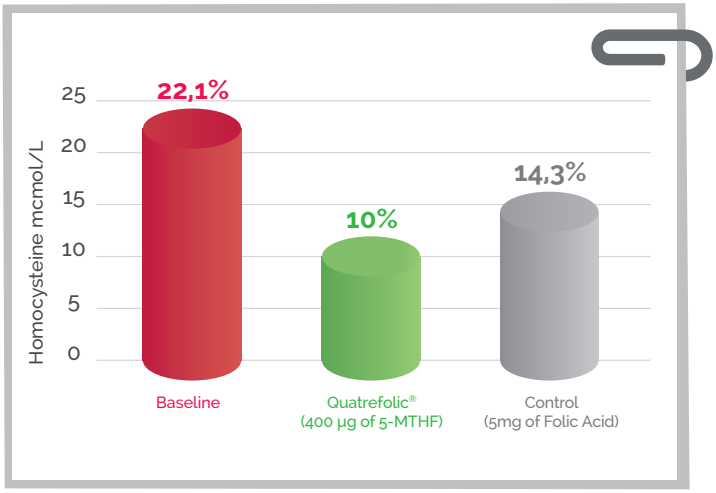
This study opens a window on potential billions of people in the world who may have low levels of folate and where the percentage of the polymorphism of the MTHFR gene C677T is underestimated. **In these subjects, the supplementation of right folate such as Quatrefolic® bypasses the reduction of folate metabolism and, hence, lower circulating levels of folate.**

Quatrefolic® ↓ Hcy

The homocysteine-lowering and -normalizing effect of Quatrefolic®, in comparison with high dosage of folic acid in hypertensive subjects at low cardiovascular risk, has been tested by Mazza et al in 2016.

400 mcg of Quatrefolic® plus B6 and B12 was tested versus a conventional vitamin supplementation with 5 mg/day of folic acid, in patients with stage 1 hypertension and serum hyperhomocysteinemia (Hcys >15 µmol/L) at low cardiovascular risk.

The results of Quatrefolic® group showed a significant Hcys reduction in comparison with baseline from 21.5 mcmol/L to 10.0 mcmol/L versus the control group (highly dosed folic acid).
The ideal Hcys level (i.e. less than 10 µmol/L) was reached in 55.8% of cases in the Quatrefolic® group, and it was significantly higher than in the control one.



Quatrefolic® is once again a greatest and a healthiest solution for a right folate supplementation. It offers tangible advantages versus folic acid and can promote healthier heart life, especially for people with MTHFR polymorphism.

Huo Y. et al. JAMA 2015; Mazza et al. Biol Regul Homeost Agents. 2016.

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by LESAFFRE

Gnosis S.p.A.
Via Lavoratori Autobianchi, 1
20832 Desio (MB) - Italy
E-mail: info@gnosis-bio.com

Gnosis USA Inc.
4259 West Swamp Road, 3rd Floor Suite 305
Doylestown, Pennsylvania 18902 - USA
E-mail: info@gnosis-us.com

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