News from Science

Quatrefolic®
The innovACTIVE folate!

FOLATE AND THE ELDERLY: CHALLENGES AND OPPORTUNITIES

Prenatal & Lactation
Cellular Health
Neurological
Mood

gnosis
advanced biotech

Scientific Focus on Quatrefolic®: **Folate in the Elderly**

Aging population and folate levels

The aging process involves changes in the morphology and physiology of different organs and tissues which could possibly affect the correct nutritional status in the elderly.

In particular, folate deficiency is high among individuals aged ≥ 65 years and may reach approximately 30%. The lack of this vitamin derives mainly from the reduced dietary intake, the intestinal malabsorption and the impairment of metabolism. In fact humans cannot synthesize folate and due to its water soluble nature, the body stores folate to a limited extent.

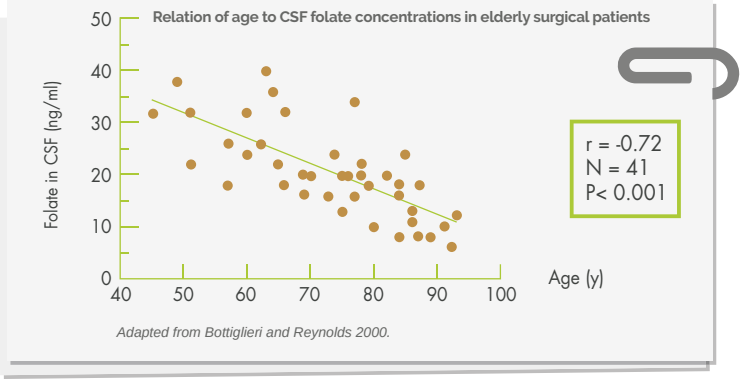
Inadequate folate status is associated with an increased risk for chronic diseases that may have a negative impact on the health of the aging population.

In the brain, folate is involved in the production of key neurotransmitters. In 2000, Bottiglieri and Reynolds showed that the concentration of folate in the cerebrospinal fluid (CSF) decreases with age, particularly in older adults over 70 of age. This provided further evidence of a link between folate concentration and age, and for the first time, highlighted this connection directly in the nervous system.

Mitchell E. S. e al. Neuroscience & Biobehavioral Reviews, 2014
Selhub J. et al. Jama, 1993
Selhub J et al. The American journal of clinical nutrition, 2000
Rampersaud, G.C. et al. Journal of the American College of Nutrition, 2003
Bottiglieri T, Reynolds E. et al. Journal of Neurology, Neurosurgery & Psychiatry, 2000

Inadequate folate status may result also in hyperhomocysteinemia, a significant risk factor for atherosclerotic vascular disease, for changes in DNA that may result in pro-carcinogenic effects and for increased risk for cognitive dysfunction.

Quatrefolic® supplementation is suggested to guarantee the right dosage of biologically active folate and to efficiently support methylation, DNA biosynthesis, and nervous system function.



Adapted from Bottiglieri and Reynolds 2000.

MTHFR CAUSES OF FOLATE DEFICIENCY IN OLDER INDIVIDUALS

· NUTRITIONAL
Deficient in food source

· INTESTINAL MALABSORPTION
Atrophic gastritis
Intestinal diseases
(Crohn's disease, celiac disease)
Gastric and intestinal resection

· REDUCED DIETARY INTAKE
Decreased sensory function and appetite
Dysphagia

· DISEASE STATES
Cancer
Liver Disease
Hemodialysis

· DEFECTS IN UTILIZATION
Alcohol use
Pregnancy and Lactation

· DRUG INDUCED
Antifolates
Inhibitors of gastric acid secretion
Antiepileptics

· GENETIC POLYMORPHISMS
Methylenetetrahydrofolate reductase (MTHFR)

· AUTO-ANTIBODIES FOLATE RECEPTOR (FR-α)
Cerebral folate deficiency

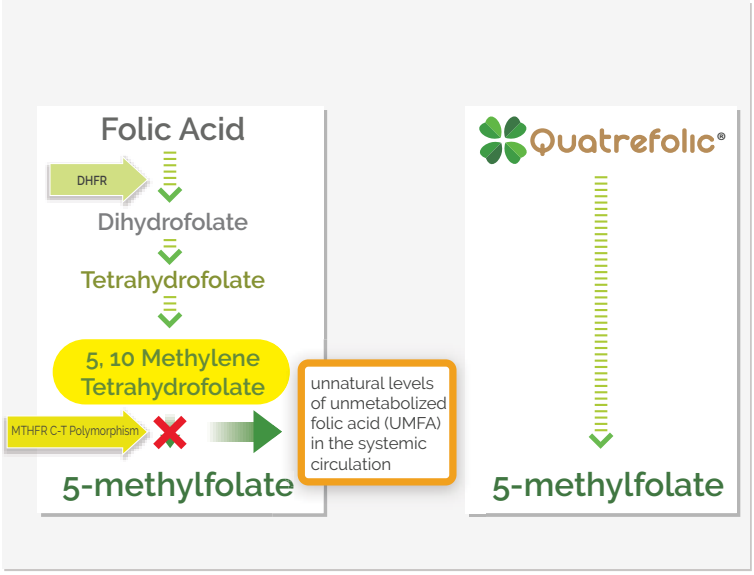
Araújo J. et al. Ageing research reviews, 2015

Quatrefolic® The innovACTIVE folate!

In older adults and the elderly the supplementation of the proper form of folate is essential to quickly re-establish the plasma folate levels and to counter the variety of physiologic and pathological changes that influence folate status and that need for medical care.

Quatrefolic® provides the naturally occurring 5-methyltetrahydrofolate (5-MTHF):
- **the well absorbed folate even when gastrointestinal pH is altered**
- **the only species normally found in the circulation**
- **the folate that is normally transported into peripheral tissues to be used for cellular metabolism**
- **the only form able to cross the BBB (Blood Brain Barrier)**

Quatrefolic® bioavailability is not affected by multi-steps process of conversion and by metabolic defects typical of folic acid and food folate, such as the polymorphism of the enzyme MTHFR (methyltetrahydrofolate reductase).
In fact, some individuals due to their unique genetic patterns and expression, have a polymorphic form of this enzyme and do not produce adequate or effective form of it, with impaired folate metabolism and with exacerbation of folate deficiency. These genetic alterations are already involved in the increase of homocysteine blood level.

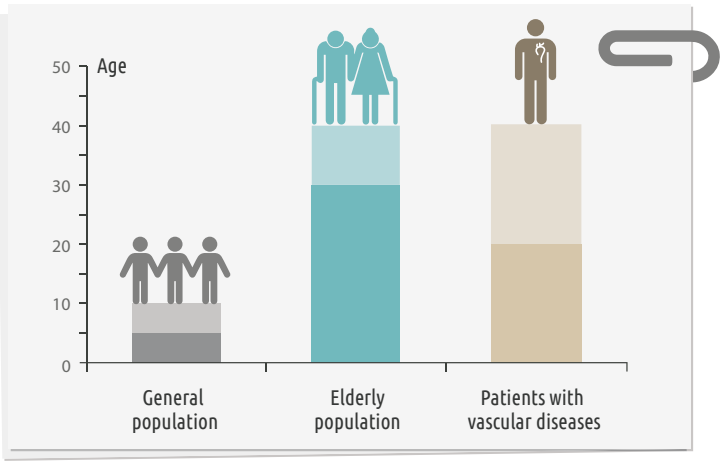


Patanwala I et al. Am J Clin Nutr. 2014
Scaglione F, Panzavolta G. Xenobiotica. 2014
Ulrich CM, Potter JD. Cancer Epidemiol Biomarkers Prev. 2006

Scientific Focus on Quatrefolic®

Quatrefolic® and Homocysteine in Health

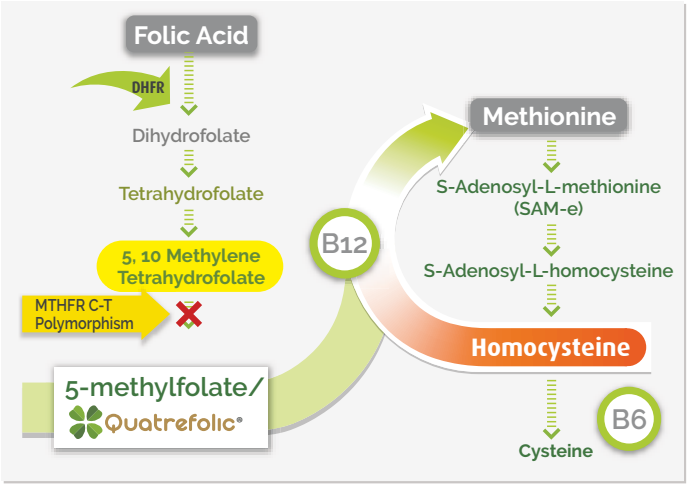
Homocysteine is a metabolite of methionine metabolism in the one carbon metabolism and exists at a critical biochemical intersection - between S-adenosylmethionine, the indispensable ubiquitous methyl donor, and 5-MTHF and vitamin B12.
Prevalence of hyperhomocysteinemia varies with the target population and tends to increase with age. **The incidence of hyperhomocysteinemia in elderly population is significant:**



The relationship between serum folate, cardiovascular disease and poor cognitive function may be due to the role of folate in controlling/reducing homocysteine blood and its effects on the vascular system. Folate deficiency is one of the main cause of hyperhomocysteinemia; among other causes there are genetic and environmental factors, renal pathologies and specific conditions such as pregnancies, menopause, and oral contraceptive pharmacological therapies.

Supplementation of folate, such as Quatrefolic®, has demonstrated to lower the buildup of homocysteine and to be an effective contribution to health, even in presence of other risk factors. Moreover, Quatrefolic® may be also a valid nutritional support for people with alterations in the metabolism of folate and, consequently, of homocysteine.

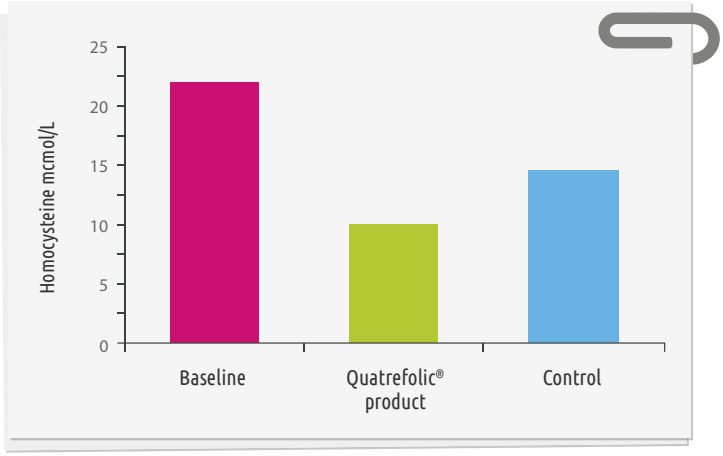
In these subjects, genetic alterations cause deficiencies in the enzymes involved in the elimination process of homocysteine increasing the risk to develop homocysteinemie. The most prevalent is the polymorphism of the MTHFR enzyme methylenetetrahydrofolate-reductase that impairs the availability of 5-methylfolate (5-MTHF). Quatrefolic®, already providing 5-MTHF is the best folate to help to maintain ideal levels of HCys in humans.



Miller A.L.. Altern Med Rev. 2003
Refusun H, Ueland PM, Nygard O, et al. Annu Rev Med 1998
Tavares J.R. et al. Arquivos brasileiros de cardiologia, 2002
Caruso et al. J Cardiovasc Pharmacol 2006
Scott JM, Weir DG. J Cardiovasc Risk.1998

Quatrefolic® is effective in lowering Homocysteine

A new study (Mazza et al 2016) has investigated the efficacy of Quatrefolic® (400 mcg of Quatrefolic® plus B6, and B12) in lowering homocysteine serum levels (HCys) versus a conventional vitamin supplementation with highly dosed folic acid (5 mg/day) in hypertensive subjects at low cardiovascular risk (104 patients with HCys ≥15 μ mol/L).



The result shows significant HCys reduction in comparison with baseline from 21.5 mcmol/L to 10.0 mcmol/L with the product containing Quatrefolic®.
The treatment was significantly effective and the ideal HCys level was reached in 55.8% of cases in the Quatrefolic® group, and it was significantly higher than in controls.

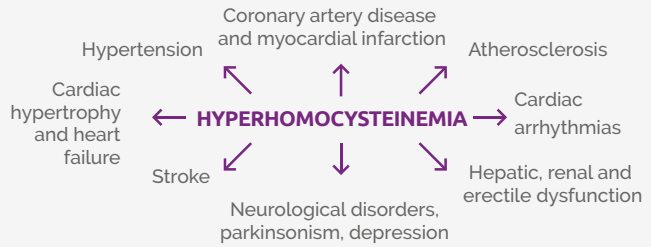
Mazza et al. Biol Regul Homeost Agents. 2016

Homocysteine: disease development and longevity

Homocysteinemia plays a crucial role for disease development determining longevity and health throughout a person's life and is seen as a predictor of potential health problems.
The mechanism by which high levels of homocysteine exert disease effects depends by the production of free-reactive oxygen species that cause oxidative stress.

The Classification of Homocysteinemia

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



In 2015, a meta-analysis has shown that the elevated Hcy level is an independent predictor for subsequent cardiovascular mortality or all-cause mortality in the general population, and that the risks are more pronounced among elderly persons.

Selhub J, Jacques PF, Wilson PWF, et al. JAMA 1993
Peng H. et al. Journal of Zhejiang University Science B, 2015

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