

The role of folate metabolism and genetic polymorphisms in coronary artery disease

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Folate is an essential form of vitamin B9 that facilitates the transfer of single-carbon groups and plays an important role in DNA methylation, conversion of homocysteine to methionine, nucleotide synthesis, and DNA repair. Folate deficiency has been reported to be associated with an increased risk of coronary artery disease (CAD). Although the biochemical mechanisms linking folate deficiency to CAD have been extensively studied, the genetics of folate metabolism and the clinical implications of folate supplementation remain areas of ongoing investigation. We integrated three interconnected domains—biochemistry, genetics, and nutritional supplementation—to provide a comprehensive synthesis of current knowledge on the folate metabolism in CAD. There is strong evidence that elevated plasma homocysteine levels are associated with increased cardiovascular mortality and long-term adverse events in patients with CAD, often due to folate deficiency. Elevated plasma homocysteine levels contribute to endothelial dysfunction, oxidative stress, inflammation, and atherosclerotic plaque formation, all of which play roles in pathogenesis of CAD¹. The genes encoding the enzymes methylenetetrahydrofolate reductase (MTHFR) and methyltetrahydrofolate-homocysteine methyltransferase reductase (MTRR) play a central role in the metabolism of folate, homocysteine, and consequently in methylation. The MTHFR gene is involved in the conversion of methylenetetrahydrofolate to methyltetrahydrofolate, which is the main circulating form of folate and the carbon donor for the remethylation of homocysteine to methionine. Meanwhile, MTRR gene plays a role in the remethylation of homocysteine to methionine via cobalamin in a folate-dependent reaction. Polymorphisms in the MTHFR and MTRR genes can influence the risk of CAD by altering the metabolism of homocysteine. Of particular importance is the MTHFR C677T polymorphism, while the A1298C polymorphism and, especially, the MTRR A66G polymorphism have shown less consistent associations with CAD risk^{2,3}. In addition, folate supplementation lowers homocysteine levels, particularly in individuals with the MTHFR C677T TT genotype, which is associated with reduced enzyme activity involved in homocysteine metabolism⁴. Importantly, although folic acid supplementation reduces plasma homocysteine, systematic reviews and meta-analyses show no significant effect on CAD risk or cardiovascular mortality. These findings highlight the need for further research to better understand the mechanisms and conditions under which folate supplementation might offer cardiovascular protection.

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LITERATURE

1. Zhang S, Lv Y, Luo X, Weng X, Qi J, Bai X, et al. Homocysteine promotes atherosclerosis through macrophage pyroptosis via endoplasmic reticulum stress and calcium disorder. *Mol Med.* 2023 Jun 12;29(1):73. <https://doi.org/10.1186/s10020-023-00656-z>
2. Samii A, Aslani S, Imani D, Razi B, Samaneh Tabaei S, Jamialahmadi T, et al. MTHFR gene polymorphisms and susceptibility to myocardial infarction: Evidence from meta-analysis and trial sequential analysis. *Int J Cardiol Heart Vasc.* 2023 Nov 22;49:101293. <https://doi.org/10.1016/j.ijcha.2023.101293>
3. Singh PR, Lele SS. Folate gene polymorphisms MTR A2756G, MTRR A66G, and BHMT G742A and risk for coronary artery disease: a meta-analysis. *Genet Test Mol Biomarkers.* 2012 Jun;16(6):471-5. <https://doi.org/10.1089/gtmb.2011.0237>
4. Mazokopakis EE, Papadomanolaki MG, Papadakis JA. The effects of folic acid and L-methylfolate supplementation on serum total homocysteine levels in healthy adults. *Clin Nutr ESPEN.* 2023 Dec;58:14-20. <https://doi.org/10.1016/j.clnesp.2023.09.002>