MTHFR and *MTRR* Polymorphisms in Homocysteine Regulation (Literature Review)

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ABSTRACT

Background:
Homocysteine is a sulfur-containing amino acid central to one-carbon metabolism, and elevated homocysteine (hyperhomocysteinemia) has been implicated in cardiovascular, neurological, and developmental disorders. Genetic polymorphisms in key enzymes methylenetetrahydrofolate reductase (*MTHFR*) and methionine synthase reductase (*MTRR*) can disrupt homocysteine metabolism (Klerk et al., 2002). *MTHFR* C677T and A1298C variants reduce enzyme activity, while the *MTRR* A66G variant impairs regeneration of methylcobalamin (Brown et al., 2000). These genetic factors, together with B-vitamin cofactor status (folate, B_2, B_6, B_{12}), modulate homocysteine levels and influence disease risk (Steluti et al., 2017).

Methods:
We conducted a comprehensive literature review of mechanistic and epidemiological studies on homocysteine metabolism, focusing on *MTHFR* and *MTRR* polymorphisms and their interactions with B-vitamin nutrition. We included original research and meta-analyses up to 2025. Key outcomes of interest were biochemical effects on homocysteine, gene–nutrient interactions, clinical associations with cardiovascular disease, cancer, birth defects, and neurocognitive decline.

Results:
MTHFR 677T and *MTRR* 66G variants are consistently associated with elevated plasma homocysteine, particularly in individuals with low intake of folate, B12, or riboflavin (Klerk et al., 2002; Steluti et al., 2017; García-Minguillán et al., 2014). Riboflavin supplementation has been shown to reduce homocysteine levels in *MTHFR* 677TT individuals (McNulty et al., 2006), while B12 and folate are broadly effective across genotypes (Brown et al., 2000). Large-scale analyses also demonstrate that the *MTHFR* A1298C variant, though milder, contributes to elevated homocysteine and modestly increases stroke and myocardial infarction risk (Dong et al., 2021; Samii et al., 2023). *MTRR* A66G shows smaller and context-dependent effects: large cohorts report no independent impact (Siddiqi et al., 2025), but case–control and meta-analyses link it to increased neural tube defect and stroke risk in hyperhomocysteinemic individuals (Wang et al., 2015; Li et al., 2020).

Discussion:
The impact of common genetic polymorphisms in homocysteine metabolism is highly modifiable by B-vitamin intake (McNulty et al., 2006; García-Minguillán et al., 2014). Nutritional genomics offers a promising avenue for targeted interventions in individuals with elevated genetic risk (Steluti et al., 2017). Understanding gene–nutrient interactions allow for a more nuanced approach to disease prevention. Future studies should continue to explore the role of personalized B-vitamin therapy in mitigating the functional consequences of *MTHFR* and *MTRR* variants (Brown et al., 2000; Han et al., 2012).

Subjects Genetics, Nutrition **Keywords:** Genetics, Polymorphism, Nutrition, Homocysteine

INTRODUCTION

Homocysteine (Hcy) is a non-proteinogenic amino acid formed as an intermediary during methionine metabolism. Under normal conditions, homocysteine is efficiently removed by remethylation to methionine or by conversion to cysteine. Disruption of these processes can lead to elevated homocysteine in the blood, a condition known as hyperhomocysteinemia. Even moderate increases in homocysteine are of clinical interest because epidemiological studies have linked hyperhomocysteinemia with increased risk of a variety of diseases, particularly cardiovascular disease (Wald et al., 2002). Additionally, high homocysteine has been associated with neurodegenerative diseases, venous thrombosis, birth defects (neural tube defects), pregnancy complications, and others (Brustolin et al., 2010). It remains a matter of debate whether homocysteine is a causal risk factor or a marker of underlying B-vitamin status and metabolic perturbations. Nonetheless, the regulation of homocysteine is of considerable interest given its potential role in disease prevention.

Homocysteine levels in the population are influenced by both nutritional and genetic factors. Deficiencies of the B-vitamins that serve as cofactors or substrates in homocysteine metabolism – notably folate (vitamin B_9), cobalamin (vitamin B_{12}), and pyridoxine (vitamin B_6) – are well-established causes of elevated homocysteine. Lifestyle factors can also play a role; for example, chronic alcohol intake and smoking are associated with higher homocysteine, partly via effects on vitamin status and oxidative metabolism (Brustolin et al., 2010). In addition, common genetic polymorphisms in enzymes that metabolize homocysteine can lead to inter-individual differences in baseline homocysteine levels and the response to vitamins. The most prevalent and well-studied is the 677C>T variant in the *MTHFR* gene, which encodes methylenetetrahydrofolate reductase. This enzyme is critical for regenerating 5-methyltetrahydrofolate, the active form of folate required for homocysteine remethylation to methionine. Individuals with the homozygous *MTHFR* 677TT genotype have a thermolabile, less active enzyme, especially under low folate conditions (Raghubeer & Matsha, 2021). As a result, they tend to have higher circulating homocysteine and lower folate levels compared to those with the wild-type genotype (Steluti et al., 2017; Raghubeer & Matsha, 2021).

Another common functional variant is *MTHFR* A1298C, which causes a milder reduction in enzyme activity but can still lead to measurable increases in homocysteine, particularly in homozygous carriers or when vitamin status is marginal (Liew et al., 2015; Dong et al., 2021; Samii et al., 2023). Large meta-analyses have linked A1298C to modestly elevated risk of stroke and myocardial infarction, confirming its clinical importance alongside C677T.

Beyond *MTHFR*, the *MTRR* A66G polymorphism affects the regeneration of methylcobalamin needed for methionine synthase function. Although its effect on homocysteine is weaker and sometimes absent in well-nourished populations (Siddiqi et al., 2025), it has been associated with increased neural tube defect risk (Wang et al., 2015) and stroke in hyperhomocysteinemic patients (Li et al., 2020).

These genetic factors – *MTHFR* C677T, *MTHFR* A1298C, and *MTRR* A66G – together with nutritional status, constitute the main determinants of homocysteine regulation in humans (McNulty et al., 2006; García-Minguillán et al., 2014).

In this review, we examine the mechanisms of homocysteine metabolism and regulation, then discuss how genetic polymorphisms and nutrition interplay to affect homocysteine levels. We highlight key findings from clinical studies and genetic analyses, including the effect of B-vitamin interventions and gene–nutrient interactions that can inform personalized nutritional strategies to optimize homocysteine levels (Smith et al., 2018; Brown et al., 2000).

Homocysteine Metabolism and Genetic Polymorphisms

The *MTHFR* gene harbors two common functional variants: C677T and A1298C. While C677T produces a thermolabile enzyme with a marked reduction in activity, A1298C (Glu429Ala) confers a milder decrease in *MTHFR* function that can still limit the generation of 5-methyltetrahydrofolate under suboptimal folate or riboflavin intake (Steluti et al., 2017; Raghubeer & Matsha, 2021). Large population studies in the post-fortification era confirm that A1298C is associated with modest shifts in folate and homocysteine distributions, with effects smaller than but directionally similar to C677T (Steluti et al., 2017). Laboratory and comparative clinical studies also report that A1298C relates to altered folate/homocysteine status and indices of DNA stability (Liew et al., 2015).

Homocysteine metabolism involves two main pathways: remethylation to methionine and transsulfuration to cysteine (Brown et al., 2000). These processes depend on several B-vitamin-dependent enzymes. *MTHFR* converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, enabling the remethylation of homocysteine via methionine synthase (*MTR*), which requires methylcobalamin (vitamin B12). *MTRR* is responsible for regenerating methylcobalamin and maintaining *MTR* activity (García-Minguillán et al., 2014). Variants such as *MTHFR* C677T and *MTRR* A66G reduce the efficiency of these enzymes and contribute to elevated homocysteine, especially under conditions of low folate or B12 intake (Steluti et al., 2017).

MTHFR C677T produces a thermolabile enzyme with reduced activity, particularly affecting individuals homozygous for the T allele. The *MTRR* 66G variant is linked to compromised remethylation and increased homocysteine, especially in vitamin-deficient states (Han et al., 2012). These effects may be compounded when individuals carry multiple polymorphisms (Guimarães et al., 2011).

Understanding the biochemical basis of these pathways provides insight into how genetic variants disrupt homocysteine regulation. This knowledge underpins efforts to develop nutrition-based strategies to reduce disease risks associated with hyperhomocysteinemia (Smith et al., 2018).

Table 1: Prominent Human Studies on Genetic Variants Regulating Homocysteine & Nutrient Interactions

Study (Author, Year)	Study Design	Population (Size, Characteristics)	SNP(s) / Focus	Primary Outcome/Key Findings
Brown et al., 2000	Case–control (angiography)	180 angiography patients (<58y), CAD vs no CAD	*MTRR* A66G (rs1801394)	GG associated with ↑ premature CAD risk (~1.5×); Hcy not genotype-dependent (Brown, 2000).
Gaughan et al., 2001	Cross-sectional (genetic assoc.)	Northern Ireland population sample (N not shown)	*MTRR* A66G	G allele associated with ↑ plasma homocysteine (Gaughan, 2001).
García-Minguillán et al., 2014	Cross-sectional (gene–nutrient)	771 adults (Spain), 18–75y	*MTHFR* C677T; *MTRR* A66G + folate/B2/B12	Low folate/B-vitamin status amplified genotype–Hcy effects; adequate status attenuated differences (García-Minguillán, 2014).
Zeng et al., 2011	Case–control	599 CHD cases vs 672 controls (China)	*MTRR* A66G; *MTRR* C524T	Risk alleles associated with ↑ CHD susceptibility (Zeng, 2011).
Cai et al., 2014	Meta-analysis	9 studies (CHD; multi-ethnic)	*MTRR* A66G; *MTR* A2756G	*MTRR* A66G showed modest ↑ CHD risk; *MTR* A2756G not clearly associated (Cai, 2014).
Yu et al., 2014	Meta-analysis	8 studies (CHD; >3,000 cases)	*MTRR* A66G	Pooled data supported ↑ CHD risk with A66G (Yu, 2014).
Shivkar et al., 2022	Case–control	200 young CAD (<45y) vs 200 controls (India)	*MTHFR* C677T/A1298C + folate/B12	677T linked to ↑ Hcy and young CAD; A1298C less consistent (Shivkar, 2022).
Bouzidi et al., 2020	Case–control	172 CAD vs 166 controls	*MTHFR* C677T	TT associated with ↑ Hcy and higher odds of severe CAD (OR ~9.1) (Bouzidi, 2020).
Cheng et al., 2022	Cross-sectional (trial baseline)	2,328 hypertensive adults (China)	*MTHFR* C677T + 5-methyl-THF	Genotype modified folate–Hcy slope; low folate disproportionately increased Hcy in TT (Cheng, 2022).
Zhang et al., 2022	Prospective cohort	212 ischemic stroke pts (China), 2-week f/u	*MTHFR* C677T + Hcy	TT associated with ↑ post-stroke depression; effect partly mediated by Hcy (Zhang, 2022).
van der Put et al., 1998	Case–control	86 NTD cases vs 403 controls (Dutch)	*MTHFR* A1298C (± C677T)	1298C reduces *MTHFR* function; compound heterozygotes (677CT/1298AC) had ↑ NTD risk (OR ~2.0) and ↑ Hcy/↓ folate (van der Put, 1998).
Weisberg et al., 2001	Functional + association	In vitro expression + human association (N not stated in abstract snippet)	*MTHFR* A1298C (± C677T)	1298C lowered activity (~68% of WT); with 677T activity fell further; compound heterozygotes showed ↑ Hcy (Weisberg, 2001).

Guimarães et al., 2011	Case–control	113 sporadic colorectal adenocarcinoma vs 188 controls	Folate/methionine pathway (incl. *MTRR* A66G)	*MTRR* 66GG associated with ↑ sporadic CRC risk (reported OR ~2.2); risk stronger with combined genotypes (Guimarães, 2011).
Pardini et al., 2011	Case–control	666 CRC cases vs 1,377 controls (Brazil)	*MTHFR* C677T/A1298C; *MTR* A2756G; *MTRR* A66G	*MTHFR* 677TT associated with ↓ CRC risk; MTRR 66GG with ↑ CRC risk (Pardini, 2011).
Wu et al., 2015	Meta-analysis	15 studies: 6,020 cases, 8,317 controls	*MTRR* A66G	Pooled data: 66G showed small ↑ CRC susceptibility (significant esp. in Caucasians) (Wu, 2015).
Zhou et al., 2012	Meta-analysis	41 studies (~17,500 cases; ~26,000 controls)	*MTHFR* C677T/A1298C; *MTRR* A66G; *MTR* A2756G	Pattern consistent with divergent one-carbon gene effects on CRC risk; *MTRR* A66G generally ↑ risk, *MTHFR* 677T often ↓ risk (Zhou, 2012).
Chmurzynska et al., 2020	Cross-sectional (pregnancy cohort)	n=103 healthy Polish women, 18–44y; 3rd trimester (PubMed)	*MTHFR* rs1801133, *BHMT* rs7356530, *PEMT* rs12325817; folate & choline intake; plasma tHcy	Folic acid supplementation associated with lower tHcy; PEMT rs12325817 C-allele carriers had ~20–25% lower tHcy when meeting folate/choline needs (gene–nutrient pattern) (Chmurzynska, 2020).
Al-Batayneh et al., 2018	Case–control (PubMed)	n=200 Jordanians: 100 vitamin B12-deficient vs 100 controls (PubMed)	*MTHFR* C677T (rs1801133); *MTHFR* A1298C (rs1801131); B12 deficiency susceptibility	*MTHFR* 677C>T associated with vitamin B12 deficiency risk; A1298C not associated (Al-Batayneh, 2018).
Steluti et al., 2017	Cross-sectional, population study (post-fortificatio n) (PubMed)	n=750 Brazilians ≥12y (after folic-acid flour fortification) (PubMed)	One-carbon polymorphisms incl. *MTHFR* C677T (rs1801133), *MTHFR* A1298C (rs1801131), *MTR* 2756A>G (rs1805087), *MTRR* A66G (rs1801394), *RFC1* rs1051266, *DHFR* 19-bp del; tHcy/folate	*MTHFR* 677CT/TT showed higher tHcy vs CC, even with adequate folate; allele frequencies varied across self-reported race groups (Steluti, 2017).

Gene–Nutrient Interactions

Folate and riboflavin deficiency amplify the impact of *MTHFR* variants, especially C677T, but also A1298C, which can lead to milder yet clinically relevant increases in homocysteine (Liew et al., 2015; Dong et al., 2021; Samii et al., 2023). Supplementing riboflavin lowers homocysteine in *MTHFR* 677TT individuals (García-Minguillán et al., 2014). B12 and folate supplementation are standard approaches for hyperhomocysteinemia. Emerging studies suggest that riboflavin status is equally important in genetically susceptible groups, including those with *MTRR* A66G polymorphisms, where reduced enzyme function may further impair homocysteine

remethylation (McNulty et al., 2006; Han et al., 2012). This opens the door to personalized nutritional interventions that go beyond population-level fortification strategies (Smith et al., 2018).

CONCLUSION

MTHFR and *MTRR* polymorphisms are among the most influential genetic factors in homocysteine metabolism (Klerk et al., 2002; Brown et al., 2000). Their effects are closely modulated by nutritional status, especially levels of folate, vitamin B12, riboflavin, and vitamin B6. Adequate intake of these vitamins can mitigate the effects of reduced enzyme function and help normalize homocysteine concentrations (McNulty et al., 2006; García-Minguillán et al., 2014), reinforcing the potential of nutrition-based strategies in genetically predisposed individuals (Steluti et al., 2017).

The interplay of genetics and nutrition in homocysteine regulation serves as a strong example of how personalized health interventions may be designed. Genetic screening may be beneficial in specific contexts, particularly for individuals with a family history of vascular, cognitive, or developmental disorders (Smith et al., 2018).

Public health efforts like folic acid fortification have been successful in reducing homocysteine levels and related birth defects (Zhu et al., 2003; Bouzidi et al., 2020). However, interindividual variability remains significant, highlighting the need for more refined, genotype-informed approaches (Bouzidi et al., 2020; McNulty et al., 2006). As research into nutrigenetics advances, clinical practice may begin to incorporate personalized B-vitamin recommendations as part of routine preventative care, particularly in populations at higher genetic risk (Han et al., 2012). Emerging evidence also suggests that these polymorphisms may contribute to neuropsychiatric and cognitive outcomes (Zhang et al., 2022).

Moving forward, interdisciplinary research that combines molecular genetics, nutritional science, and clinical trials will be essential to fully realize the potential of personalized strategies in homocysteine management (Smith et al., 2018). In conclusion, while homocysteine represents a complex biomarker influenced by both genetic and environmental factors, it is also a modifiable one (Klerk et al., 2002). Applying the principles of nutritional genomics can help optimize metabolic health, reduce disease burden, and pave the way for a more personalized approach to preventive medicine.

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