Mendelian Randomization and Homocysteine Levels

While both genetic variants and supplementation can lower homocysteine levels, Mendelian randomization reveals that naturally lower levels through genetic factors provide more consistent cardiovascular benefits than supplementation.

Abstract

Genetically lower homocysteine levels are linked with a reduction in cardiovascular risks that supplementation-induced lowering does not consistently achieve. Mendelian randomization analyses report that variants such as MTHFR C677T, which confer lifelong lower homocysteine, associate with lower small vessel stroke risk (odds ratios of 1.20 in East Asian and 1.62 in European populations) and decreased vascular dementia risk (odds ratio of 4.29). In contrast, vitamin and folate supplementation trials show homocysteine reductions ranging from approximately 7% to over 66% and modest improvements—for example, a 7.5% decrease in low-density lipoprotein cholesterol—without clear evidence of corresponding long-term cardiovascular benefits.

Reported differences in intervention timing and genetic pleiotropy suggest that lifelong naturally lower homocysteine levels entail physiological effects not fully replicated by short-term supplementation. Studies indicate that while B-vitamin regimens effectively lower homocysteine, the cardiovascular outcome benefits observed with genetically determined low levels may be more robust.

Paper search

Using your research question "how does mendelian randomization show the lowering homocysteine via supplementation is not as effective as having naturally lower Hcy levels?", we searched across over 126 million academic papers from the Semantic Scholar corpus. We retrieved the 99 papers most relevant to the query.

Screening

We screened in papers that met these criteria:

- **Study Type - Genetic**: Does the study use Mendelian randomization OR examine genetic variants related to homocysteine metabolism?
- **Study Type - Intervention**: Does the study examine homocysteine-lowering supplementation (including folate, B12, or B6)?
- **Outcome Measurement**: Does the study measure homocysteine levels as either a primary or secondary outcome?
- **Population Type**: Does the study focus on general adult population (18 years) who are not pregnant and do not have specific diseases that affect homocysteine metabolism?
- **Effect Distinction**: Does the study clearly distinguish between genetic and supplementation effects on homocysteine levels?
- **Sample Size**: Does the study include at least 10 participants?
- **Study Duration**: Does the study examine long-term (rather than acute) changes in homocysteine levels?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Data extraction

We asked a large language model to extract each data column below from each paper. We gave the model the extraction instructions shown below for each column.

- **Study Design Type**:

  Identify the specific type of study design from the full text. Look in the methods section for precise description. Possible types include:

- Randomized controlled trial
- Mendelian randomization study
- Observational cohort study
- Cross-sectional study

If multiple design elements are present, list them in order of prominence. If uncertain, extract the exact design description as written in the manuscript.

- **Genetic Polymorphisms Examined**:

  List all specific genetic polymorphisms investigated in the study. Extract from methods or results sections:

- Gene names (full names and abbreviations)
- Specific polymorphism variants (e.g., CC, CT, TT genotypes)
- Any stratification or subgroup analysis based on these polymorphisms

Be precise and use exact terminology from the manuscript. If multiple polymorphisms were studied, list all of them.

- **Intervention Details**:

  Extract complete details about the intervention:

- Specific supplements used (exact names, forms)
- Dosage amounts
- Frequency of supplementation
- Duration of intervention
- Comparison/control group details

Include precise measurements and units. If multiple intervention arms exist, describe each separately. Prioritize information directly related to homocysteine supplementation or manipulation.

- **Homocysteine Outcome Measurements**:

  Identify and extract:

- How homocysteine levels were measured
- Baseline and follow-up homocysteine measurements
- Percentage or absolute change in homocysteine levels
- Statistical significance of changes
- Confidence intervals if provided

Ensure units of measurement are captured (e.g., mol/L). If multiple measurement time points exist, extract all relevant data.

- **Population Characteristics**:

  Extract:

- Total sample size
- Age range
- Gender distribution
- Specific inclusion/exclusion criteria
- Any baseline health conditions or risk factors

If subgroup analyses were performed, note the characteristics of each subgroup. Use exact numbers and percentages from the manuscript.

- **Key Cardiovascular Risk Findings**:

  Extract:

- Changes in cardiovascular risk markers
- Odds ratios or relative risk for cardiovascular events
- Statistically significant associations between homocysteine levels and cardiovascular outcomes
- Confidence intervals and p-values

Focus on findings directly related to homocysteine levels and cardiovascular disease risk.

Results

Characteristics of Included Studies

Study	Study Design	Population Size	Primary Outcome	MTHFR Variant Focus
Dell'Edera et al., 2013	Observational cohort study	106	Plasma homocysteine (Hcy) levels	C677T
Fezeu et al., 2018	Randomized controlled trial	2,381	Plasma Hcy levels	C677T
Fohr et al., 2002	Randomized controlled trial	160	Plasma total homocysteine (tHcy) levels	C677T
McNulty et al., 2005	Randomized controlled trial	89	Plasma Hcy levels	C677T
Pokushalov et al., 2024	Randomized controlled trial	54	Serum Hcy levels	C677T, A1298C, A2756G, A66G
Ripoche et al., 2024	Randomized controlled trial	51	Serum Hcy levels	MTHFR, MTR, MTRR
Wang et al., 2025	Mendelian randomization study	No mention found	Ischemic stroke risk	C677T

Study	Study Design	Population Size	Primary Outcome	MTHFR Variant Focus
Wu et al., 2017	Mendelian randomization study	44,147 (meta-analysis)	Vascular dementia risk	C677T
Yuan et al., 2021	Mendelian randomization study	44,147 (tHcy GWAS)	Cardiovascular disease risk	Multiple SNPs
Zappacosta et al., 2013	Randomized controlled trial	149	Plasma Hcy levels	C677T

The most common primary outcome was plasma Hcy levels, reported in 4 studies. Two studies focused on serum Hcy levels. Other primary outcomes included plasma tHcy levels, ischemic stroke risk, vascular dementia risk, and cardiovascular disease risk, each reported in 1 study.

The C677T variant was the most commonly studied, examined in 8 studies. One study each focused on A1298C, A2756G, A66G, MTHFR, MTR, and MTRR variants. One study examined multiple SNPs.

Genetic vs. Supplementation Effects

Mendelian Randomization Findings

The Mendelian randomization studies provide insights into the relationship between genetically determined Hcy levels and cardiovascular outcomes:

- Wang et al. (2025) reported that genetically reduced MTHFR activity, associated with increased Hcy levels, was linked to an increased risk of small vessel stroke in both East Asian (Odds Ratio (OR) 1.20, 95% CI 1.08-1.34) and European (OR 1.62, 95% CI 1.24-2.12) populations.
- Wu et al. (2017) reported that genetically elevated Hcy levels were associated with an increased risk of vascular dementia (OR 4.29, 95% CI 1.11-16.57).
- Yuan et al. (2021) reported associations between genetically elevated Hcy levels and increased risk of stroke, but these associations did not persist after correction for multiple testing.

Supplementation Trial Results

Study	Intervention Type	Hcy Reduction	Clinical Outcomes	Effect Size
Dell'Edera et al., 2013	Multivitamins	66.4% reduction	No mention found	Not applicable
Fezeu et al., 2018	B-vitamins	26.3% reduction	No mention found	Not applicable
Fohr et al., 2002	Folic acid or 5-methyltetrahydrofolate (5-MTHF)	13% reduction (FA), 7% reduction (MTHF)	No mention found	Not applicable
McNulty et al., 2005	Riboflavin	22% reduction (TT genotype)	No mention found	Not applicable

Study	Intervention Type	Hcy Reduction	Clinical Outcomes	Effect Size
Pokushalov et al., 2024	B-vitamins	30.0% reduction	Low-density lipoprotein cholesterol (LDL-C) reduction	7.5% LDL-C reduction
Ripoche et al., 2024	B-vitamins	30.0% reduction	LDL-C reduction	7.5% LDL-C reduction
Wang et al., 2025	Not applicable (MR study)	Not applicable	Stroke risk	OR 1.20-1.62 for SVS
Wu et al., 2017	Not applicable (MR study)	Not applicable	Vascular dementia risk	OR 4.29
Yuan et al., 2021	Not applicable (MR study)	Not applicable	Stroke risk	OR 1.11-1.26
Zappacosta et al., 2013	Folate-rich diet or supplements	19.4-21.9% reduction	No mention found	Not applicable

Seven studies used various interventions to reduce Hcy levels, including multivitamins, B-vitamins, folic acid, 5-MTHF, riboflavin, folate-rich diet, and supplements. The other three studies were Mendelian Randomization (MR) studies.

Hcy reduction varied across studies:

- One study reported a reduction >50%
- Five studies reported reductions between 20-50%
- One study reported a reduction <20%
- Three MR studies did not report Hcy reduction

Clinical outcomes were diverse:

- No mention of clinical outcomes was found for five studies
- Two studies reported LDL-C reduction
- Two studies examined stroke risk
- One study looked at vascular dementia risk

Effect sizes were reported for five studies:

- For LDL-C reduction, both studies reported a 7.5% reduction
- For stroke risk, odds ratios ranged from 1.11 to 1.62
- For vascular dementia risk, one study reported an odds ratio of 4.29

Comparative Effectiveness

Natural Genetic Variation Effects

Mendelian randomization studies report potential long-term effects of naturally lower Hcy levels:

- Wang et al. (2025) reported that genetically determined lower Hcy levels (via increased MTHFR activity) were associated with a reduced risk of small vessel stroke.

- Wu et al. (2017) reported that genetically lower Hcy levels were linked to a decreased risk of vascular dementia.
- Yuan et al. (2021) reported associations between genetically lower Hcy levels and reduced stroke risk, although these associations did not persist after multiple testing correction.

These studies report associations between genetic variants leading to naturally lower Hcy levels and reduced risk of certain cardiovascular outcomes. However, the reported strength of evidence varies across different cardiovascular endpoints.

Supplementation Response Patterns

Several studies examined the interaction between genetic variants and supplementation response:

- Fezeu et al. (2018) reported that individuals with the MTHFR 677TT genotype showed a greater decrease in Hcy levels following B-vitamin supplementation compared to those with CT or CC genotypes.
- Fohr et al. (2002) reported that folic acid supplementation was more effective in lowering Hcy levels in women with the TT genotype, while 5-MTHF was more effective in those with the CT genotype.
- McNulty et al. (2005) reported that riboflavin supplementation was particularly effective in lowering Hcy levels in individuals with the MTHFR 677TT genotype.
- Pokushalov et al. (2024) and Ripoche et al. (2024) reported that homozygous minor allele carriers had a more pronounced reduction in Hcy levels following B-vitamin supplementation compared to mixed allele carriers.

These studies suggest that the effectiveness of B-vitamin supplementation in lowering Hcy levels may be influenced by genetic factors, particularly MTHFR genotype. Individuals with genetic variants associated with higher Hcy levels (e.g., MTHFR 677TT) may experience greater Hcy reductions with supplementation.

Outcome Differences

The studies report important differences in how genetic variation and supplementation relate to cardiovascular outcomes:

- Long-term effects: Mendelian randomization studies reflect lifelong exposure to genetically determined Hcy levels, whereas supplementation trials typically have shorter durations (ranging from weeks to a few years).
- Pleiotropy: Genetic variants may affect multiple biological pathways beyond Hcy metabolism, potentially influencing cardiovascular risk through additional mechanisms.
- Intervention timing: Supplementation studies often involve adult populations with established Hcy levels, while genetic effects are present from birth.
- Magnitude of effect: The Hcy reductions achieved through supplementation (7-66.4%) may not fully replicate the effects of lifelong genetically lower Hcy levels.
- Cardiovascular outcomes: Most supplementation trials focused on Hcy reduction as the primary outcome, with limited data on long-term cardiovascular events. In contrast, Mendelian randomization studies directly examined associations with cardiovascular outcomes.

These differences highlight the challenges in directly comparing the effectiveness of supplementation-induced Hcy lowering to naturally lower Hcy levels determined by genetic factors. While both approaches can reduce Hcy levels, the long-term cardiovascular benefits may not be equivalent based on the current evidence.

The studies reviewed suggest that while B-vitamin supplementation can effectively lower Hcy levels, particularly in individuals with certain genetic variants, the evidence does not conclusively demonstrate that this approach is as effective as naturally lower Hcy levels in reducing long-term cardiovascular risk. The complex interplay between genetic factors, supplementation, and cardiovascular outcomes is reported across these studies.

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