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The causal role of homocysteine in multiple diseases: a systematic review of Mendelian randomization studies

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Abstract

Background Homocysteine (Hcy) has been implicated in the development of multiple diseases; however, its causal role remains unclear. Mendelian randomization (MR) studies provide a robust approach to assessing causality by minimizing confounding and reverse causation.

Objective This study aimed to evaluate the causal role of Hcy in various diseases by synthesizing evidence from MR studies.

Methods We performed a comprehensive literature search in PubMed, the Cochrane Library, Embase, and Web of Science for MR studies published up to May 30, 2024. Studies investigating the association between genetic predisposition to Hcy levels and specific diseases were included.

Results Findings from 33 MR studies (covering 31 distinct primary outcomes) suggest that genetically elevated Hcy levels are associated with an increased risk of several health conditions, including: Five cardiovascular diseases: small vessel stroke, small artery occlusion stroke, stroke, subarachnoid hemorrhage, and ischemic stroke. Six musculoskeletal diseases: soft tissue disorders, osteoporosis with pathological fractures, hospital-diagnosed osteoarthritis (OA), overall OA, knee OA, and hip OA. One musculoskeletal biomarker: waist-to-hip ratio (WHR) adjusted for BMI. Two digestive system diseases: gastric cancer and non-alcoholic fatty liver disease. Three digestive biomarkers: alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST). One urogenital system disease: chronic kidney disease. Two mental disorders: schizophrenia and bipolar disorder type I. One metabolic disorder: metabolic syndrome. Conversely, elevated Hcy levels are associated with a reduced risk of: One neurological disorder: multiple sclerosis. Two neurological biomarkers: gray matter volume and total brain volume. Five musculoskeletal biomarkers: heel bone mineral density (BMD), right/left grip strength, walking pace, and appendicular lean mass. One urogenital system biomarker: estimated glomerular filtration rate. Additionally, genetically reduced plasma Hcy levels correlated with higher forearm BMD.

Conclusion These findings provide significant evidence for the role of Hcy in disease causation and may contribute to the development of future preventive measures or therapeutic strategies.

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Keywords Homocysteine, Mendelian randomization, Nervous system diseases, Cardiovascular diseases, Musculoskeletal system diseases

Introduction

Homocysteine (Hcy), a sulfur-containing non-protein amino acid, serves as a metabolic intermediate between methionine and cysteine. While neither methionine nor cysteine is directly involved in protein synthesis, both play a crucial role in the methylation process. Hcy is a key component in methionine metabolism, ensuring stable methionine levels, which in turn support protein synthesis and DNA repair. It can be remethylated to methionine or converted into cysteine with the aid of certain B vitamins [1].

Beyond its metabolic role, Hcy exhibits multiple biological functions, including antioxidant and immune system regulation, all of which are essential for maintaining overall health [2, 3]. Previous observational studies have established strong associations between Hcy and various diseases, such as neurodegenerative disorders [4], cardiovascular disease [5], venous thromboembolism [6], and cancer [7]. However, these studies are inherently limited by confounding factors and reverse causation, making it difficult to establish a causal relationship between Hcy and disease risk. Although Mendelian randomization (MR) is not entirely free from these limitations, it is less prone to such biases compared to conventional observational studies.

MR is a causal inference method based on the principles of genetics. The core idea is to use single nucleotide polymorphisms (SNPs) in the human genome as an instrumental variable to mimic the process of randomly assigning genotypes in Mendelian inheritance experiments, and thus to infer potential causal relationships between the exposure (as genetically proxied) and the outcome. MR studies rely on three major assumptions [8]:

1. **The assumption of correlation**–SNPs must be significantly associated with the exposure of interest.
2. **The assumption of independence**–SNPs should be independent of confounding variables.
3. **The assumption of exclusivity**–SNPs must influence the outcome solely through their effect on the exposure factor.

Traditional observational studies are often susceptible to bias due to confounding factors and reverse causation, potentially leading to misleading conclusions. In contrast, MR leverages genetic variants as instrumental variables to mitigate these biases, thereby enhancing causal inference [9].

To the best of our knowledge, this study is the first comprehensive review and robustness assessment of MR-based research investigating the causal effects of Hcy on multiple diseases. The primary objective of this review is to systematically evaluate and synthesize existing evidence to provide robust support for the causal role of Hcy in disease development.

Methods

This systematic review adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [10]. The review protocol has been registered with PROSPERO (International Prospective Register of Systematic Reviews) and is available online under the identifier CRD42024549647.

Literature search and study selection

A comprehensive literature search was conducted in PubMed, the Cochrane Library, Embase, and Web of Science on May 30, 2024, following a pre-established search strategy. The search incorporated the term "Mendelian randomization" in combination with "homocysteine", along with relevant synonyms and associated keywords. Database-specific filters were applied to include only studies involving human participants and published in English. Additionally, the reference lists of selected studies were manually screened to identify any potentially relevant literature that might have been omitted in the primary search. The detailed search strategies for each database are provided in Supplementary Material 1.

Two independent investigators, both experienced in evidence-based medicine and Mendelian randomization research, conducted the study selection. They utilized EndNote X9.3.3 software to remove duplicates, screen articles, and extract relevant data based on predefined inclusion and exclusion criteria. The extracted data were subsequently cross-verified for accuracy. Any discrepancies or uncertainties were resolved through discussion with a third researcher to reach a consensus.

Eligibility criteria

This review considers studies that examine outcomes suggested to be causally associated with Hcy within an MR framework. The inclusion criteria were as follows:

1. Language and Population: Studies published in English and exclusively involving human participants.

2. Study Design: Studies employing Mendelian randomization (MR) as the primary methodological approach.
3. Exposure and Outcomes: Studies investigating the causal relationship between Hcy levels and various health outcomes.

Studies were excluded if they met any of the following criteria:

1. Study Type: Systematic reviews or meta-analyses.
2. Relevance: Studies irrelevant to the research question or those using inappropriate exposure measures.
3. Methodological Approach: Studies that did not employ Mendelian randomization analysis.
4. Availability: Studies without accessible full texts.

Data extraction

A data extraction protocol, aligned with PRISMA guidelines, was established to ensure standardized and systematic data collection. Data extraction was conducted independently by two investigators with expertise in Mendelian randomization research. Following extraction, both investigators cross-verified the data for consistency. Any discrepancies or uncertainties were resolved through consultation with a third researcher to reach a consensus.

Extracted data from each study included the first author's name, publication year, exposure variable, source of exposure data, exposure sample size, primary ancestry of exposure participants, outcome variable, source of outcome data, primary ancestry of outcome participants, outcome sample size, number of SNPs used, primary MR analysis method, odds ratios (ORs), and associated *P*-values.

For dichotomous outcome variables, if studies reported only beta coefficients, OR values were calculated using Formula 1 in R software (version 4.3.2), and their 95% confidence intervals were calculated using Formulas 2 and 3:

1. Formula 1: $OR = e^{\beta}$
2. Formula 2: $95\%\ \mathrm{CI}_{\mathrm{down}} = e^{\beta - 1.96\times SE}$
3. Formula 3 is as follows: $95\%\ \mathrm{CI}_{\mathrm{up}} = e^{\beta + 1.96\times SE}$

where SE represents the standard error of the beta value, and 1.96 is the critical value of the standard normal distribution at the 95% confidence level.

Quality assessment

To evaluate study quality, data extraction was conducted using a template designed based on the STROBE-MR (Strengthening the Reporting of Observational Studies in Epidemiology with Mendelian Randomization) criteria [11–12]. This template included 20 main items and 30 subitems for assessing MR study reporting quality. After converting quality assessment scores into percentages, the 20 studies included in our analysis were categorized according to their risk of bias:

1. High risk: Scores below 75%.
2. Medium risk: Scores between 75% and 85%.
3. 3Low risk: Scores above 85%.

Findings

Screening of literature and evaluation of study quality

The search strategy identified 202 relevant studies. After excluding 111 duplicates and irrelevant articles, an additional 49 studies were eliminated following the title and abstract review. Full-text assessment led to the exclusion of 9 more studies: 1 was not a systematic review, 2 were irrelevant or had inappropriate exposure, 2 were not Mendelian randomization analyses, 2 did not utilize MR methodology, and 2 had inaccessible full texts. Ultimately, 33 studies [13–45] met the pre-established criteria for inclusion in the quantitative synthesis (as shown in Fig. 1).

Supplementary Material 2 details the quality assessment outcomes of the included studies. While all studies explicitly identified MR as the study design in their titles and abstracts and systematically addressed key methodological components—including research rationale, objectives, key findings, study settings, participant characteristics, data accessibility, and conflict of interest disclosures—several methodological limitations were noted. Reporting Gaps: 13 studies [16, 19, 22, 24–27, 32, 35, 39, 40, 42, 44] did not report assessment methods and diagnostic criteria for exposures, outcomes, and related variables. 23 studies [14, 17, 19, 20, 22–25, 28–30, 32, 34–37, 39–45] lacked detailed descriptions of statistical methods used for instrumental variable selection. 28 studies [13–17, 19, 20, 22–25, 27–30, 32–35, 37–45] did not document procedures for handling missing data. 1 study [13] did not report sensitivity analyses or supplementary analyses. Protocol Registration: None of the included studies provided information on protocol pre-registration. Additionally, four studies [14, 16, 17, 33] did not discuss the generalizability of findings across populations, exposure durations, or exposure levels.

Study description

The distribution of included studies across various outcome categories was as follows: Nervous system diseases: 5 studies [13, 22, 27, 32, 43]. Cardiovascular diseases: 7 studies [14, 16, 20, 23, 25–26, 42]. Both neurological and cardiovascular diseases: 1 study [19]. Musculoskeletal system diseases: 7 studies [24, 30–31, 34, 37, 39, 41]. Urogenital diseases: 4 studies [17, 21, 33, 45]. Digestive system diseases: 3 studies [15, 28, 38]. Mental disorders:

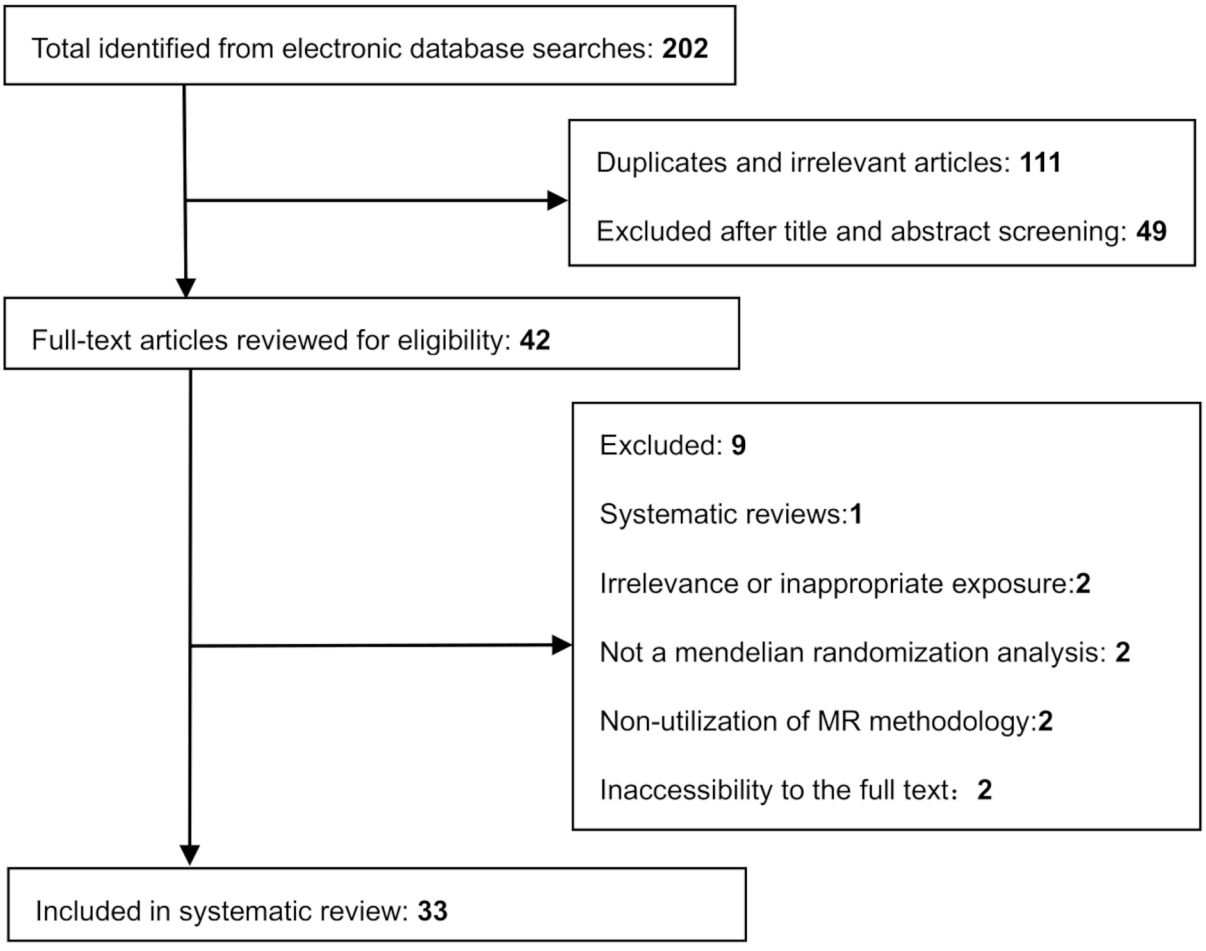


Fig. 1 Flowchart of search results and study retrieval

2 studies [35, 44]. Metabolic diseases: 2 studies [18, 29]. Skin and connective tissue diseases: 1 study [36]. Respiratory tract diseases: 1 study [40]. In total, 93 distinct outcome variables were examined. Table 1 provides an overview of the design characteristics of the included studies.

Among the included MR studies on Hcy, only two [18, 20] did not use genetic variations from a genome-wide association study (GWAS) that encompassed 10 European population cohorts, totaling 44,147 individuals. The average age across these cohorts ranged between 47.5 and 74.4 years, with participants' ages spanning from 17 to 79 years [46]. A single investigation into Hcy employed genetic variants sourced from the Korean Genome and Epidemiology Study (KoGES) Consortium, encompassing a total of 8840 individuals from Korean cohorts [47]. Another study sourced Hcy data from imputed genotype data in the UK Biobank, including 57,644 individuals [20]. Outcome data for all MR studies were sourced from a large GWAS meta-analysis, along with data from the UK Biobank, FinnGen study, MEGASTROKE consortium, and potentially other similar sources. The majority of these outcome databases represent individuals of European and East Asian ancestry. For further details, See Table 1.

Except for one study, all MR studies on Hcy reported results using the inverse-variance weighted (IVW) method as the primary approach [13]. Additionally, most studies provided detailed secondary results from the weighted median (WM) method and MR-Egger regression. A comprehensive summary of the studies included in the main MR analyses and their respective findings is available in Table 1.

Figure 2. Associations with genetically predicted higher levels of homocysteine (using the inverse-variance weighted method) in the systematic review of Mendelian randomization studies. CI, confidence interval; OR, odds ratio; SNPs, single nucleotide polymorphisms.

Table 1 Summary of all published Mendelian randomization (MR) estimates for the association between homocysteine (Hcy) and multiple diseases

Author, Year	Exposure Variable	Exposure Data Source	Exposure Sample Size	Primary Ancestry of Exposure	Outcome Variable	Outcome Data Source	Outcome Sample Size	Primary Ancestry of Outcome	Number of SNPs	Main MR Analysis Method	OR (95% CI)	P-Value	Reverse Causality Assessed (Significance)
Roostaei et al, 2018 [13]	Hcy	GWAS meta-analysis	44,147	European	AD	IGAP	17,008 cases; 37,154 controls	European	13	NR	1.01 (0.89, 1.15)	0.84	No (Not assessed)
Larsson et al, 2019 [14]	tHcy	GWAS meta-analysis	44,147	European	SVS	MEGASTROKE consortium	16,952 cases; 404,630 noncases	European	18	IVW	1.34 (1.13, 1.58)	**6.7×10^{-4}**	No (Not assessed)
										WM	1.54 (1.20, 1.97)	**0.001**	
										MR-Egger	1.35 (0.81, 2.27)	0.25	
					LAS					IVW	1.01 (0.84, 1.21)	0.89	
					CES					IVW	0.94 (0.81, 1.07)	0.35	
					AIS					IVW	1.09 (1.02, 1.17)	**0.02**	
					CAD					IVW	1.02 (0.95, 1.09)	0.61	
Wang et al, 2020 [15]	PHL	GWAS meta-analysis	44,147	European	Gastric cancer	Published GWAS	2,631 cases; 4,373 controls	Chinese	15	IVW	1.09 (1.01, 1.18)	**0.034**	No (Not assessed)
										wGRS	1.07 (1.01, 1.12)	**0.011**	
										WM	1.107 (1.016, 1.207)	**0.02**	
										MR-Egger	1.089 (0.914, 1.300)	0.342	
Chen et al, 2021 [16]	Hcy	GWAS meta-analysis	44,147	European	AF	GWAS meta-analysis	60,620 cases; 970,216 controls	European	9	IVW	1.077 (0.993, 1.168)	0.075	No (Not assessed)

Table 1 (continued)

Author, Year	Exposure Variable	Exposure Data Source	Exposure Sample Size	Primary Ancestry of Exposure	Outcome Variable	Outcome Data Source	Outcome Sample Size	Primary Ancestry of Outcome	Number of SNPs	Main MR Analysis Method	OR (95% CI)	P-Value	Reverse Causality Assessed (Significance)
										WM	1.106 (0.998, 1.226)	0.054	
										MR-Egger	1.071 (0.856, 1.340)	0.551	
He et al, 2021 [17]	PHL	GWAS meta-analysis	44,147	European	Overall BRCA	GWAS meta-analysis	133,384 cases; 113,789 controls	European	15	IVW	0.97 (0.90, 1.06)	0.543	No (Not assessed)
										WM	0.988 (0.918, 1.064)	0.757	
										MR-Egger	1.115 (0.891, 1.395)	0.341	
					Overall PrCa		79,148 cases; 61,106 controls			IVW	1.01 (0.93, 1.11)	0.774	
										WM	1.011 (0.916, 1.116)	0.83	
										MR-Egger	0.990 (0.752, 1.302)	0.941	
					RCC in men		3,227 cases; 4,916 controls			IVW	0.99 (0.73, 1.34)	0.929	
										WM	0.756 (0.439, 1.302)	0.582	
										MR-Egger	0.402 (0.129, 1.262)	0.115	
					RCC in women		1,992 cases;3,095 controls			IVW	0.89 (0.61, 1.31)	0.563	
										WM	0.891 (0.591, 1.344)	0.313	

Table 1 (continued)

Author, Year	Exposure Variable	Exposure Data Source	Exposure Sample Size	Primary Ancestry of Exposure	Outcome Variable	Outcome Data Source	Outcome Sample Size	Primary Ancestry of Outcome	Number of SNPs	Main MR Analysis Method	OR (95% CI)	P-Value	Reverse Causality Assessed (Significance)
										MR-Egger	0.681 (0.272, 1.707)	0.412	
Lee et al, 2021 [18]	Hcy	KoGES Consortium	2090 cases; 3812 controls	Korean	MetS	KoGES Consortium	HEXA (676 cases; 3017 controls) and CAVAS (1052 cases; 764 controls)	Korean	27	IVW	2.054 (1.649, 2.560)	**< 0.001**	No (Not assessed)
										WM	2.085 (1.730, 2.517)	**< 0.001**	
										MR-Egger	2.784 (1.478, 2.517)	**0.002**	
									5	IVW	2.061 (1.642, 2.563)	**< 0.001**	
										WM	2.083 (1.723, 2.517)	**< 0.001**	
										MR-Egger	7.950 (1.523, 41.471)	**0.014**	
Liu et al, 2021 [19]	Hcy	GWAS meta-analysis	44,147	European	IS (Non-subtyped)	MEGASTROKE consortium	34,217 cases; 440,328 subjects	European	13	IVW	1.098 (0.980, 1.229)	0.107	No (Not assessed)
					LAS						1.093 (0.878, 1.312)	0.424	
					CES						0.920 (0.785, 1.080)	0.308	
					SAS						1.329 (1.047, 1.612)	**0.048**	
					TIA	UK Biobank	1,364 cases; 461,646 controls				1.000 (0.999, 1.001)	0.858	

Table 1 (continued)

Author, Year	Exposure Variable	Exposure Data Source	Exposure Sample Size	Primary Ancestry of Exposure	Outcome Variable	Outcome Data Source	Outcome Sample Size	Primary Ancestry of Outcome	Number of SNPs	Main MR Analysis Method	OR (95% CI)	P-Value	Reverse Causality Assessed (Significance)
					MS	IMSGC	14,498 cases; 24,091 controls				1.154 (0.888, 1.500)	0.283	
					AD	IGAP	21,982 cases; 41,944 controls				1.081 (0.960, 1.217)	0.198	
					PD	IPDGC	33,674 cases; 449,056 controls				0.985 (0.853, 1.137)	0.837	
					ALS	IALSGC	20,806 cases; 59,804 controls				1.085 (0.948, 1.241)	0.235	
					FTD	IFLDC	515 case; 2,509 controls				1.268 (0.416, 3.863)	0.676	
Miao et al, 2021 [20]	Hcy	UK Biobank	57,644	European	CHD	CARDIoGRAM and CARDIoGRAMplusC4D consortium	184,305	European	9	IVW	1.015 (0.923, 1.106)	0.752	No (Not assessed)
										WM	0.916 (0.789, 1.042)	0.17	
					AMI		171,875			IVW	1.037 (0.932, 1.142)	0.499	
										WM	0.967 (0.826, 1.108)	0.64	
Park et al, 2021 [21]	Hcy	GWAS meta-analysis	44,147	European	eGFR	GWAS meta-analysis	567,460	European	18	IVW	-	**< 0.001**	No (Not assessed)
										MR-Egger	-	**< 0.001**	
Peng et al, 2021 [22]	Hcy	GWAS meta-analysis	44,147	European	MS	IMSGC	47,429 cases; 68,374 controls	European	14	IVW	0.780 (0.640, 0.940)	**0.0106**	No (Not assessed)
										WM	0.85 (0.68, 1.06)	0.141	

Table 1 (continued)

Author, Year	Exposure Variable	Exposure Data Source	Exposure Sample Size	Primary Ancestry of Exposure	Outcome Variable	Outcome Data Source	Outcome Sample Size	Primary Ancestry of Outcome	Number of SNPs	Main MR Analysis Method	OR (95% CI)	P-Value	Reverse Causality Assessed (Significance)
										MR-Egger	0.73 (0.46, 1.16)	0.2096	
Sun et al, 2021 [23]	Hcy	GWAS meta-analysis	44,147	European	AF	GWAS meta-analysis	65 446 cases; 522 744 controls	European	13	IVW	0.972 (0.919, 1.027)	0.308	No (Not assessed)
										WM	0.984 (0.911, 1.064)	0.694	
										MR-Egger	1.021(0.900, 1.158)	0.754	
									8	IVW	1.005(0.913, 1.106)	0.919	
										WM	1.050(0.926, 1.191)	0.444	
										MR-Egger	1.281(0.960, 1.708)	0.143	
Wang et al, 2021 [24]	Hcy increase	GWAS meta-analysis	44,147	European	FA BMD	GWAS meta-analysis	10,805	European	8	IVW	-	0.153	No (Not assessed)
										WM	-	0.368	
										MR-Egger	-	0.478	
					FN BMD	GWAS meta-analysis	49,988		5	IVW	-	0.731	
										WM	-	0.929	
										MR-Egger	-	0.599	
					LS BMD	GWAS meta-analysis	44,731		5	IVW	-	0.989	
										WM	-	0.864	
										MR-Egger	-	0.383	
					eBMD	UK Biobank	426,824		5	IVW	-	0.468	
										WM	-	0.864	
										MR-Egger	-	0.383	
					Bone fracture	UK Biobank	426,795		5	IVW	-	0.562	
										WM	-	0.475	
										MR-Egger	-	0.784	

Table 1 (continued)

Author, Year	Exposure Variable	Exposure Data Source	Exposure Sample Size	Primary Ancestry of Exposure	Outcome Variable	Outcome Data Source	Outcome Sample Size	Primary Ancestry of Outcome	Number of SNPs	Main MR Analysis Method	OR (95% CI)	P-Value	Reverse Causality Assessed (Significance)
	Hcy decrease	GWAS meta-analysis	44,147	European	FA BMD	GWAS meta-analysis	10,805		6	IVW	-	**0.0007**	
										WM	-	**0.041**	
										MR-Egger	-	0.236	
					FN BMD	GWAS meta-analysis	49,988		6	IVW	-	0.582	
										WM	-	0.703	
										MR-Egger	-	0.421	
					LS BMD	GWAS meta-analysis	44,731		6	IVW	-	0.572	
										WM	-	0.912	
										MR-Egger	-	0.169	
					eBMD	UK Biobank	426,824		6	IVW	-	0.328	
										WM	-	0.053	
										MR-Egger	-	0.988	
					Bone fracture	UK Biobank	426,795		6	IVW	-	0.544	
										WM	-	0.909	
										MR-Egger	-	0.882	
Xu et al, 2021 [25]	Hcy	GWAS meta-analysis	44,147	European	CAD	Published GWAS	3,968 cases; 11,696 controls	European	9	IVW	1.14 (0.82, 1.58)	0.43	No (Not assessed)
										WM	1.46 (0.71, 3.00)	0.33	
										MR-Egger	1.70 (0.69, 4.24)	0.25	
										MR-PRESSO	1.14 (0.84, 1.55)	0.43	
Yuan et al, 2021 [26]	tHcy	GWAS meta-analysis	44,147	European	AA	UK Biobank and FinnGen	UK Biobank (2,261 cases; 365,300 controls) and FinnGen (1,919 cases; 167,843 controls)	European	14	IVW	1.11 (0.92, 1.35)	0.286	No (Not assessed)

Table 1 (continued)

Author, Year	Exposure Variable	Exposure Data Source	Exposure Sample Size	Primary Ancestry of Exposure	Outcome Variable	Outcome Data Source	Outcome Sample Size	Primary Ancestry of Outcome	Number of SNPs	Main MR Analysis Method	OR (95% CI)	P-Value	Reverse Causality Assessed (Significance)
					AF	Consortium and FinnGen	Consortium (60,620 cases; 970,216 controls) and FinnGen (17,325 cases; 97,214 controls)	European			0.96 (0.91, 1.01)	0.098	
					AVS	UK Biobank	UK Biobank (3,528 cases; 364,033 controls)	European			1.14 (0.85, 1.5)	0.356	
					CAD	CARDIoGRAMplusC4D + UKBB	122,733 cases; 424,528 controls	Mixed			1.05 (0.96, 1.15)	0.098	
					HF	HERMES consortium and FinnGen	HERMES consortium (47,309 cases; 930,014 controls)and FinnGen (9,576 cases; 159,286 controls)	European			0.96 (0.88, 1.05)	0.372	
					Stroke	MEGASTROKE consortium、UK Biobank and FinnGen	MEGASTROKE consortium (40,585 cases; 406,111 controls)、UK Biobank (12,036 cases; 355,525 controls) and FinnGen (14,171 cases; 133,027controls)	European			1.11 (1.03, 1.20)	**0.008**	
					IH	ISGC and FinnGen	ISGC (3,223 cases; 3,725 controls) and FinnGen (1,504 cases; 366,057 controls)	European			1.09 (0.89, 1.34)	0.411	

Table 1 (continued)

Author, Year	Exposure Variable	Exposure Data Source	Exposure Sample Size	Primary Ancestry of Exposure	Outcome Variable	Outcome Data Source	Outcome Sample Size	Primary Ancestry of Outcome	Number of SNPs	Main MR Analysis Method	OR (95% CI)	P-Value	Reverse Causality Assessed (Significance)
					SH	consortium and FinnGen	consortium (7,495 cases; 71,934 controls) and FinnGen (1,019 cases; 163,508 controls)	European			1.26 (1.05, 1.51)	**0.013**	
					IS	MEGASTROKE consortium、UK Biobank and FinnGen	MEGASTROKE consortium (34,217)、UK Biobank (6,566 cases; 360,995 controls) and FinnGen (8,046 cases; 164,286 controls)	European			1.11 (1.03, 1.21)	**0.011**	
					TIA	UK Biobank and FinnGen	UK Biobank (4,813 cases; 362,748 controls) and FinnGen (6,729 cases; 164,286 controls)	European			1.15 (0.99, 1.16)	0.066	
					VT	UK Biobank and FinnGen	UK Biobank (16,412 cases; 351,149 controls) and FinnGen (6,913 cases; 169,986 controls)	European			1.05 (0.94, 1.16)	0.392	
					PAD	UK Biobank and FinnGen	UK Biobank (4,593 cases; 362,968 controls) and FinnGen (5,323 cases; 167,843 controls)	European			1.06 (0.91, 1.23)	0.486	
Zhao et al, 2021 [27]	tHcy	GWAS meta-analysis	44,147	European	PD risk	GWAS meta-analysis	33,674 cases; 449,056 controls	European	14	IVW	1.010 (0.880, 1.160)	0.868	No (Not assessed)

Table 1 (continued)

Author, Year	Exposure Variable	Exposure Data Source	Exposure Sample Size	Primary Ancestry of Exposure	Outcome Variable	Outcome Data Source	Outcome Sample Size	Primary Ancestry of Outcome	Number of SNPs	Main MR Analysis Method	OR (95% CI)	P-Value	Reverse Causality Assessed (Significance)
										WM	1.03 (0.87, 1.23)	0.715	
										MR-Egger	1.22 (0.90, 1.64)	0.199	
										MR-PRESSO	1.01 (0.92, 1.11)	0.815	
					Age at onset of PD	IPDGC GWAS	17,996 cases			IVW	0.522 (0.183, 1.492)	0.222	
										WM	-0.32 (-1.56, 0.92)	0.715	
										MR-Egger	-0.33 (-2.74, 2.08)	0.788	
										MR-PRESSO	-0.65 (-1.70, 0.40)	0.244	
Chen et al, 2022 [28]	Hcy	GWAS meta-analysis	44,147	European	NAFLD	GWAS meta-analysis	1,578 cases; 307576 controls	European	12	IVW	1.264 (0.924, 1.728)	0.143	No (Not assessed)
										WM	1.231 (0.973, 2.203)	0.068	
										MR-Egger	1.398 (0.807, 3.001)	0.187	
					NASH		99 cases; 309055 controls			IVW	1.891 (0.509, 7.022)	0.341	
										WM	2.321 (0.261, 7.092)	0.714	
										MR-Egger	4.332 (0.07, 21.977)	0.882	
					Cirrhosis		826 cases; 306145 controls			IVW	0.811 (0.498, 1.322)	0.401	
										WM	1.384 (0.361, 1.293)	0.242	

Table 1 (continued)

Author, Year	Exposure Variable	Exposure Data Source	Exposure Sample Size	Primary Ancestry of Exposure	Outcome Variable	Outcome Data Source	Outcome Sample Size	Primary Ancestry of Outcome	Number of SNPs	Main MR Analysis Method	OR (95% CI)	P-Value	Reverse Causality Assessed (Significance)
										MR-Egger	1.605 (0.149, 0.952)	**0.039**	
Cheng et al, 2022 [29]	Hcy	GWAS meta-analysis	44,147	European	T2DM	GWAS meta-analysis	74,124 cases; 824,006 controls	European	14	IVW	1.08 (0.95, 1.21)	0.249	No (Not assessed)
										WM	1.148 (1.023, 1.289)	**0.019**	
										MR-Egger	1.071 (0.791, 1.452)	0.666	
Fu et al, 2022 [30]	Hcy	GWAS meta-analysis	44,147	European	Musculoskeletal system diseases	FinnGen	218,792	European	13	IVW	1.074 (0.994, 1.159)	0.07	No (Not assessed)
										WM	1.057 (0.973, 1.148)	0.187	
										MR-Egger	1.121 (0.940, 1.337)	0.205	
					Soft tissue disorders				13	IVW	1.069 (1.001, 1.141)	**0.045**	
										WM	1.069 (0.982, 1.163)	0.122	
										MR-Egger	1.109 (0.962, 1.277)	0.155	
					Knee OA	UK Biobank	455,221		14	IVW	1.119 (1.032, 1.214)	**0.007**	
										WM	1.078 (0.977, 1.189)	0.134	

Table 1 (continued)

Author, Year	Exposure Variable	Exposure Data Source	Exposure Sample Size	Primary Ancestry of Exposure	Outcome Variable	Outcome Data Source	Outcome Sample Size	Primary Ancestry of Outcome	Number of SNPs	Main MR Analysis Method	OR (95% CI)	P-Value	Reverse Causality Assessed (Significance)
										MR-Egger	1.122 (0.906, 1.390)	0.291	
					Hip OA				14	IVW	1.066 (0.942, 1.206)	0.311	
										WM	1.038 (0.903, 1.193)	0.603	
										MR-Egger	1.128 (0.842, 1.513)	0.419	
					Hospital-diagnosed OA	UK Biobank	327,918		14	IVW	1.178 (1.012, 1.370)	**0.034**	
										WM	1.206 (0.985, 1.476)	0.069	
										MR-Egger	1.312 (0.935, 1.842)	0.117	
					Osteoporosis with pathological fracture	FinnGen	173,619		13	IVW	1.597 (1.036, 2.460)	**0.034**	
										WM	1.673 (0.889, 3.149)	0.11	
										MR-Egger	2.110 (0.824, 5.404)	0.12	
					Body fat percentage	UK Biobank	331,117		14	IVW	-	0.703	
										WM	-	0.715	
										MR-Egger	-	0.504	
					Trunk fat percentage				14	IVW	-	0.721	
										WM	-	0.125	
										MR-Egger	-	0.521	

Table 1 (continued)

Author, Year	Exposure Variable	Exposure Data Source	Exposure Sample Size	Primary Ancestry of Exposure	Outcome Variable	Outcome Data Source	Outcome Sample Size	Primary Ancestry of Outcome	Number of SNPs	Main MR Analysis Method	OR (95% CI)	P-Value	Reverse Causality Assessed (Significance)
					Left arm fat percentage				14	IVW	-	0.46	
										WM	-	0.216	
										MR-Egger	-	0.491	
					Right arm fat percentage				14	IVW	-	0.609	
										WM	-	0.275	
										MR-Egger	-	0.328	
					Left leg fat percentage				14	IVW	-	0.963	
										WM	-	0.624	
										MR-Egger	-	0.432	
					Right leg fat percentage				14	IVW	-	0.871	
										WM	-	0.51	
										MR-Egger	-	0.548	
					Pediatric BMD	Published GWAS	8327		13	IVW	-	0.693	
										WM	-	0.877	
										MR-Egger	-	0.144	
					Lean body mass				13	IVW	-	0.82	
										WM	-	0.185	
										MR-Egger	-	0.204	
					Whole mass	GEFOS	38292		13	IVW	-	0.183	
										WM	-	0.076	
										MR-Egger	-	**0.021**	
					Append mass				13	IVW	-	0.176	
										WM	-	**0.003**	
										MR-Egger	-	**0.008**	
Fu et al, 2022 [31]	Hcy	GWAS meta-analysis	44,147	European	FA BMD	GEFOS Consortium	8,143	European	11	IVW	-	0.545	No (Not assessed)
										WM	-	0.59	
										MR-Egger	-	0.403	
					FN BMD	GEFOS Consortium	32,735		9	IVW	-	0.163	
										WM	-	0.621	

Table 1 (continued)

Author, Year	Exposure Variable	Exposure Data Source	Exposure Sample Size	Primary Ancestry of Exposure	Outcome Variable	Outcome Data Source	Outcome Sample Size	Primary Ancestry of Outcome	Number of SNPs	Main MR Analysis Method	OR (95% CI)	P-Value	Reverse Causality Assessed (Significance)
										MR-Egger	-	0.382	
					LS BMD	GEFOS Consortium	28,498		9	IVW	-	0.297	
										WM	-	0.209	
										MR-Egger	-	0.391	
					Heel BMD	UK Biobank	142,487		11	IVW	-	**9.59E-04**	
										WM	-	**0.013**	
										MR-Egger	-	0.268	
					Total body BMD	GEFOS Consortium	66,628		11	IVW	-	0.211	
										WM	-	0.22	
										MR-Egger	-	0.137	
					Total body BMD of age 0–15	GEFOS Consortium	11,807		11	IVW	-	0.779	
										WM	-	0.418	
										MR-Egger	-	0.142	
					Total body BMD of age 15–30	GEFOS Consortium	4,180		11	IVW	-	0.741	
										WM	-	0.905	
										MR-Egger	-	0.99	
					Total body BMD of age 30–45	GEFOS Consortium	10,062		11	IVW	-	0.707	
										WM	-	0.535	
										MR-Egger	-	0.108	
					Total body BMD of age 45–60	GEFOS Consortium	18,805		11	IVW	-	0.472	
										WM	-	0.526	
										MR-Egger	-	0.512	
					Total body BMD of age over 60	GEFOS Consortium	22,504		11	IVW	-	0.342	
										WM	-	0.276	
										MR-Egger	-	0.383	
Ma et al, 2022 [32]	Hcy	GWAS meta-analysis	44,147	European	IA	Published GWAS	7,495 cases; 71,934 controls	European	9	IVW	1.124 (0.923, 1.368)	0.246	No (Not assessed)

Table 1 (continued)

Author, Year	Exposure Variable	Exposure Data Source	Exposure Sample Size	Primary Ancestry of Exposure	Outcome Variable	Outcome Data Source	Outcome Sample Size	Primary Ancestry of Outcome	Number of SNPs	Main MR Analysis Method	OR (95% CI)	P-Value	Reverse Causality Assessed (Significance)
										WM	1.204 (0.932, 1.555)	0.155	
										MR-Egger	1.236 (0.818, 1.869)	0.348	
					SAH		2,070 cases; 71,934 controls		9	IVW	1.104 (0.878, 1.387)	0.398	
										WM	1.239 (0.927, 1.657)	0.148	
										MR-Egger	1.291 (0.799, 2.085)	0.332	
					UIA		5,140 cases; 71,934 controls		7	IVW	1.126 (0.682, 1.858)	0.644	
										WM	1.091 (0.604, 1.969)	0.774	
										MR-Egger	1.103 (0.311, 3.913)	0.885	
Xiong et al, 2022 [33]	tHcy	GWAS meta-analysis	44,147	European	CKD	CKDGen consortium and PAGE	CKDGen consortium (41,395 cases; 439,303 controls)and PAGE (49,839)	European	14	IVW	1.24 (1.07, 1.44)	**< 0.05**	No (Not assessed)
					eGFR					IVW	-	**< 0.01**	
										WM	-	**< 0.001**	
										MR-Egger	-	**0.049**	
					eGFR (Excluding diabetes patients)					IVW	-	**0.008**	
										WM	-	**0.002**	
										MR-Egger	-	0.076	

Table 1 (continued)

Author, Year	Exposure Variable	Exposure Data Source	Exposure Sample Size	Primary Ancestry of Exposure	Outcome Variable	Outcome Data Source	Outcome Sample Size	Primary Ancestry of Outcome	Number of SNPs	Main MR Analysis Method	OR (95% CI)	P-Value	Reverse Causality Assessed (Significance)
Yu et al, 2022 [34]	Hcy increase	GWAS meta-analysis	44,147	European	Grip strength (right)	UK Biobank	461,089	European	7	IVW	-	**5.53×10^{-4}**	No (Not assessed)
										WM	-	**6.02E–03**	
										MR-Egger	-	0.69	
					Grip strength (left)		461,026		7	IVW	-	**1.45×10^{-5}**	
										WM	-	**6.80E–04**	
										MR-Egger	-	0.579	
					Walking pace		335,349		7	IVW	-	**3.18×10^{-4}**	
										WM	-	**5.66E–03**	
										MR-Egger	-	0.0747	
					ALM		450,243		7	IVW	-	**1.03×10^{-5}**	
										WM	-	**1.01E–03**	
										MR-Egger	-	0.226	
	Hcy decrease	GWAS meta-analysis	44,147	European	Grip strength (right)	UK Biobank	461,089	European	4	IVW	-	0.82	
										WM	-	0.42	
										MR-Egger	-	0.93	
					Grip strength (left)		461,026		3	IVW	-	0.64	
										WM	-	0.81	
										MR-Egger	-	0.43	
					Walking pace		335,349		5	IVW	-	0.61	
										WM	-	0.39	
										MR-Egger	-	0.67	
					ALM		450,243		4	IVW	-	0.06	
										WM	-	0.14	
										MR-Egger	-	0.99	
Yu et al, 2022 [35]	Hcy	GWAS meta-analysis	44,147	European	SCZ	GWAS meta-analysis	67,390 cases; 94,015 controls	European	10	IVW	1.110 (1.028, 1.198)	**2.74×10^{-3}**	No (Not assessed)
										GSMR	1.115(1.041, 1.194)	**1.73E-03**	

Table 1 (continued)

Author, Year	Exposure Variable	Exposure Data Source	Exposure Sample Size	Primary Ancestry of Exposure	Outcome Variable	Outcome Data Source	Outcome Sample Size	Primary Ancestry of Outcome	Number of SNPs	Main MR Analysis Method	OR (95% CI)	P-Value	Reverse Causality Assessed (Significance)
					MDD	Published GWAS	16,823 cases; 25,632 controls		13	IVW	0.948 (0.890, 1.009)	0.115	
										GSMR	0.951 (0.890, 1.017)	0.139	
					BD	GWAS meta-analysis	41,917 cases; 371,549 controls		11	IVW	1.081 (0.998, 1.171)	0.054	
										GSMR	1.088 (1.006, 1.177)	**0.037**	
					BD-I	GWAS meta-analysis	25,060 cases; 449,978 controls		13	IVW	1.133 (1.031, 1.245)	**9.44×10^{-3}**	
										GSMR	1.144 (1.041, 1.257)	**5.23E-03**	
					BD-II	GWAS meta-analysis	6,781 cases; 364,075 controls		13	IVW	0.977 (0.832, 1.147)	0.773	
										GSMR	0.977 (0.832, 1.147)	0.783	
Chen et al, 2023 [36]	Hcy	GWAS meta-analysis	44,147	European	Psoriasis	FinnGen consortium	9,267 cases; 364,071 controls	European	11	IVW	0.995 (0.863, 1.146)	0.941	No (Not assessed)
										WM	0.985 (0.834, 1.164)	0.862	
										MR-Egger	0.959 (0.704, 1.305)	0.795	
Fu et al, 2023 [37]	Hcy	GWAS meta-analysis	44,147	European	Birth weight	Published GWAS	133,903	European	9	IVW	-	0.06	Yes (p = 0.666)
					Childhood BMI		39,620				-	0.627	Yes (p = 0.607)

Table 1 (continued)

Author, Year	Exposure Variable	Exposure Data Source	Exposure Sample Size	Primary Ancestry of Exposure	Outcome Variable	Outcome Data Source	Outcome Sample Size	Primary Ancestry of Outcome	Number of SNPs	Main MR Analysis Method	OR (95% CI)	P-Value	Reverse Causality Assessed (Significance)
					WC adjusted for BMI		231,353				-	0.349	Yes (p = 0.473)
					WHR adjusted for BMI		210,082				-	**0.03**	Yes (p = 0.542)
					BMI		454,884				-	0.368	Yes (p = 0.01)
					BFFM		454,850				-	0.105	Yes (p = 0.57)
					BFM		454,137				-	0.221	Yes (p = 0.659)
					BFP		454,633				-	0.095	Yes (p = 0.592)
Fu et al, 2023 [38]	Hcy	GWAS meta-analysis	44,147	European	NAFLD	Two meta-analyses of GWAS	8,434 cases; 770,180 controls	European	9	IVW	1.21 (1.01, 1.43)	**0.041**	Yes (p = 0.156)
					(Ghodsian et al GWAS)					WM	1.20 (0.97, 1.43)	0.067	
					NAFLD		1,483 cases; 17,781 controls			IVW	1.52 (1.01, 2.13)	**0.048**	
					(Anstee et al GWAS)					WM	1.50 (0.66, 2.33)	0.189	
					ALP	UK Biobank	344,292			IVW	-	**0.039**	No (Not assessed)
										WM	-	0.074	
										MR-PRESSO	-	0.071	
					ALT		344,136			IVW	-	**0.007**	
										WM	-	**0.002**	
										MR-PRESSO	-	**0.031**	
					AST		342,990			IVW	-	**0.018**	
										WM	-	**0.026**	
										MR-PRESSO	-	0.064	
Hong et al, 2023 [39]	Hcy	GWAS meta-analysis	44,147	European	Overall OA	Published GWAS	177,517 cases; 649,173 controls	European and East Asian	11	IVW	1.098 (1.044, 1.155)	**< 0.001**	No (Not assessed)
										WM	1.074 (1.000, 1.154)	**0.05**	
										MR-Egger	1.120 (0.941, 1.333)	0.233	

Table 1 (continued)

Author, Year	Exposure Variable	Exposure Data Source	Exposure Sample Size	Primary Ancestry of Exposure	Outcome Variable	Outcome Data Source	Outcome Sample Size	Primary Ancestry of Outcome	Number of SNPs	Main MR Analysis Method	OR (95% CI)	P-Value	Reverse Causality Assessed (Significance)
					Knee OA	NR	NR			IVW	1.080 (1.000, 1.167)	**0.05**	
										WM	1.088 (0.979, 1.208)	0.118	
										MR-Egger	1.191 (0.917, 1.546)	0.223	
					Hip OA					IVW	1.171 (1.057, 1.297)	**0.002**	
										WM	1.155 (1.001, 1.334)	**0.049**	
										MR-Egger	1.395 (0.952, 2.044)	0.126	
					Spine OA					IVW	1.112 (0.995, 1.243)	0.062	
										WM	1.071 (0.921, 1.244)	0.374	
										MR-Egger	1.210 (0.868, 1.686)	0.289	
					Hand OA					IVW	1.040 (0.907, 1.193)	0.574	
										WM	1.071 (0.884, 1.299)	0.483	
										MR-Egger	0.856 (0.506, 1.450)	0.578	
					Thumb OA					IVW	1.057 (0.874, 1.278)	0.571	

Table 1 (continued)

Author, Year	Exposure Variable	Exposure Data Source	Exposure Sample Size	Primary Ancestry of Exposure	Outcome Variable	Outcome Data Source	Outcome Sample Size	Primary Ancestry of Outcome	Number of SNPs	Main MR Analysis Method	OR (95% CI)	P-Value	Reverse Causality Assessed (Significance)
										WM	1.083 (0.840, 1.395)	0.54	
										MR-Egger	0.836 (0.456, 1.532)	0.576	
Hu et al, 2023 [40]	Hcy	GWAS meta-analysis	44,147	European	COPD hospital admissions	IEU Open GWAS	6,500 cases; 212,292 controls	European	14	IVW	1.06 (0.91, 1.24)	0.42	No (Not assessed)
										WM	1.08 (0.88–1.33)	0.44	
										MR-Egger	1.10 (0.79–1.53)	0.57	
					Asthma/COPD		21,444 cases; 186,723 controls			IVW	0.97 (089, 1.06)	0.55	
										WM	1.01 (0.89–1.15)	0.84	
										MR-Egger	1.09 (0.90–1.33)	0.4	
					COPD-related chronic (opportunistic) infections		234 cases; 186,723 controls			IVW	1.50 (0.57, 3.99)	0.42	
										WM	2.32 (0.57–9.48)	0.24	
										MR-Egger	0.09 (0.05–1.54)	0.12	
					COPD/asthma/ILD-related pneumonia or pneumonia-derived septicemia		27,715 cases; 159,867 controls			IVW	0.93 (0.86, 1.02)	0.13	
										WM	1.02 (0.91–1.14)	0.71	
										MR-Egger	1.07 (0.89–1.28)	0.47	
					COPD-related respiratory insufficiency		1,031 cases; 186,723 controls			IVW	1.00 (0.70, 1.44)	0.99	

Table 1 (continued)

Author, Year	Exposure Variable	Exposure Data Source	Exposure Sample Size	Primary Ancestry of Exposure	Outcome Variable	Outcome Data Source	Outcome Sample Size	Primary Ancestry of Outcome	Number of SNPs	Main MR Analysis Method	OR (95% CI)	P-Value	Reverse Causality Assessed (Significance)
										WM	1.01 (0.62–1.67)	0.96	
										MR-Egger	1.28 (0.59–2.81)	0.54	
Wang et al, 2023 [41]	Hcy	GWAS meta-analysis	44,147	European	FA BMD	GEFOS UK Biobank	8,143	European	8	IVW	0.957 (0.771, 1.188)	0.69	No (Not assessed)
										WM	0.942 (0.779, 1.139)	0.537	
										MR-Egger	1.084 (0.680, 1.729)	0.746	
					Lumbar BMD		28,498		7	IVW	0.856 (0.720, 1.016)	0.077	
										WM	0.844 (0.711, 1.001)	0.051	
										MR-Egger	0.635 (0.317, 1.274)	0.256	
					Heel BMD		142,487		8	IVW	0.960 (0.927, 0.990)	**0.011**	
										WM	0.967 (0.929, 1.005)	0.084	
										MR-Egger	0.981 (0.918, 1.049)	0.607	
Wang et al, 2023 [42]	Hcy	GWAS meta-analysis	44,147	European	Congestive heart failure	Published GWAS	897 cases; 455,451 controls	European	3	IVW	1.753 (0.674, 4.562)	0.25	No (Not assessed)
										WM	1.849 (1.014, 3.372)	**0.045**	

Table 1 (continued)

Author, Year	Exposure Variable	Exposure Data Source	Exposure Sample Size	Primary Ancestry of Exposure	Outcome Variable	Outcome Data Source	Outcome Sample Size	Primary Ancestry of Outcome	Number of SNPs	Main MR Analysis Method	OR (95% CI)	P-Value	Reverse Causality Assessed (Significance)
										MR-Egger	5.472(1.797, 16.665)	0.205	
					Cardiomyopathy	FinnGen study	3100 cases; 156,711 controls		12	IVW	0.805 (0.583, 1.112)	0.189	
										WM	0.829(0.596, 1.154)	0.267	
										MR-Egger	1.126(0.576, 2.199)	0.736	
					Non-ischemic cardiomyopathy	FinnGen study	11,400 cases; 1.751.752 controls		12	IVW	1.064 (0.927, 1.222)	0.379	
										WM	1.004 (0.845, 1.194)	0.961	
										MR-Egger	1.006(0.744, 1.361)	0.97	
Gao et al, 2024 [43]	Hcy	GWAS meta-analysis	44,147	European	GMV	UK Biobank imaging database	7,916	European and White British	9	IVW	0.976 (0.871, 1.094)	0.068	No (Not assessed)
										WM	1.068 (0.938, 1.214)	0.324	
										MR-Egger	1.103 (0.895, 1.360)	0.388	
									8	IVW	0.858 (0.738, 0.999)	**0.048**	
										WM	0.836 (0.684, 1.021)	0.076	
										MR-Egger	0.725 (0.446, 1.178)	0.242	
					BV				9	IVW	0.958 (0.808, 1.135)	0.621	

Table 1 (continued)

Author, Year	Exposure Variable	Exposure Data Source	Exposure Sample Size	Primary Ancestry of Exposure	Outcome Variable	Outcome Data Source	Outcome Sample Size	Primary Ancestry of Outcome	Number of SNPs	Main MR Analysis Method	OR (95% CI)	P-Value	Reverse Causality Assessed (Significance)
										WM	1.078 (0.928, 1.252)	0.323	
										MR-Egger	1.113 (0.805, 1.540)	0.537	
									8	IVW	0.808 (0.652, 1.000)	**0.049**	
										WM	0.845 (0.651, 1.096)	0.202	
										MR-Egger	0.607 (0.301, 1.222)	0.211	
Jin et al, 2024 [44]	Hcy	GWAS meta-analysis	44,147	European	ASD	iPSYCH-PGC	18,382 cases; 27,969 controls	European	13	IVW	1.03 (0.92, 1.15)	0.63	No (Not assessed)
										WM	1.02 (0.88, 1.18)	0.84	
										MR-Egger	1.04 (0.82, 1.33)	0.74	
Lin et al, 2024 [45]	Hcy	GWAS meta-analysis	44,147	European	PCOS	FinnGen GWAS	994; 165,817 controls	European	14	IVW	1.163 (0.705, 1.919)	0.556	No (Not assessed)

Table 1 (continued)

Author, Year	Exposure Variable	Exposure Data Source	Exposure Sample Size	Primary Ancestry of Exposure	Outcome Variable	Outcome Data Source	Outcome Sample Size	Primary Ancestry of Outcome	Number of SNPs	Main MR Analysis Method	OR (95% CI)	P-Value	Reverse Causality Assessed (Significance)
						Tyrmi et al GWAS	3,609; 229,788 controls				0.988 (0.814, 1.200)	0.906	
						Day et al	4,138; 20,129 controls				1.903 (0.817, 1.464)	0.548	

Abbreviations: OR, odds ratio; CI, confidential interval; NR, not reported; IVW, inverse variance weighted; WM, weighted median; wGRS, weighted genetic risk score; GSMR, Generalized Summary-data based Mendelian Randomization; Hcy, homocysteine; CAD, coronary artery disease; MI, myocardial infarction; AD, Alzheimer's disease; IGAP, International Genomics of Alzheimer's Project; tHcy, total homocysteine; SVS, small vessel stroke; LAS, large artery atherosclerosis stroke; CES, cardioembolism stroke; SAS, small artery occlusion stroke; AIS, all ischemic stroke; PHL, plasma homocysteine level; AF, atrial fibrillation; BRCA, breast cancer; PrCa, prostate cancer; RCC, renal cell carcinoma; MetS, metabolic syndrome; IS, ischemic stroke; IH, Intracerebral hemorrhage; SH, Subarachnoid hemorrhage; AA, Aortic aneurysm; AVS, Aortic valve stenosis; TIA, transient ischemic attack; VT, Venous thromboembolism; PVD, Peripheral vessel disease; ISGC, International Stroke Genetic Consortium; MS, multiple sclerosis; PD, Parkinson's disease; ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; IMSGC, International Multiple Sclerosis Genetics Consortium; IPDGC, International Parkinson's Disease Genomics Consortium; IALSGC, International Amyotrophic Lateral Sclerosis Genomics Consortium; IFLDC, International Frontotemporal Lobar Degeneration Collaboration; CHD, coronary heart disease; AMI, acute myocardial infarction; CARDIoGRAM, Coronary ARtery Disease Genome wide Replication and Meta-analysis; C4D, Coronary Artery Disease; BMD, bone mineral density; FA: forearm; FN, femoral neck; LS, lumbar spine; eBMD, estimated heel BMD; GEFO, Genetic Factors for Osteoporosis Consortium; CAD, coronary artery disease; IA, intracranial aneurysm; SAH, subarachnoid hemorrhage; UIA, unruptured intracranial aneurysm; eGFR, estimated glomerular filtration rate; PAGE, Population Architecture using Genomics and Epidemiology; CKD, chronic kidney disease; ALM, appendicular lean mass; SCZ, schizophrenia; BD, bipolar disorder; MDD, major depressive disorder; NAFLD, nonalcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus; BMI, body mass index; WHR, waist-to-hip ratio; WC, waist circumference; BFFM, body fat-free mass; BFP, body fat percentage; BFM, body fat mass; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; OA, osteoarthritis; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; OP, osteoporosis; BV, brain volume; GMV, gray matter volume; ASD, autism spectrum disorder; UKB, UK biobank; PCOS, Polycystic ovary syndrome

Nervous system diseases

Genetically predicted total homocysteine (tHcy) levels demonstrated an inverse association with multiple sclerosis (MS) (OR = 0.780, 95% CI = 0.640–0.940) (Table 1; Fig. 2). One study found no causal relationship between plasma Hcy levels and brain atrophy, despite the use of nine genetic variants associated with Hcy levels. However, after excluding one SNP (rs1801133), the remaining eight SNPs suggested a potential causal relationship between plasma Hcy levels and both gray matter volume (GMV) and brain volume (BV) [43]. No heterogeneity was detected among the studies, and no significant associations were identified between genetically predicted Hcy levels and other neurological disorders.

Cardiovascular diseases

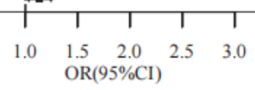
Elevated genetically predicted circulating tHcy levels were associated with an increased risk of several cardiovascular diseases, including: Small vessel stroke (SVS) (OR = 1.340, 95% CI = 1.130–1.580). Small artery occlusion stroke (SAS) (OR = 1.329, 95% CI = 1.047–1.612). Stroke (OR = 1.110, 95% CI = 1.030–1.200). Subarachnoid hemorrhage (SH) (OR = 1.260, 95% CI = 1.050–1.510). Ischemic stroke (IS) (OR = 1.110, 95% CI = 1.030–1.210) (Table 1; Fig. 2). Moderate heterogeneity was observed in analyses of stroke ($I^2 > 50\%$) and ischemic stroke (IS) ($I^2 > 50\%$), likely due to variations in data sources [26]. Specifically: The MEGASTROKE consortium includes multi-ethnic populations. The UK Biobank focuses on middle-aged and older individuals in the UK. The FinnGen study is derived from a genetically distinct Finnish population. These differences in ancestry, demographic characteristics, and methodological heterogeneity (e.g., phenotyping criteria, genotyping platforms) may collectively contribute to the observed inconsistencies between studies. Additionally, MR-Egger analysis for IS within the FinnGen dataset suggested potential pleiotropy [26]. No significant associations were detected between Hcy levels and 13 other cardiovascular conditions, including atrial fibrillation (AF).

Musculoskeletal system diseases

Individuals with genetically predicted higher Hcy levels showed an increased risk for all 13 musculoskeletal conditions and related markers examined (Table 1; Fig. 2). Positive associations were found between Hcy levels and osteoporosis with pathological fractures, forearm bone mineral density (FA BMD), body composition reflected by the waist-to-hip ratio (WHR) adjusted for BMI, soft tissue disorders, and knee osteoarthritis (OA). Conversely, Hcy levels were negatively correlated with heel BMD, grip strength in both dominant and non-dominant hands, and walking pace (Table 1; Fig. 2). There was slight heterogeneity in IVs related to grip strength

A. Disease outcomes associated with genetically predicted plasma homocysteine levels

First author	SNPs	Outcome	Cases	OR(95%CI)	P-Value
Liu W	13	SAS	34217	1.329 (1.047, 1.612)	0.048
Larsson SC	18	SVS	16952	1.340 (1.130, 1.580)	<0.001
Larsson SC	18	AIS	16952	1.090 (1.020, 1.170)	0.02
Yuan S	14	IS	48829	1.110 (1.030, 1.210)	0.011
Yuan S	14	Stroke	66792	1.110 (1.030, 1.200)	0.008
Yuan S	14	SH	8514	1.260 (1.050, 1.510)	0.013
Fu L	13	Soft tissue disorders		1.069 (1.001, 1.141)	0.045
Fu L	14	Hospital-diagnosed OA		1.178 (1.012, 1.370)	0.034
Fu L	13	Osteoporosis with pathological fracture		1.597 (1.036, 2.460)	0.034
Fu L	14	Knee OA		1.119 (1.032, 1.214)	0.007
Hong H	11	Knee OA		1.080 (1.000, 1.167)	0.05
Hong H	11	Overall OA	177517	1.098 (1.044, 1.155)	<0.001
Hong H	11	Hip OA		1.171 (1.057, 1.297)	0.002
Wang T	15	Gastric cancer	2631	1.090 (1.010, 1.180)	0.034
Fu L	9	NAFLD(Ghodsian GWAS)	8434	1.210 (1.010, 1.430)	0.041
Fu L	9	NAFLD(Anstee GWAS)	1483	1.520 (1.010, 2.130)	0.048
Xiong Y	14	CKD	41395	1.240 (1.070, 1.440)	<0.05
Lee HS	27	MetS	1728	2.054 (1.649, 2.560)	<0.001
Yu J	10	SCZ	67390	1.110 (1.028, 1.198)	0.00274
Yu J	13	BD-I	25060	1.133 (1.031, 1.245)	0.00944



B. Biomakers associated with genetically predicted plasma homocysteine levels

First author	SNPs	Outcome	Participants	Change(95%CI)	P–Value
Gao W	8	GMV	7916	0.858 (0.738, 0.999)	0.048
Gao W	8	BV	7916	0.808 (0.652, 1.000)	0.049
Wang P	6	FA BMD	10805	0.348 (0.146, 0.550)	0.001
Fu L	11	Heel BMD	142487	−0.046 (−0.073, −0.019)	<0.001
Yu H	7	Grip strength (right)	461089	−0.036 (−0.056, −0.016)	<0.001
Yu H	7	Grip strength (left)	461026	−0.045 (−0.065, −0.025)	<0.001
Yu H	7	Walking pace	335349	−0.038 (−0.060, −0.016)	<0.001
Yu H	7	ALM	450243	−0.058 (−0.083, −0.033)	<0.001
Fu L	9	WHR adjusted for BMI	210082	0.309 (0.029, 0.589)	0.030
Park S	18	eGFR	567460	−0.950 (−1.210, −0.690)	<0.001
Xiong Y	14	eGFR	530537	−0.027 (−0.048, −0.007)	<0.01
Fu L	9	ALP	344292	0.690 (0.040, 1.340)	0.039
Fu L	9	ALT	344136	0.560 (0.150, 0.970)	0.007
Fu L	9	AST	342990	0.570 (0.100, 1.040)	0.018

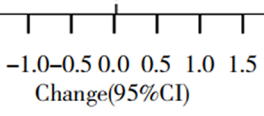


Fig. 2 Associations with genetically predicted higher levels of homocysteine (using the inverse-variance weighted method) in the systematic review of Mendelian randomization studies. CI, confidence interval; OR, odds ratio; SNPs, single nucleotide polymorphisms

(right) (Q_pval = 0.05) and walking pace (Q_pval = 0.02). Additionally, BMI appeared to significantly influence Hcy levels ($p = 0.01$), whereas Hcy had no significant effect on BMI (Table 1).

Urogenital diseases

Elevated Hcy levels were associated with a reduction in the estimated glomerular filtration rate (eGFR), contributing to the progression of chronic kidney disease (CKD)

and subsequent renal function deterioration (Table 1; Fig. 2). Evidence testing revealed heterogeneity in CKD for the data from the CKDGen study (Q_pval < 0.05) [33]. However, the current findings do not support a causal relationship between Hcy levels and the risk of: Breast cancer (BRCA), Prostate cancer (PrCa), Renal cell carcinoma (RCC), and Polycystic ovary syndrome (PCOS). (Table 1).

Digestive system diseases

High plasma homocysteine level (PHL) may play a causal role in the etiology of gastric cancer (OR = 1.090, 95% CI = 1.010–1.180) (Table 1; Fig. 2). Furthermore, increased Hcy concentrations may increase the levels of relevant liver enzymes and may contribute to the risk of nonalcoholic fatty liver disease (NAFLD) (Table 1; Fig. 2). No heterogeneity was observed in any of the aforementioned studies.

Mental disorders

Elevated plasma Hcy levels were associated with a higher risk of: Schizophrenia (SCZ) (OR = 1.110, 95% CI = 1.028–1.198). Bipolar disorder-I (BD-I) (OR = 1.133, 95% CI = 1.031–1.245). However, no significant association was identified between Hcy levels and the risk of: Major depressive disorder (MDD), Bipolar disorder (BD), Bipolar disorder-II (BD-II), Autism spectrum disorder (ASD). (Table 1; Fig. 2).

Metabolic diseases

A significant correlation was observed between Hcy levels and an increased risk of developing metabolic syndrome (MetS) (OR = 2.054, 95% CI = 1.649–2.560), while no such association was found in the context of type 2 diabetes mellitus (T2DM) (Table 1; Fig. 2). Low heterogeneity was observed among studies investigating MetS [18].

Respiratory and dermal system diseases

No causal relationship was detected between genetically determined circulating Hcy levels and the risk of Psoriasis, Chronic obstructive pulmonary disease (COPD) (Table 1).

Discussion

This study examined the association between Hcy levels and 31 different outcome variables in MR studies, providing evidence for potential causality. Elevated Hcy levels were associated with an increased risk of several neurological, cardiovascular, musculoskeletal, urogenital, and digestive disorders, including SVS, SAS, stroke, SH, soft tissue disorders, OA, osteoporosis with pathological fractures, gastric cancer, CKD, SCZ, BD-I, and MetS. Conversely, higher Hcy levels were associated with a reduced risk of MS.

Hyperhomocysteinemia may elevate the risk of IS through multiple mechanisms. Excess Hcy can induce neuronal damage and blood-brain barrier dysfunction by triggering oxidative stress, protein homocysteinylation, and calcium dysregulation [48]. Additionally, Hcy-induced DNA hypomethylation can exacerbate apoptosis, neuronal cell death, and vascular dysfunction, increasing susceptibility to IS. Three studies [14, 26, 49] support the causal role of hereditary elevated Hcy levels in IS, and another study [50] suggests that hyperhomocysteinemia increases the risk of stroke recurrence in affected patients.

2 studies [30, 39] consistently indicated that genetically elevated Hcy levels increase the risk of knee OA, despite discrepancies in statistical significance, likely due to sample size variations and population heterogeneity. Observational studies in Chinese populations [51] further corroborate this finding, demonstrating that patients with severe OA exhibit significantly higher serum Hcy levels than those with mild OA. Mechanistically, Hcy suppresses the SIRT1/AMPK/PGC-1α signaling pathway in chondrocytes, leading to mitochondrial dysfunction, oxidative stress, and apoptosis. Further mechanistic studies indicate that Hcy-mediated inhibition of the SIRT1/AMPK/PGC-1α/PPAR-γ axis upregulates NF-κB, COX-2, IL-8, and MMP-13, contributing to chondrocyte homeostasis disruption [52]. Similarly, studies by Fu [31] and Wang [41] suggest that Hcy may be a significant risk factor for heel fractures, potentially impairing bone quality by disrupting collagen cross-linking and destabilizing the collagen network [53, 54]. However, further research is needed to confirm Hcy's role in knee OA, heel bone mineral density (BMD), and heel fractures.

Although some studies report that Hcy negatively affects hip OA [39], another study found no significant evidence of this relationship [30]. Hcy-induced chondrocyte dysfunction, oxidative stress, and inflammation are hypothesized to contribute to hip OA progression [52]. However, ancestral differences in genetic studies—where Published GWAS included both European and East Asian populations, while UK Biobank included only European individuals—may explain inconsistencies. Additionally, differences in selected genetic variants (SNPs) as instrumental variables may also influence study outcomes. Further research is required to determine whether Hcy is a significant risk factor for hip OA, particularly in East Asian populations.

1 study [24] found that genetically reduced plasma Hcy levels correlated with higher FA-BMD, while increased Hcy levels were not significantly associated with FA-BMD. However, limitations such as a small number of instrumental variables and insufficient statistical power

may have affected these results. Additionally, standardization of effect alleles prior to MR analysis is necessary to ensure accurate causal inferences.

This review identified divergent findings regarding the association between Hcy levels and NAFLD. Chen' s study [28] found insufficient evidence to establish a causal link, whereas Fu' s study [38] reported a positive genetic correlation between Hcy levels, NAFLD, and elevated liver enzymes. Discrepancies may stem from differences in genetic databases, which may reflect variations in genetic background, lifestyle, and dietary habits. Despite these inconsistencies, current evidence suggests a significant correlation between elevated Hcy levels and the incidence of NAFLD. This association may be explained by Hcy-induced oxidative stress, which may trigger iNOS activation and suppress eNOS expression in microvascular endothelial cells (MVECs) [55], leading to mitochondrial dysfunction, lipid peroxidation, hepatic inflammation, and fibrosis [56, 57]. Future research should account for population differences to better elucidate Hcy's role in NAFLD development.

Study limitations

This study has several limitations: Quality Variability: Among the included MR studies, 23 had a low risk of bias, 9 had a moderate risk, and 1 had a high risk, potentially affecting result reliability. Reverse Causality: Only two studies performed bidirectional MR analysis, limiting our ability to rule out reverse causation. Study Selection Bias: The search strategy may have excluded studies that employed MR as a secondary analysis, potentially overlooking relevant findings. Publication Bias: Restricting analysis to full-text, peer-reviewed publications may introduce bias by excluding conference papers, abstracts, and grey literature. Language Restriction: Only English-language studies were included, potentially limiting geographical representation. Predominance of Western Populations: Most studies focused on Western cohorts, limiting generalizability to other populations. Differences in environment, lifestyle, and healthcare systems may influence the applicability of findings to non-Western populations.

Conclusion

In summary, this study provides genetic evidence indicating that elevated homocysteine (Hcy) levels increase the risk of multiple conditions, including multiple sclerosis (MS), small artery occlusion stroke (SAS), subarachnoid hemorrhage (SH), hospital-diagnosed osteoarthritis (OA), soft tissue disorders, osteoporosis with pathological fractures, and gastric cancer. These findings offer substantial support for the role of Hcy in disease causation, with potential implications for the development of preventive measures and therapeutic strategies.

However, heterogeneity in genetic instruments, methodological quality variations, and conflicting results between studies create uncertainty regarding the causal relationship between Hcy levels and stroke, small vessel stroke (SVS), ischemic stroke (IS), chronic kidney disease (CKD), OA (overall, knee, and hip), nonalcoholic fatty liver disease (NAFLD), schizophrenia (SCZ), and bipolar disorder-I (BD-I). To confirm these findings, well-designed, long-term, large-scale randomized controlled trials (RCTs) are needed, particularly in non-European populations, to ensure the generalizability of results across diverse ethnic and demographic backgrounds.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12986-025-00933-0.

Supplementary Material 1

Supplementary Material 2

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Not applicable.

Author contributions
Xiuyuan Zhu and Ning Liu designed the study; Xiuyuan Zhu and Jiangnan Wei developed the analytical strategy; Xiuyuan Zhu, Jiangnan Wei, and Jingling Li analyzed and interpreted the data; Shunli Zuo and Jiaxian Wang conducted the research quality assessment; Ning Liu supervised the implementation of the study; Xiuyuan Zhu and Jiangnan Wei drafted the manuscript. All authors have read and approved the final version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Ganguly P, Alam SF. Role of homocysteine in the development of cardiovascular disease. Nutr J. 2015;14:6. https://doi.org/10.1186/1475-2891-14-6.
2. Liu HH, Shih TS, Huang HR, Huang SC, Lee LH, Huang YC. Plasma homocysteine is associated with increased oxidative stress and antioxidant enzyme activity in welders. ScientificWorldJournal. 2013;2013:370487. https://doi.org/10.1155/2013/370487.
3. Veeranki S, Gandhapudi SK, Tyagi SC. Interactions of hyperhomocysteinemia and T cell immunity in causation of hypertension. Can J Physiol Pharmacol. 2017;95(3):239–46. https://doi.org/10.1139/cjpp-2015-0568.
4. Zhou L. Homocysteine and Parkinson's disease. CNS Neurosci Ther. 2024;30(2):e14420. https://doi.org/10.1111/cns.14420.
5. Gospodarczyk A, Marczewski K, Gospodarczyk N, Widuch M, Tkocz M, Zalejska-Fiolka J. Homocysteine and cardiovascular disease - a current review. Wiad Lek. 2022;75(11 pt 2):2862–6. https://doi.org/10.36740/WLek202211224.
6. Aday AW, Duran EK, Van Denburgh M, Kim E, Christen WG, Manson JE, Ridker PM, Pradhan AD. Homocysteine is associated with future venous thromboembolism in 2 prospective cohorts of women. Arterioscler Thromb Vasc Biol. 2021;41(7):2215–24. https://doi.org/10.1161/ATVBAHA.121.316397.
7. Hasan T, Arora R, Bansal AK, Bhattacharya R, Sharma GS, Singh LR. Disturbed homocysteine metabolism is associated with cancer. Exp Mol Med. 2019;51(2):1–13. https://doi.org/10.1038/s12276-019-0216-4.
8. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. BMJ. 2018;362:k601. https://doi.org/10.1136/bmj.k601.
9. Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. Hum Mol Genet. 2014;23(R1):R89–98. https://doi.org/10.1093/hmg/ddu328.
10. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372(71):1–9.
11. Skrivankova VW, Richmond RC, Woolf BAR, Davies NM, Swanson SA, VanderWeele TJ, Timpson NJ, Higgins JPT, Dimou N, Langenberg C, Loder EW, Golub RM, Egger M, Davey Smith G, Richards JB. Strengthening the reporting of observational studies in epidemiology using Mendelian randomisation (STROBE-MR): explanation and elaboration. BMJ. 2021;375:n2233. https://doi.org/10.1136/bmj.n2233.
12. Skrivankova VW, Richmond RC, Woolf BAR, Yarmolinsky J, Davies NM, Swanson SA, VanderWeele TJ, Higgins JPT, Timpson NJ, Dimou N, Langenberg C, Golub RM, Loder EW, Gallo V, Tybjaerg-Hansen A, Davey Smith G, Egger M, Richards JB. Strengthening the reporting of observational studies in epidemiology using Mendelian randomization: the STROBE-MR statement. JAMA. 2021;326(16):1614–21. https://doi.org/10.1001/jama.2021.18236.
13. Roostaei T, Felsky D, Nazeri A, De Jager PL, Schneider JA, Bennett DA, Voineskos AN. Alzheimer's disease neuroimaging initiative. Genetic influence of plasma homocysteine on Alzheimer's disease. Neurobiol Aging. 2018;62:243.e7-243.e14.
14. Larsson SC, Traylor M, Markus HS. Homocysteine and small vessel stroke: A Mendelian randomization analysis. Ann Neurol. 2019;85(4):495–501. https://doi.org/10.1002/ana.25440.
15. Wang T, Ren C, Ni J, Ding H, Qi Q, Yan C, Deng B, Dai J, Li G, Ding Y, Jin G. Genetic association of plasma homocysteine levels with gastric Cancer risk: A Two-Sample Mendelian randomization study. Cancer Epidemiol Biomarkers Prev. 2020;29(2):487–92. https://doi.org/10.1158/1055-9965.EPI-19-0724.
16. Chen S, Yang F, Xu T, Wang Y, Zhang K, Fu G, Zhang W. Appraising the causal association of plasma homocysteine levels with atrial fibrillation risk: A Two-Sample Mendelian randomization study. Front Genet. 2021;12:619536. https://doi.org/10.3389/fgene.2021.619536.
17. He Q, Yang Z, Sun Y, Qu Z, Jia X, Li J, Lin Y, Luo Y. The impact of homocysteine on the risk of Hormone-Related cancers: A Mendelian randomization study. Front Nutr. 2021;8:645371. https://doi.org/10.3389/fnut.2021.645371.
18. Lee HS, In S, Park T. The homocysteine and metabolic syndrome: A Mendelian randomization study. Nutrients. 2021;13(7):2440. https://doi.org/10.3390/nu13072440.
19. Liu W, Zhang L, Li S, Liu C, Tong Y, Fang H, Zhang R, Song B, Xia Z, Xu Y. A Mendelian randomization study of plasma homocysteine levels and cerebrovascular and neurodegenerative diseases. Front Genet. 2021;12:653032. https://doi.org/10.3389/fgene.2021.653032.
20. Miao L, Deng GX, Yin RX, Nie RJ, Yang S, Wang Y, Li H. No causal effects of plasma homocysteine levels on the risk of coronary heart disease or acute myocardial infarction: A Mendelian randomization study. Eur J Prev Cardiol. 2021;28(2):227–34. https://doi.org/10.1177/2047487319894679.
21. Park S, Lee S, Kim Y, Cho S, Kim K, Kim YC, Han SS, Lee H, Lee JP, Joo KW, Lim CS, Kim YS, Kim DK. Causal effects of homocysteine, folate, and cobalamin on kidney function: A Mendelian randomization study. Nutrients. 2021;13(3):906. https://doi.org/10.3390/nu13030906.
22. Peng H, Wu X, Lin J, Guan W. Genetically predicted Circulating homocysteine, vitamin B12, and folate levels and risk of multiple sclerosis: evidence from a two-sample Mendelian randomization analysis. Mult Scler Relat Disord. 2021;56:103255. https://doi.org/10.1016/j.msard.2021.103255.
23. Sun X, Lu Y, Wang Z, Wang Q, Zheng L. No causal association between plasma homocysteine levels and atrial fibrillation: A Mendelian randomization study. Nutr Metab Cardiovasc Dis. 2021;31(2):587–91. https://doi.org/10.1016/j.numecd.2020.10.012.
24. Wang P, Liu L, Lei SF. Causal effects of homocysteine levels on the changes of bone mineral density and risk for bone fracture: A two-sample Mendelian randomization study. Clin Nutr. 2021;40(4):1588–95. https://doi.org/10.1016/j.clnu.2021.02.045.
25. Xu T, Chen S, Yang F, Wang Y, Zhang K, Fu G, Zhang W. The impact of homocysteine on the risk of coronary artery diseases in individuals with diabetes: a Mendelian randomization study. Acta Diabetol. 2021;58(3):301–7. https://doi.org/10.1007/s00592-020-01608-3.
26. Yuan S, Mason AM, Carter P, Burgess S, Larsson SC, Homocysteine. B vitamins, and cardiovascular disease: a Mendelian randomization study. BMC Med. 2021;19(1):97. https://doi.org/10.1186/s12916-021-01977-8.
27. Zhao Y, Tian D, Guo N, Zhang C, Zhu R, Liu X, Zhang J. Investigating the causality of metabolites involved in one-carbon metabolism with the risk and age at onset of Parkinson's disease: A two-sample Mendelian randomization study. Neurobiol Aging. 2021;108:196–9. https://doi.org/10.1016/j.neurobiolaging.2021.06.023.
28. Chen P, Yang Z, Guo L, Huang Y, Li J, Chen X. Effects of homocysteine on nonalcoholic fatty liver related disease: A Mendelian randomization study. Front Mol Biosci. 2022;9:1083855. https://doi.org/10.3389/fmolb.2022.1083855.
29. Cheng Y, Wang C, Zhang X, Zhao Y, Jin B, Wang C, Lu Z, Zheng F. Circulating homocysteine and folate concentrations and risk of type 2 diabetes: A retrospective observational study in Chinese adults and a Mendelian randomization analysis. Front Cardiovasc Med. 2022;9:978998. https://doi.org/10.3389/fcvm.2022.978998.
30. Fu L, Wang Y, Hu YQ. Causal effects of B vitamins and homocysteine on obesity and musculoskeletal diseases: A Mendelian randomization study. Front Nutr. 2022;9:1048122. https://doi.org/10.3389/fnut.2022.1048122.
31. Fu L, Wang Y, Hu YQ. Inferring causal effects of homocysteine and B-vitamin concentrations on bone mineral density and fractures: Mendelian randomization analyses. Front Endocrinol (Lausanne). 2022;13:1037546. https://doi.org/10.3389/fendo.2022.1037546.
32. Ma C, Zhang W, Mao L, Zhang G, Shen Y, Chang H, Xu X, Li Z, Lu H. Hyperhomocysteinemia and intracranial aneurysm: A Mendelian randomization study. Front Neurol. 2022;13:948989. https://doi.org/10.3389/fneur.2022.948989.
33. Xiong Y, Zhang Y, Zhang F, Wu C, Luo P, Qin F, Yuan J. Genetic evidence supporting the causal role of homocysteine in chronic kidney disease: A Mendelian randomization study. Front Nutr. 2022;9:843534. https://doi.org/10.3389/fnut.2022.843534.
34. Yu H, Luo G, Sun T, Tang Q. Causal effects of homocysteine levels on the components of sarcopenia: A two-sample Mendelian randomization study. Front Genet. 2022;13:1051047. https://doi.org/10.3389/fgene.2022.1051047.
35. Yu J, Xue R, Wang Q, Yu H, Liu X. The effects of plasma homocysteine level on the risk of three major psychiatric disorders: A Mendelian randomization study. Front Psychiatry. 2022;13:841429. https://doi.org/10.3389/fpsyt.2022.841429.
36. Chen C, Liu S, Liu J, Zheng Z, Zheng Y, Lin Z, Liu Y. No causal effect of genetically determined Circulating homocysteine levels on psoriasis in the European population: evidence from a Mendelian randomization study. Front Immunol. 2023;14:1288632. https://doi.org/10.3389/fimmu.2023.1288632.
37. Fu L, Cheng H, Gao L, Zhao X, Mi J. Genetically proxied vitamin B12 and homocysteine in relation to life course adiposity and body composition. Diabetes Metab Syndr. 2023;17(11):102883. https://doi.org/10.1016/j.dsx.2023.102883.
38. Fu L, Wang Y, Hu YQ. Association between homocysteine and nonalcoholic fatty liver disease: Mendelian randomisation study. Eur J Clin Invest. 2023;53(3):e13895. https://doi.org/10.1111/eci.13895.

39. Hong H, Chen L, Zhong Y, Yang Z, Li W, Song C, Leng H. Associations of homocysteine, folate, and vitamin B12 with osteoarthritis: A Mendelian randomization study. Nutrients. 2023;15(7):1636. https://doi.org/10.3390/nu15071636.
40. Hu Y, Tan P, Wang J, Zeng J, Li Q, Yan S, Hao W, He L, Song X, Zhang C, Lyu C. Mendelian randomization study to investigate the causal relationship between plasma homocysteine and chronic obstructive pulmonary disease. World J Emerg Med. 2023;14(5):367–71. https://doi.org/10.5847/wjem.j.1920-8642.2023.078.
41. Wang C, Zhang X, Qiu B. Genetically predicted Circulating serum homocysteine levels on osteoporosis: a two-sample Mendelian randomization study. Sci Rep. 2023;13(1):9063. https://doi.org/10.1038/s41598-023-35472-2.
42. Wang X, Chen Z, Tian W, Zhang J, Li Q, Ju J, Xu H, Chen K. Plasma homocysteine levels and risk of congestive heart failure or cardiomyopathy: A Mendelian randomization study. Front Cardiovasc Med. 2023;10:1030257. https://doi.org/10.3389/fcvm.2023.1030257.
43. Gao W, Zhu WW, Yu YH, Wang J. Plasma homocysteine level, estradiol level, and brain atrophy: a Mendelian randomization study. Cereb Cortex. 2024;34(3):bhae112. https://doi.org/10.1093/cercor/bhae112.
44. Jin T, Huang W, Pang Q, He Z, Yuan L, Zhang H, Xing D, Guo S, Zhang T. Inferring the genetic effects of serum homocysteine and vitamin B levels on autism spectral disorder through Mendelian randomization. Eur J Nutr. 2024;63(3):977–86. https://doi.org/10.1007/s00394-024-03329-7.
45. Lin X, Jin Y, Hong S. Causal relationships between homocysteine and the polycystic ovary syndrome: A Mendelian randomization analysis. Int J Endocrinol. 2024;2024:3090797. https://doi.org/10.1155/2024/3090797.
46. van Meurs JB, Pare G, Schwartz SM, et al. Common genetic loci influencing plasma homocysteine concentrations and their effect on risk of coronary artery disease. Am J Clin Nutr. 2013;98(3):668–676. https://doi.org/10.3945/ajcn.112.044545
47. Kim Y, Han BG; KoGES group. Cohort profile: The Korean genome and epidemiology study (KoGES) consortium. Int J Epidemiol. 2017;46(2):e20. https://doi.org/10.1093/ije/dyv316
48. Lehotský J, Tothová B, Kovalská M, et al. Role of homocysteine in the ischemic stroke and development of ischemic tolerance. Front Neurosci. 2016;10:538. https://doi.org/10.3389/fnins.2016.00538
49. Zhang T, Jiang Y, Zhang S, et al. The association between homocysteine and ischemic stroke subtypes in Chinese: A meta-analysis. Med (Baltim). 2020;99(12):e19467. https://doi.org/10.1097/MD.0000000000019467.
50. Liu W, Ma XL, Gu HQ, Li H, Li ZX, Wang YJ. Elevated levels of total homocysteine after ischemic stroke: a potential marker for in-hospital outcomes. Neurol Res. 2023;45(6):497–504. https://doi.org/10.1080/01616412.2022.2159137.
51. Zhang Q, Li H, Zhang Z, Yang F, Chen J. Serum metabolites as potential biomarkers for diagnosis of knee osteoarthritis. Dis Markers. 2015;2015:684794. https://doi.org/10.1155/2015/684794.
52. Ma CH, Chiua YC, Wu CH, et al. Homocysteine causes dysfunction of chondrocytes and oxidative stress through repression of SIRT1/AMPK pathway: A possible link between hyperhomocysteinemia and osteoarthritis. Redox Biol. 2018;15:504–12. https://doi.org/10.1016/j.redox.2018.01.010.
53. Blouin S, Thaler HW, Korninger C, et al. Bone matrix quality and plasma homocysteine levels. Bone. 2009;44(5):959–64. https://doi.org/10.1016/j.bone.2008.12.023.
54. Lubec B, Fang-Kircher S, Lubec T, Blom HJ, Boers GH. Evidence for McKusick's hypothesis of deficient collagen cross-linking in patients with homocystinuria. Biochim Biophys Acta. 1996;1315(3):159–62. https://doi.org/10.1016/0925-4439(95)00119-0.
55. Tyagi N, Sedoris KC, Steed M, Ovechkin AV, Moshal KS, Tyagi SC. Mechanisms of homocysteine-induced oxidative stress. Am J Physiol Heart Circ Physiol. 2005;289(6):H2649–56. https://doi.org/10.1152/ajpheart.00548.2005.
56. Rolo AP, Teodoro JS, Palmeira CM. Role of oxidative stress in the pathogenesis of nonalcoholic steatohepatitis. Free Radic Biol Med. 2012;52(1):59–69. https://doi.org/10.1016/j.freeradbiomed.2011.10.003.
57. Buzzetti E, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). Metabolism. 2016;65(8):1038–48. https://doi.org/10.1016/j.metabol.2015.12.012.

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