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ORIGINAL RESEARCH ARTICLE

Causal associations between neurodegenerative diseases, cardiovascular diseases, cardiovascular risk factors, and lifestyle factors: Evidence from a Mendelian randomization study

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Abstract

Introduction: Increasing evidence links cardiovascular disorders (CVDs) and related risk factors to neurodegenerative disease development; however, causal mechanisms are poorly defined.

Objective: This study aims to investigate the causal relationships between neurodegenerative diseases, CVDs, and cardiovascular risk factors, as well as the associations between modifiable lifestyle factors and CVDs and their associated risk factors.

Methods: Single-nucleotide polymorphisms demonstrating associations with neurodegenerative disorders, lifestyle factors, and CVDs were extracted from publicly available genome-wide association study databases.

Results: The findings revealed that Alzheimer's disease (AD) was negatively associated with pulmonary embolism, heart failure, and type 2 diabetes. In addition, Parkinson's disease (PD) was linked to an increased risk of hypertension and ischemic stroke. Amyotrophic lateral sclerosis (ALS) correlated positively with hypertension and atrial fibrillation; however, it exhibited a negative relationship with peripheral arterial disease. Coffee intake was positively associated with coronary heart disease, peripheral artery disease, and type 2 diabetes. Alcohol intake was linked to elevated risks of coronary heart disease, hypertension, atrial fibrillation, heart failure, myocardial infarction, and type 2 diabetes. In contrast, tea intake demonstrated inverse associations with coronary heart disease and heart failure.

Conclusion: The present study indicates that ALS, PD, coffee intake, and alcohol intake are associated with an elevated risk of CVDs. Conversely, tea intake demonstrated a protective association against the development of CVDs, whereas AD showed inverse associations with certain cardiovascular risk factors.

Keywords: Alzheimer's disease; Parkinson's disease; Amyotrophic lateral sclerosis; Lifestyle factors; Cardiovascular disease; Mendelian randomization

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1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of global mortality and loss of healthy life years, constituting a major contributor to the global disease burden and significantly increasing health-care expenditure and adversely affecting health outcomes.[1,2] According to the World Economic Forum, over 50% of non-communicable disease-related deaths are attributable to CVDs, with projections indicating that these conditions may cause more than 22.2 million deaths by 2030. Furthermore, the American Heart Association estimates that CVD-related health-care costs will reach approximately USD 1.1 trillion by 2035.[2]

Neurodegenerative disorders, characterized by progressive neural cell degeneration, result in declining central nervous system function and give rise to cognitive and behavioral impairments that are linked to affected brain regions.[3] These disorders span a wide spectrum, from congenital leukodystrophies—resulting in childhood white matter injury—to age-related pathologies such as Alzheimer's disease (AD), Parkinson's disease (PD), and age-related macular degeneration.[4] As global populations continue to age, the prevalence of neurodegenerative diseases (e.g., AD and PD) is increasing substantially. These diseases not only compromise patients' quality of life but also impose growing socioeconomic burdens.[5,6] Developing effective therapies necessitates a comprehensive understanding of disease etiologies, pathogenic mechanisms, and their interconnections. However, the relationships between neurodegenerative diseases, CVDs, and associated risk factors remain incompletely understood and are the subject of ongoing investigation.

Mendelian randomization (MR) represents a methodological framework for investigating potential causal relationships. Rooted in genetic principles, this approach capitalizes on the randomized segregation of alleles during meiosis.[7] By utilizing instrumental variables derived from prevalent genetic polymorphisms associated with modifiable exposures, magnetic resonance (MR) has become a widely adopted strategy for exploring causal links between environmental factors and health outcomes.[8-10] This technique substantially mitigates susceptibility to confounding factors, reverse causation, and measurement error—limitations that frequently compromise conventional epidemiological studies. Consequently, MR-derived associations provide greater confidence in causal inference compared to standard observational analyses.[11,12] Collectively, MR serves as a robust causal inference tool that complements traditional observational study designs.

In this context, the present study employed a rigorous two-sample MR framework to delineate putative genetic causal pathways between major neurodegenerative diseases and CVDs, using large-scale, publicly available genome-wide association study (GWAS) datasets. In addition, the established MR approach was applied to critically evaluate specific causal relationships between neurodegenerative diseases and well-established cardiovascular risk factors (e.g., fasting blood glucose and dyslipidemia). Although prior studies have suggested potential associations, the existing evidence remains inconsistent and confounded. Recognizing the multifactorial etiology of CVDs, the study further extended its scope to assess the causal effects of modifiable lifestyle factors (e.g., coffee, alcohol, and tea intake) on cardiovascular outcomes, aiming to provide deeper mechanistic insights.

2. Materials and methods

2.1. Study design

This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology using MR guidelines.[13] This study aimed to investigate the causal relationships between neurodegenerative diseases and CVDs, along with their associated risk factors, as well as to evaluate the causal associations of modifiable lifestyle factors with CVDs and their associated risk factors, using genetic epidemiology and a complementary observational approach.

The schematic representation and key elements of the study rationale are illustrated in Figure 1. The study was divided into four main phases: (i) Instrumental variables derived from genetic variants were established for the exposures of interest; (ii) GWAS data were obtained for three neurodegenerative disorders, 10 CVDs, eight associated cardiovascular risk factors, and three lifestyle factors; (iii) MR analyses were performed to evaluate the causal relationships between CVDs and neurodegenerative disease risk factors, along with the associations between lifestyle factors and CVDs; and (iv) further literature mining was conducted to provide supporting evidence for the observed causal relationships.

Valid MR analysis necessitates strict adherence to three core assumptions: (i) The selected genetic variants (instruments) must be strongly and reliably associated with the exposure of interest; (ii) these genetic instruments must not be significantly associated with known or potential confounders; and (iii) the instruments must influence the outcome exclusively through the target exposure, without alternative biological pathways.[14]

2.2. Data source

All clinical datasets included in this study were obtained from large-scale, population-based biobank platforms

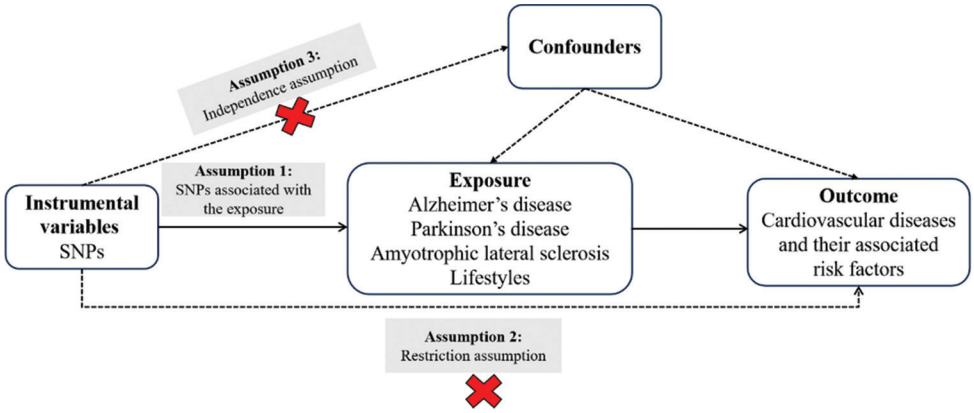


Figure 1. Schematic diagram of the research principle
Abbreviation: SNP: Single-ucleotide polymorphism.

with unrestricted public access. At the time of the original studies, all data were collected in accordance with strict ethical guidelines and obtained with patients' informed consent. The establishment of these public databases underwent rigorous ethical review and adhered to standardized operational procedures. Patients were informed during enrollment in the original studies that their data could be used for future scientific research and provided signed informed consent.

Genome-wide data were collected for the following CVDs: Coronary heart disease (60,801 cases and 123,504 controls); hypertension (129,909 cases and 354,689 controls); atrial fibrillation (AF) (60,620 cases and 970,216 controls); pulmonary embolism (407,746 cases); peripheral artery disease (7,114 cases and 475,964 controls); heart failure (47,309 cases and 930,014 controls); type 2 diabetes (38,841 cases and 451,248 controls); ischemic stroke (34,217 cases and 406,111 controls); myocardial infarction (20,917 cases and 440,906 controls); and transient ischemic attack (8835 cases and 205,799 controls).

Exposure data were also collected for neurodegenerative diseases: AD (39,106 cases and 46,828 controls); PD (33,674 cases and 449,056 controls); and amyotrophic lateral sclerosis (ALS) (27,205 cases and 110,881 controls). In addition, the following cardiovascular risk and lifestyle factors were analyzed: Systolic blood pressure (757,601 cases); diastolic blood pressure (757,601 cases); body mass index (BMI) (532,396 cases); total cholesterol levels (437,878 cases); triglycerides (441,016 cases); high-density lipoprotein (HDL) (24,616 cases); low-density lipoprotein (LDL) (440,546 cases); fasting blood glucose (200,622 cases); coffee intake (428,860 cases); tea intake (447,485 cases); and alcohol intake (462,346 cases).

2.3. Selection of single-nucleotide polymorphisms (SNPs)

The selection of instrumental SNPs was performed in three key steps. First, SNPs significantly associated with AD, PD, ALS, coffee intake, tea intake, or alcohol intake were filtered based on genome-wide significance ($p<5\times10^{-8}$). Second, linkage disequilibrium (LD) among the selected SNPs was assessed: within a 10,000 kb window, if the LD (r^2) exceeded 0.001, the less informative SNP, determined by a higher p-value or fewer correlated variants, was excluded.[15] Third, SNPs with excessive leverage on the overall analysis were identified and removed, after which the dataset was re-analyzed to ensure robustness.

2.4. Mendelian randomization analysis

Statistical validation of methodological assumptions was performed by assessing horizontal pleiotropy and defining association thresholds.[16] In the bidirectional MR design, causal relationships between neurodegenerative disorders, beverage consumption (e.g., coffee, tea, and alcohol), and CVDs were primarily estimated using the inverse-variance weighted (IVW) approach with random-effects modeling.[17] To ensure analytical robustness, sensitivity analyses, including MR-Egger regression and MR-PRESSO, were systematically implemented. Under the Instrument Strength Independent of Direct Effect assumption, MR-Egger identified directional pleiotropic bias, whereas MR-PRESSO addressed horizontal pleiotropy through outlier detection and correction, particularly for statistically significant IVW estimates.[15] Heterogeneity was quantified using Cochrane's Q-test, with $p<0.05$ or $I^2 > 25\%$ indicating statistically significant heterogeneity.[16,17] Statistical analyses and figure generation were performed using

R software version 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria). The TwoSampleMR package (R software version 0.6.8) was used for the MR analyses.

3. Results

3.1. Overview of the MR analysis

The data included in this study were published between 2015 and 2021 and primarily derived from the European population. After selecting the exposure data, the number of SNPs ranged from 0 to 99 for each neurodegenerative disease and lifestyle factor. Detailed information is outlined in Table 1.

3.2. Predicted genetic consequences of AD on cardiovascular disorders and associated risk factors

Genetic prediction of causal relationships between AD and CVDs, along with their associated risk factors, indicated a negative association between AD and three CVDs—namely, pulmonary embolism (odds ratio [OR] = 0.90; 95% confidence interval [CI] = 0.81–1.00; p=0.0484), heart failure (OR = 0.94; 95% CI = 0.90–0.97; p=0.0011), and type 2 diabetes (OR = 0.96; 95% CI = 0.93–0.99; p=0.0027)—as determined by the IVW analysis (Figure 2A).

Based on the findings, AD was negatively associated with systolic blood pressure (effect estimate = −0.39; 95% CI = −0.63–−0.15; p=0.0013), BMI (effect estimate = −0.03; 95% CI = −0.04–−0.02; p<0.0001), and triglycerides (effect estimate = −0.02; 95% CI = −0.03–0.00; p=0.0081), and positively associated with LDL (effect estimate = 0.03; 95% CI = 0.02–0.04; p=0.0001) (Figure 2B). Compared to IVW, MR-Egger and the weighted median yielded similar results, albeit with slightly lower precision (Table 2). No horizontal pleiotropy was detected for any CVD or risk factor.

The Supplementary Materials (supplementary data are available on the Zenodo platform under the DOI: 10.5281/zenodo.16552628) contain several figures that illustrate analyses of the association between AD and CVDs. Specifically, Supplementary Figure 1 presents a scatterplot; Supplementary Figure 2 displays a forest plot; Supplementary Figure 3 shows a funnel plot; and Supplementary Figure 4 summarizes the results of sensitivity analyses for this association. In addition, correlations between AD and specific cardiovascular risk factors were further explored through scatterplots (Supplementary Figure 5), forest plots (Supplementary Figure 6), funnel plots (Supplementary Figure 7), and sensitivity analyses (Supplementary Figure 8).

3.3. Genetically predicted effects of PD on cardiovascular disorders and associated risk factors

Genetic prediction of causal relationships between PD and CVDs, along with their associated risk factors, revealed a significant positive correlation between PD and two CVDs—namely, hypertension (OR = 1.01; 95% CI = 1.00–1.01; p=0.0056) and ischemic stroke (OR = 1.05; 95% CI = 1.01–1.09; p=0.0156), as determined by the IVW analysis (Figure 3A). In addition, the analysis indicated that PD was positively correlated with fasting blood glucose (effect estimate = 0.01; 95% CI = 0.0025–0.0158; p=0.0071) (Figure 3B). These findings were further supported by two additional methods, MR-Egger and the weighted median, which yielded similar outcomes, albeit with slightly lower precision compared to the IVW method (Table 3). Notably, no horizontal pleiotropy was detected across all examined CVDs and risk factors.

The results of the scatterplot, forest plot, funnel plot, and sensitivity analyses of the associations between PD and CVDs are illustrated in Supplementary Figure 9, Supplementary Figure 10, Supplementary Figure 11, and Supplementary Figure 12, respectively. Scatterplots, forest plots, funnel plots, and sensitivity analyses of the correlations between PD and cardiovascular risk factors are shown in Supplementary Figure 13, Supplementary Figure 14, Supplementary Figure 15, and Supplementary Figure 16, respectively.

Table 1. Summary of genetic data sources and associated single-nucleotide polymorphisms

Disease/lifestyle factor	Sample size (case, control)	Sex	Number of associated SNPs ($p<5\times10^{-8}$)
Alzheimer's disease	85,934 (39,106; 46,828)	N/A	59
Parkinson's disease	482,730 (33,67; 449,056)	Both	23
Amyotrophic lateral sclerosis	138,086 (27,205; 110,881)	N/A	14
Coffee intake	428,860 (428,860; 0)	Both	40
Alcohol intake	462,346 (462,346; 0)	Both	99
Tea intake	447,485 (447,485; 0)	Both	41

Abbreviations: N/A: Not available; SNP: Single-nucleotide polymorphism.

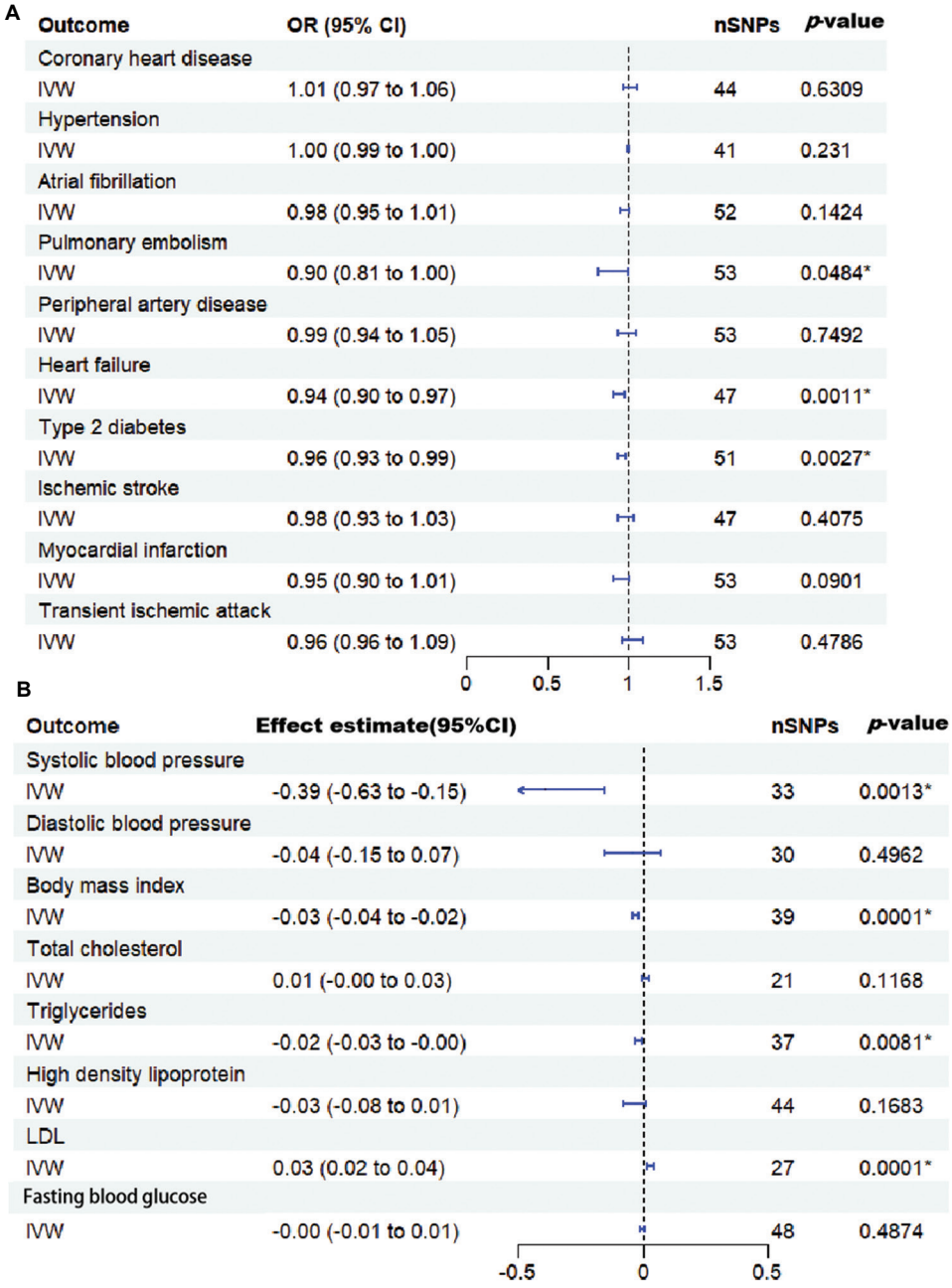


Figure 2. Genetically predicted associations between Alzheimer's disease and (A) cardiovascular disorders and (B) their associated risk factors
Note: Asterisk (*) indicates a statistically significant difference at $p<0.05$
Abbreviations: CI: Confidence interval; HDL: High-density lipoprotein; IVW: Inverse-variance weighted; LDL: Low-density lipoprotein; nSNP: Number of single-nucleotide polymorphisms; OR: Odds ratio

3.4. Genetically predicted effects of ALS on cardiovascular disorders and associated risk factors

The results of IVW analyses indicated that ALS was positively associated with AF (OR = 1.08; 95% CI = 1.03–1.14; p=0.0021). However, ALS was negatively associated with peripheral arterial disease (OR = 0.89; 95% CI = 0.80–0.99; p=0.0249 (Figure 4A). In addition, the findings revealed a positive correlation between ALS and total cholesterol (effect estimate = 0.03; 95% CI = 0.0076–0.0454; p=0.0060) (Figure 4B). The weighted median and MR-Egger approaches demonstrated converging results, albeit with reduced precision compared to IVW (Table 4). No horizontal pleiotropy was detected for CVDs or associated risk factors.

Table 2. Predicted effects of Alzheimer's disease on cardiovascular risk factors using weighted median and MR-Egger methods

Outcome	Weighted median		MR-Egger		Pleiotropy		Heterogeneity	
	Effect estimate (95% CI)	*p*-value	Effect estimate (95% CI)	*p*-value	Intercept	*p*-value	*Q*	*p*-value
Systolic blood pressure	−0.30 (−0.54–−0.05)	0.0169	0.15 (−0.61–0.91)	0.6995	−0.0429	0.1501	65	0.0004
Diastolic blood pressure	0.02 (−0.12–0.16)	0.7503	0.12 (−0.08–0.33)	0.2523	−0.0171	0.0796	46	0.0182
Body mass index	−0.03 (−0.05–−0.01)	0.0084	−0.03 (−0.05–−0.01)	0.0001	0.0004	0.7295	73	0.0004
Total cholesterol	0.01 (−0.01–0.03)	0.2511	−0.01 (−0.05–0.04)	0.8278	0.0015	0.3994	23	0.2185
Triglycerides	−0.02 (−0.03–−0.01)	0.0096	−0.01 (−0.03–0.02)	0.7189	−0.0012	0.3292	67	0.0008
HDL	−0.08 (−0.14–−0.01)	0.0165	−0.10 (−0.20–−0.01)	0.0355	0.0079	0.0932	30	0.9105
LDL	0.03 (0.01–0.05)	0.0043	0.02 (−0.02–0.07)	0.3859	0.0007	0.6456	31	0.1746
Fasting blood glucose	−0.01 (−0.02–0.01)	0.3026	0.00 (−0.02–0.02)	0.7786	−0.0006	0.4862	71	0.0098

Abbreviations: CI: Confidence interval; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

Table 3. Predicted effects of Parkinson's disease on cardiovascular risk factors using weighted median and MR-Egger

Outcome	Weighted median		MR-Egger		Pleiotropy		Heterogeneity	
	Effect estimate (95% CI)	*p*-value	Effect estimate (95% CI)	*p*-value	Intercept	*p*-value	*Q*	*p*-value
Systolic blood pressure	0.05 (−0.13–0.23)	0.5953	0.10 (−0.30–0.51)	0.6304	−0.0056	0.8696	22	0.0220
Diastolic blood pressure	0.04 (−0.06–0.15)	0.4082	0.01 (−0.16–0.19)	0.8801	0.0108	0.4962	14	0.2354
Body mass index	0.02 (0.00–0.04)	0.0130	0.01 (−0.03–0.05)	0.6044	0.0007	0.8228	39	0.0998
Total cholesterol	0.00 (−0.01–0.01)	0.8622	−0.01 (−0.04–0.01)	0.2972	0.0027	0.3222	12	0.1609
Triglycerides	0.01 (−0.01–0.02)	0.3955	0.01 (−0.02–0.03)	0.5996	0.0001	0.9764	5	0.8918
HDL	−0.03 (−0.10–0.04)	0.3885	−0.05 (−0.22–0.13)	0.5963	0.0073	0.5808	8	0.7421
LDL	0.00 (−0.01–0.02)	0.4726	−0.01(−0.03–0.01)	0.5158	0.0008	0.6794	21	0.0942
Fasting blood glucose	0.01 (0.00–0.02)	0.0705	0.01 (0.00–0.03)	0.1495	−0.0006	0.6708	15	0.4287

Abbreviations: CI: Confidence interval; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

Table 4. Predicted effects of amyotrophic lateral sclerosis on cardiovascular risk factors using weighted median and MR-Egger

Outcome	Weighted median		MR-Egger		Pleiotropy		Heterogeneity	
	Effect estimate (95% CI)	*p*-value	Effect estimate (95% CI)	*p*-value	Intercept	*p*-value	*Q*	*p*-value
Systolic blood pressure	0.29 (−0.01–0.59)	0.0622	0.10 (−0.61–0.81)	0.7909	0.0011	0.9783	16	0.0375
Diastolic blood pressure	0.12 (−0.05–0.29)	0.1807	0.12 (−0.24–0.48)	0.5311	−0.0204	0.3927	11	0.1454
Body mass index	−0.01 (−0.03–0.01)	0.1657	0.02 (−0.02–0.06)	0.4436	−0.0038	0.1161	14	0.0924
Total cholesterol	0.03 (0.01–0.05)	0.0044	0.05 (0.00–0.11)	0.2082	−0.0036	0.4407	2	0.4135
Triglycerides	0.02 (0.00–0.04)	0.1356	0.02 (−0.02–0.07)	0.2902	−0.0018	0.4750	14	0.0844
HDL	−0.01 (−0.12–0.09)	0.7940	0.09 (−0.16–0.33)	0.5013	−0.0139	0.2950	7	0.4352
LDL	0.03 (0.01–0.05)	0.0144	0.05 (0.00–0.10)	0.1065	−0.0034	0.2287	10	0.1634
Fasting blood glucose	−0.01 (−0.03–0.01)	0.1764	0.02 (−0.02–0.06)	0.4494	−0.0040	0.1062	17	0.0500

Abbreviations: CI: Confidence interval; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

The associations between ALS and CVDs are illustrated through various graphical representations, including scatterplots (Supplementary Figure 17), forest plots (Supplementary Figure 18), funnel plots (Supplementary Figure 19), and sensitivity analyses (Supplementary Figure 20). In addition, the correlations between ALS and cardiovascular risk factors are illustrated through scatterplots (Supplementary Figure 21), forest plots (Supplementary Figure 22), funnel plots (Supplementary Figure 23), and sensitivity analyses (Supplementary Figure 24).

A

Outcome	OR (95% CI)	nSNPs	*p*-value
Coronary heart disease			
IVW	0.99 (0.96 to 1.03)	16	0.7898
Hypertension			
IVW	1.01 (1.00 to 1.01)	17	0.0056*
Atrial fibrillation			
IVW	0.98 (0.95 to 1.01)	14	0.2357
Pulmonary embolism			
IVW	1.00 (0.90 to 1.10)	17	0.9314
Peripheral artery disease			
IVW	1.03 (0.96 to 1.09)	17	0.4218
Heart failure			
IVW	0.97 (0.94 to 1.01)	16	0.1118
Type 2 diabetes			
IVW	1.03 (0.99 to 1.06)	15	0.0995
Ischemic stroke			
IVW	1.05 (1.01 to 1.09)	17	0.0156*
Myocardial infarction			
IVW	1.00 (0.97 to 1.04)	17	0.9286
Transient ischemic attack			
IVW	1.06 (0.99 to 1.13)	17	0.086

B

Outcome	Effect estimate(95%CI)	nSNPs	*p*-value
Systolic blood pressure			
IVW	0.07 (-0.10 to 0.24)	13	0.4082
Diastolic blood pressure			
IVW	0.07 (-0.01 to 0.15)	13	0.0807
Body mass index			
IVW	0.01 (-0.00 to 0.03)	12	0.0998
Total cholesterol			
IVW	-0.00 (-0.01 to 0.01)	10	0.7116
Triglycerides			
IVW	0.01 (-0.00 to 0.02)	12	0.2108
High density lipoprotein			
IVW	-0.00 (-0.05 to 0.05)	13	0.9994
LDL			
IVW	-0.00 (-0.01 to 0.01)	16	0.4934
Fasting blood glucose			
IVW	0.01 (0.00 to 0.02)	17	0.0071*

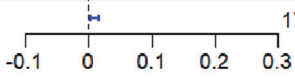


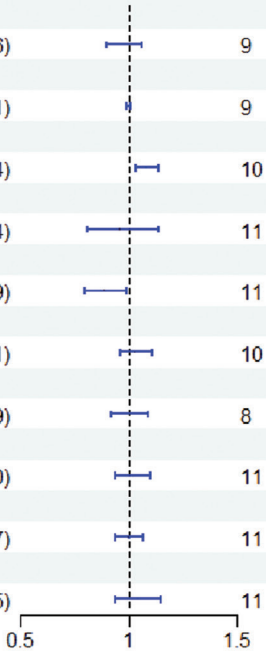
Figure 3. Genetically predicted associations between Parkinson's disease and (A) cardiovascular disorders and (B) their associated risk factors
Note: Asterisk (*) indicates a statistically significant difference at $p<0.05$
Abbreviations: CI: Confidence interval; HDL: High-density lipoprotein; IVW: Inverse-variance weighted; LDL: Low-density lipoprotein; nSNP: Number of single-nucleotide polymorphisms; OR: Odds ratio.

3.5. Genetically predicted effects of lifestyle factors on cardiovascular disorders

This study assessed the genetic prediction of causal relationships between lifestyle factors (e.g., coffee, alcohol, and tea intake) and CVDs, along with their associated risk factors. The findings revealed a positive association between coffee intake and coronary heart disease (OR = 1.53; 95% CI = 1.18–1.97; p=0.0013), peripheral artery disease (OR = 2.02; 95% CI = 1.21–3.37; p=0.0072), and type 2 diabetes (OR = 1.52; 95% CI = 1.04–2.23; p=0.0315) (Figure 5A). In addition, the analysis indicated that coffee intake was positively associated with BMI (effect estimate = 0.58; 95% CI = 0.44–0.71; $p<0.0001$) and HDL (effect estimate = 0.42; 95% CI = 0.14–0.70; p=0.0037), and negatively associated

A

Outcome	OR (95% CI)	nSNPs	*p*-value
Coronary heart disease			
IVW	0.98 (0.90 to 1.06)	9	0.5559
Hypertension			
IVW	1.00 (0.99 to 1.01)	9	0.6458
Atrial fibrillation			
IVW	1.08 (1.03 to 1.14)	10	0.0021*
Pulmonary embolism			
IVW	0.96 (0.81 to 1.14)	11	0.6411
Peripheral artery disease			
IVW	0.89 (0.80 to 0.99)	11	0.0249*
Heart failure			
IVW	1.03 (0.96 to 1.11)	10	0.3785
Type 2 diabetes			
IVW	1.00 (0.92 to 1.09)	8	0.9906
Ischemic stroke			
IVW	1.02 (0.94 to 1.10)	11	0.687
Myocardial infarction			
IVW	1.00 (0.94 to 1.07)	11	0.9375
Transient ischemic attack			
IVW	1.04 (0.94 to 1.15)	11	0.4762



B

Outcome	Effect estimate(95%CI)	nSNPs	*p*-value
Systolic blood pressure			
IVW	0.11 (-0.18 to 0.40)	10	0.4683
Diastolic blood pressure			
IVW	0.04 (-0.11 to 0.19)	9	0.6072
Body mass index			
IVW	-0.02 (-0.04 to 0.00)	10	0.1148
Total cholesterol			
IVW	0.03 (0.01 to 0.05)	4	0.0060*
Triglycerides			
IVW	0.01 (-0.01 to 0.03)	10	0.2859
High density lipoprotein			
IVW	-0.04 (-0.13 to 0.04)	9	0.3069
LDL			
IVW	0.02 (-0.00 to 0.04)	9	0.1147
Fasting blood glucose			
IVW	-0.02 (-0.04 to 0.00)	11	0.0843

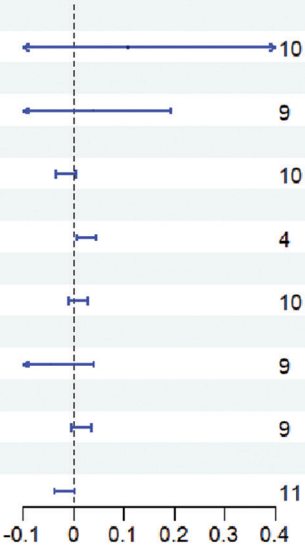


Figure 4. Genetically predicted associations between amyotrophic lateral sclerosis and (A) cardiovascular disorders and (B) their associated risk factors
Note: Asterisk (*) indicates a statistically significant difference at $p<0.05$
Abbreviations: CI: Confidence interval; HDL: High-density lipoprotein; IVW: Inverse-variance weighted; LDL: Low-density lipoprotein; nSNP: Number of single-nucleotide polymorphisms; OR: Odds ratio.

with diastolic blood pressure (effect estimate = −1.61; 95% CI = −2.63–0.59; p=0.0019) (Figure 6A).

Furthermore, alcohol intake was positively associated with coronary heart disease (OR = 1.26; 95% CI = 1.11–1.43; p=0.0003), hypertension (OR = 1.03; 95% CI = 1.01–1.04; p<0.0001), AF (OR = 1.12; 95% CI =1.03–1.22; p=0.0079), heart failure (OR = 1.21; 95% CI = 1.10–1.33; p=0.0001), myocardial infarction (OR = 1.22; 95% CI = 1.11–1.34; p=0.0001), and type 2 diabetes (OR = 1.33; 95% CI = 1.18–1.51; p<0.0001) (Figure 5B). Alcohol intake was also associated with increased BMI (effect estimate = 0.19; 95% CI = 0.15–0.23; p<0.0001) and triglycerides (effect estimate = 0.16; 95% CI = 0.12–0.20; p<0.0001) (Figure 6B).

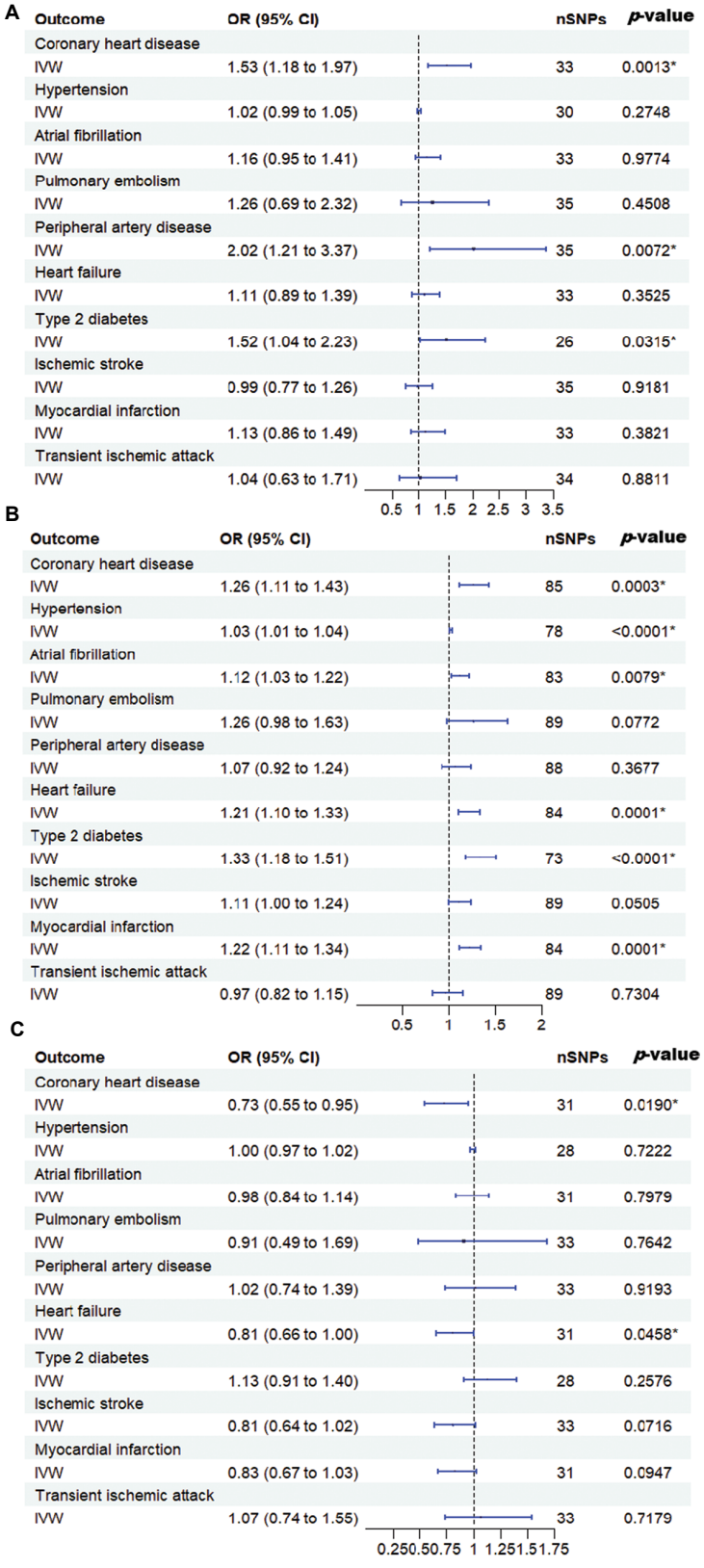


Figure 5. Genetically predicted associations between cardiovascular disorders and (A) coffee intake, (B) alcohol intake, and (C) tea intake
Note: Asterisk (*) indicates a statistically significant difference at $p<0.05$
Abbreviations: CI: Confidence interval; IVW: Inverse-variance weighted; nSNP: Number of single-nucleotide polymorphisms; OR: Odds ratio.

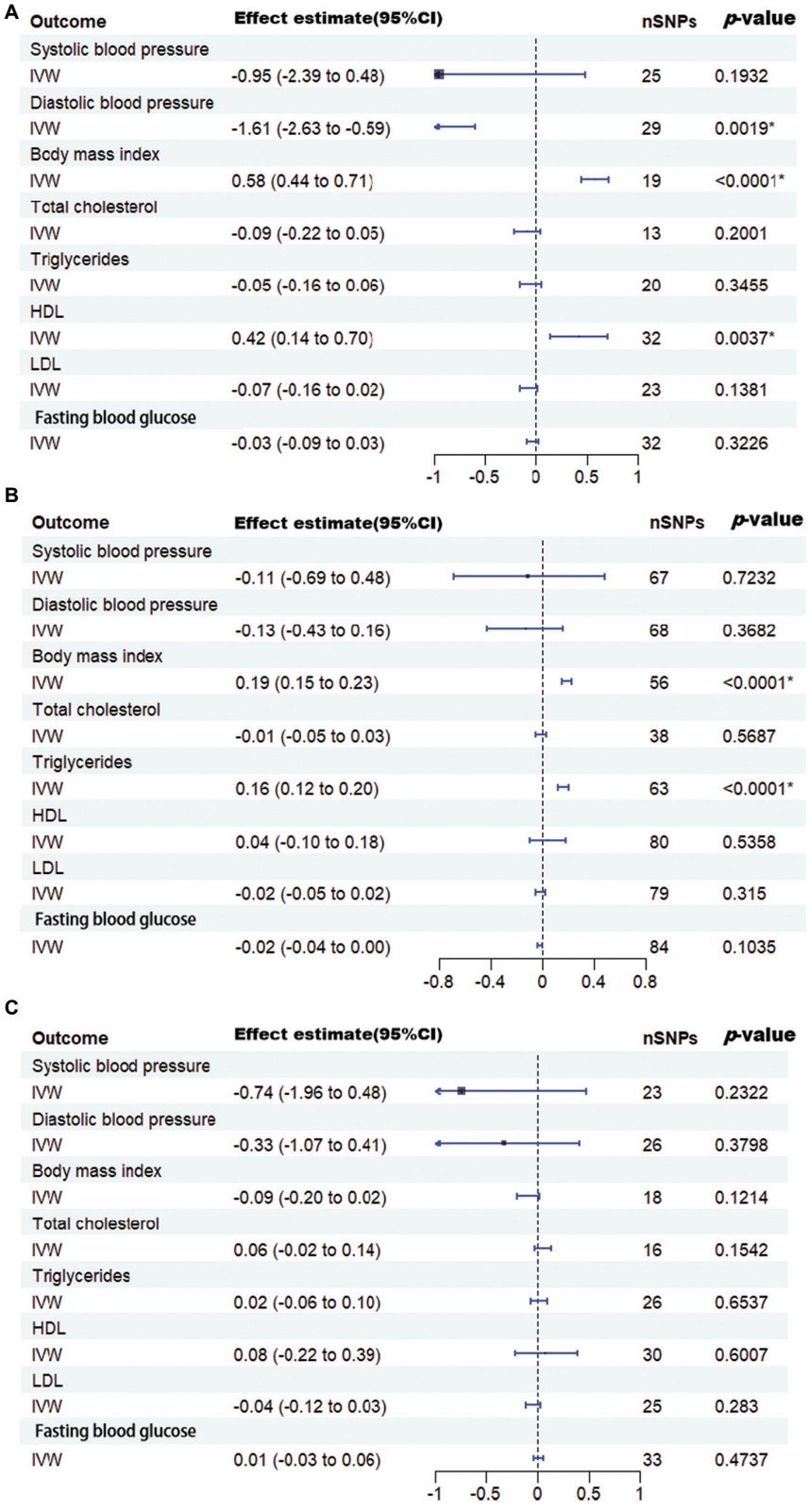


Figure 6. Genetically predicted associations between cardiovascular risk factors and (A) coffee intake, (B) alcohol intake, and (C) tea intake
Note: Asterisk (*) indicates a statistically significant difference at $p<0.05$
Abbreviations: CI: Confidence interval; HDL: High-density lipoprotein; IVW: Inverse-variance weighted; LDL: Low-density lipoprotein; nSNP: Number of single-nucleotide polymorphisms; OR: Odds ratio.

In contrast, tea intake was negatively associated with coronary heart disease (OR = 0.73; 95% CI = 0.55–0.95; p=0.0190) and heart failure (OR = 0.81; 95% CI = 0.66–1.00; p=0.0458) (Figure 5C). Both the weighted median and MR-Egger approaches yielded comparable effect sizes, albeit with reduced precision compared to IVW (Tables 5–7). No horizontal pleiotropy was detected for any CVD or lifestyle factor.

The correlations between CVDs and lifestyle factors are illustrated through various graphical representations, including scatterplots (Supplementary Figures 25–27), forest plots (Supplementary Figures 28–30), funnel plots (Supplementary Figures 31–33), and sensitivity analyses (Supplementary Figures 34–36). Scatter plots of the associations between lifestyle factors and cardiovascular risk factors are shown in Supplementary Figures 37–39; forest plots in Supplementary Figures 40–42; funnel plots in Supplementary Figures 43–45; and sensitivity analyses in Supplementary Figures 46–48.

4. Discussion

Unhealthy behavioral patterns prevalent among residents in China have substantially increased large-scale population-based exposure to cardiovascular risk factors. This vulnerability is further amplified by the accelerating demographic shift toward an aging population.[20] As such, CVDs continue to represent one of the most critical health threats in the country.[20] According to the 2023 *China Cardiovascular Health and Diseases Report*, cardiovascular conditions accounted for 48.98% of deaths in rural areas and 47.35% in urban areas in 2021. This mortality burden translates to approximately 288 CVD-related deaths per day—equivalent to two fatalities every 5 min. Current statistics indicate that there are approximately 330 million CVD patients in China, including 245 million individuals with hypertension, 13 million stroke survivors, and 11.39 million with coronary heart disease—a disease burden surpassing that of all other chronic conditions.[21]

Table 5. Predicted associations between coffee intake and cardiovascular risk factors using weighted median and MR-Egger

Outcome	Weighted median		MR-Egger	
	Effect estimate (95% CI)	*p*-value	Effect estimate (95% CI)	*p*-value
Systolic blood pressure	−0.48 (−2.16–1.20)	0.5748	0.90 (−3.87–5.67)	0.7142
Diastolic blood pressure	−1.33 (−2.42–−0.24)	0.0171	−3.28 (−6.98–0.42)	0.0937
Body mass index	0.58 (0.44–0.72)	< 0.0001	0.31 (−0.15–0.77)	0.2020
Total cholesterol	−0.08 (−0.24–0.08)	0.3248	0.13 (−0.27–0.52)	0.5456
Triglycerides	−0.04 (−0.13–0.05)	0.4021	−0.06 (−0.27–0.14)	0.5656
HDL	0.51 (0.12–0.90)	0.0099	0.63 (0.05–1.20)	0.0400
LDL	−0.09 (−0.22–0.03)	0.1489	0.07 (−0.24–0.37)	0.6752
Fasting blood glucose	−0.01 (−0.09–0.07)	0.8538	0.04 (−0.10–0.17)	0.5828

Abbreviations: CI: Confidence interval; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

Table 6. Predicted associations between alcohol intake and cardiovascular risk factors using weighted median and MR-Egger

Outcome	Weighted median		MR-Egger	
	Effect estimate (95% CI)	*p*-value	Effect estimate (95% CI)	*p*-value
Systolic blood pressure	−0.16 (−0.80–0.49)	0.6359	0.15 (−2.20–2.50)	0.8988
Diastolic blood pressure	−0.29 (−0.64–0.05)	0.0897	−0.32 (−0.93–0.30)	0.3154
Body mass index	0.17 (0.13–0.22)	<0.0001	0.14 (−0.07–0.35)	0.2060
Total cholesterol	−0.0006 (−0.05–0.05)	0.9824	0.11 (−0.03–0.25)	0.1431
Triglycerides	0.11 (−0.07–0.15)	<0.0001	0.22 (0.03–0.41)	0.0273
HDL	0.03 (−0.19–0.25)	0.7714	−0.01 (−0.55–0.53)	0.9711
LDL	−0.03 (−0.07–0.01)	0.1421	−0.0006 (−0.14–0.14)	0.9933
Fasting blood glucose	−0.03 (−0.06–0.003)	0.0753	−0.04 (−0.09–0.01)	0.1233

Abbreviations: CI: Confidence interval; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

Table 7. Predicted associations between tea intake and cardiovascular risk factors using weighted median and MR-Egger

Outcome	Weighted median		MR-Egger	
	Effect estimate (95% CI)	*p*-value	Effect estimate (95% CI)	p
Systolic blood pressure	−1.21(−2.70–0.28)	0.1105	−1.14 (−6.48–4.19)	0.6788
Diastolic blood pressure	−0.19 (−0.99–0.62)	0.6507	1.38 (−1.32–4.08)	0.3260
Body mass index	0.01 (−0.10–0.11)	0.9495	0.14 (−0.21–0.49)	0.4433
Total cholesterol	0.10 (0.01–0.18)	0.0272	0.16 (−0.03–0.35)	0.1194
Triglycerides	0.06 (−0.03–0.14)	0.2026	0.17 (−0.09–0.42)	0.2188
HDL	0.41 (0.02–0.81)	0.0394	0.85 (0.17–1.53)	0.0214
LDL	−0.03 (−0.12–0.06)	0.5719	−0.11 (−0.36–0.15)	0.4127
Fasting blood glucose	−0.01 (−0.06–0.05)	0.8615	−0.1 (−0.18–−0.02)	0.0156

Abbreviations: CI: Confidence interval; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

At present, neurodegenerative diseases affect more than 60 million people and represent the seventh leading cause of death worldwide.[22] China's aging population includes 38 million individuals diagnosed with cognitive decline. Notably, the country demonstrates an above-global-average incidence and mortality rate of AD, with a significant gender disparity indicating greater female vulnerability.[23] A previous study demonstrated an association between CVDs and neurodegenerative diseases.[24]

In the present study, a two-sample MR analysis was conducted to systematically investigate the causal relationships between neurodegenerative diseases, CVDs, and related risk factors, as well as to assess the causal effects of certain lifestyle factors on CVDs and associated risk factors. Significant causal associations between specific CVDs and neurodegenerative diseases were identified. These findings provide new insights into the etiological links between these diseases, while the use of MR analysis helps reduce the influence of confounding factors, thereby increasing the robustness and credibility of the conclusions.

Based on the genetic prediction analysis, the findings revealed a negative association between AD and three CVDs: pulmonary embolism, heart failure, and type 2 diabetes. Both AD and CVDs are associated with chronic inflammation. For example, studies have shown that neuroinflammation in AD may influence vascular function, potentially leading to adaptive responses that mitigate heart failure.[25,26] The negative association with type 2 diabetes is particularly intriguing. Metabolic dysfunction is known to be a common risk factor for both AD and CVDs. However, individuals with AD may exhibit altered metabolic pathways that confer a certain level of protection against diabetes. This phenomenon may be related to insulin signaling pathways, which have been shown to have differential impacts on cognitive function and cardiovascular health.[27]

The genetic prediction analysis highlights the role of shared genetic etiology between these conditions. For example, genetic variants influencing amyloid beta metabolism in AD may also play a crucial role in cardiovascular health. Research has indicated that variations in the amyloid precursor protein (*APP*) gene can affect vascular integrity and may contribute to the development of CVDs.[28] The association between AD and type 2 diabetes further underscores the connection between metabolic dysfunction and neurodegeneration.[29]

However, previous research has established a bidirectional relationship between unstable angina and the development of AD. Specifically, AD may elevate the risk of developing unstable angina, while unstable angina may, in turn, contribute to AD progression. This reciprocal link underscores the need to investigate the shared molecular pathways underlying both conditions. Furthermore, leveraging genetic information holds significant promise in advancing the development of personalized therapeutic strategies.[30]

The results of this study also revealed that AD was positively associated with LDL but negatively associated with systolic blood pressure, BMI, and triglycerides. Elevated LDL has been linked to an increased risk of AD, particularly through enhanced amyloid-β deposition and neuroinflammation.[31] Although lower blood pressure is generally considered beneficial, it may lead to inadequate cerebral perfusion in AD, thereby exacerbating cognitive deficits.[32] The inverse association between AD and BMI may reflect the influence of apolipoprotein E (APOE) alleles, which affect both AD risk and metabolic pathways.[33] Several studies suggest that early BMI regulation in APOE ε3 carriers can reduce AD risk.[34] Nevertheless, disease-related weight loss complicates AD management, as malnutrition further impairs cognitive function and heightens susceptibility to infections and other health

issues. A 26-year longitudinal study by Du *et al.*[35] identified cardiometabolic comorbidities, such as CVD, stroke, hypertension, and diabetes mellitus, as significant predictors of AD in patients with breast cancer, with the highest risk observed in African women and the lowest in Asian/Pacific-Islander women. Collectively, our findings suggest that AD is significantly associated with multiple cardiovascular and metabolic disorders; therefore, clinicians should monitor patients with AD for emerging CVDs.

PD was positively associated with hypertension and ischemic stroke, and showed a direct association with fasting blood glucose levels. Chronic hypertension can lead to cerebral vascular damage, thereby affecting brain function and potentially accelerating neurodegeneration in individuals with PD.[35] In addition, vascular dysfunction in PD, including altered blood–brain barrier permeability and impaired cerebral blood flow, may exacerbate the impact of hypertension on the brain, contributing to cognitive decline and motor impairments.[36] Retrospective studies indicate that approximately 33% of PD patients develop mild-to-severe supine hypertension, irrespective of age, disease duration, or progression stage. Cardiovascular comorbidities in this population substantially promote supine hypertension, representing a manifestation of underlying autonomic cardiovascular dysfunction.[37]

Ischemic stroke may occur due to impaired cerebral circulation, which is more prevalent in individuals with PD due to autonomic dysfunction and other vascular risk factors, such as hypertension and diabetes.[38] In addition, neurovascular coupling, which links neural activity to local blood flow, may be impaired in PD patients, contributing to an increased risk of stroke. The presence of ischemic stroke in PD patients could further complicate clinical management, potentially leading to increased disability, motor deterioration, and cognitive impairment.[39] The shared pathophysiological mechanisms between ischemic stroke and PD—such as chronic inflammation, oxidative stress, and vascular dysfunction—suggest a bidirectional relationship. For example, the neurodegeneration observed in PD may increase the risk of stroke due to its effects on vascular health and neuronal communication.[40] Moreover, insulin resistance and impaired glucose metabolism have been implicated in neurodegenerative diseases, including PD, in which the brain's glucose metabolism may be disrupted.[41] Hyperglycemia can worsen PD symptoms by exacerbating oxidative stress and promoting neuroinflammation, both of which are key drivers of neurodegeneration in PD.[42] Drawing on cohort data with a median 89-month follow-up, Li *et al.*[43] demonstrated significantly elevated CVD mortality among PD patients in the United States population.

The findings also revealed a positive association between ALS and both AF and total cholesterol, as well as a negative association with peripheral arterial disease. AF elevates susceptibility to cerebrovascular accidents, cardiac decompensation, and other severe comorbidities.[44] The presence of AF in ALS patients may indicate a shared pathophysiological mechanism involving neurodegeneration and cardiovascular dysfunction.[43] For example, autonomic dysfunction, which is common in neurodegenerative diseases, may predispose individuals to AF. The relationship between cholesterol levels and ALS may be influenced by several factors, including dietary habits, metabolic changes, and the impact of statin medications on neurodegeneration.[45] Several studies have revealed that cholesterol homeostasis in ALS muscles is disrupted from the pre-symptomatic stage and is associated with disease progression. Dysfunctional Niemann–Pick C1 protein disrupts lysosomal cholesterol trafficking, compromising energy metabolism in the skeletal muscle of ALS patients.[46]

In addition, a previous study suggests that frontal lobe metabolic decline is one of the distinct cortical features of ALS spectrum disorders.[47] This metabolic dysfunction leads to increased glucose accumulation, which further exacerbates neurodegeneration due to glucose imbalance. This finding contrasts with our research findings. Peripheral arterial disease causes changes in peripheral blood flow, and some studies have shown no correlation between ALS severity scores and these blood flow changes.[48] In a study of participants from the United Kingdom Biobank, with a median follow-up of 13.7 years, individuals with metabolic syndrome had a higher risk of ALS after adjusting for confounders. Specifically, high blood pressure and elevated triglyceride levels were associated with an increased risk of ALS, particularly in individuals with lower BMI.[49] These findings emphasize the intricate relationship between ALS and cardiovascular health, suggesting that patients with ALS may be at an elevated risk of developing additional comorbidities, which can significantly impact their overall health and disease management.

Furthermore, the findings of this study suggested that coffee and alcohol intake increased the risk of CVDs, whereas tea intake reduced this risk. A dose–response investigation demonstrated a significant positive association between increased coffee consumption and the risks of cardiovascular mortality and developing CVD.[50] Studies have also shown that, when consumed in moderation, caffeine may potentially reduce the risk of developing CVDs and could even serve as a protective factor.[51] The contemporary coffee market is dominated by instant coffee consumption. Products available commercially often contain added ingredients, including

sugar, creamer substitutes, and artificial flavorings. These supplementary constituents may be responsible for the differential health impacts observed.[52,53]

Several studies have demonstrated that alcohol consumption is significantly correlated with myocardial infarction, coronary heart disease,[54] cancer, liver disease, and death from non-medical causes.[55] At the methodological level, Hu[56] utilized the *ALDH2* gene rs671 locus polymorphism as an instrumental variable, effectively circumventing reverse causation and confounding bias, which often affect traditional observational studies. The study found that lower alcohol consumption in ALDH2-deficient individuals reduced systolic blood pressure by 2.1 mmHg (p=0.003). This genetic epidemiologic approach provides stronger evidence for understanding how lifestyle factors contribute to disease risk.

Moderate alcohol consumption has been associated with a reduced risk of CVD. For men, moderation is defined as up to 20 g of alcohol per day, and for women, up to 10 g/day. The proposed mechanisms underlying this association include the attenuation of LDL oxidation and the facilitation of macrophage cholesterol efflux. This cholesterol removal process initiates the reverse cholesterol transport pathway.[57,58] Alcohol tolerance varies by age, and the impact of alcohol consumption on CVD risk is influenced by multiple factors, including the amount consumed, the intake pattern (e.g., frequency), and the type of beverage.

Tea contains a variety of active ingredients, among which flavonoids, particularly flavan-3-ols, are the primary dietary source.[56] Moderate tea intake has been linked to lower CVD-related mortality.[59] Collectively, the associations between coffee, alcohol, and tea intake and cardiovascular or metabolic health highlight the need for a deeper understanding of dietary habits and their implications. While moderate coffee intake may confer some protective effects, excessive alcohol consumption is significantly detrimental. In contrast, tea intake may offer protective benefits against certain forms of CVD. Further research is warranted to explore these associations and their underlying mechanisms.

The underlying pathophysiological mechanisms linking cardiovascular and neurodegenerative disorders are not yet fully understood. Existing evidence suggests that vascular endothelial dysregulation may serve as a pathogenic nexus underlying both cerebrovascular and primary neurodegenerative conditions.[60,61] APOE, a lipid transport protein originally identified as the principal ligand for LDL receptors, modulates cholesterol homeostasis and influences cardiovascular pathology. It has since been established as a major genetic determinant of AD and related neurodegenerative disorders.[62] A previous study based on a prospective cohort from the United Kingdom Biobank found that central obesity, muscle strength, and arm-dominant fat distribution are strongly associated with neurodegenerative diseases and brain aging over an average follow-up of 9.1 years, with CVD mediating these associations in part.[22]

The onset of neurodegenerative diseases and CVD is significantly associated with aging. With advancing age, in addition to the gradual emergence of neurodegenerative diseases and cognitive decline, cholesterol and calcium deposits, as well as inflammation of endothelial cells, can impair cardiovascular function.[63] The pre-clinical latency period of neurodegenerative diseases typically begins in middle age, whereas clinical manifestations of CVD may appear several years earlier, rendering the two conditions potential predictors of one another. A previous study indicated that strokes and obesity are both associated with an elevated risk of PD, with incidence increasing with age.[64] Studies have shown that improving cardiovascular health in older adults may reduce the burden of neurodegenerative disease.[65] Collectively, the evidence highlights enhancements in body composition and the proactive management of CVD as key strategies that may lower susceptibility to neurodegenerative conditions.

Although China's government has implemented prevention and control strategies such as "Healthy China 2030," risk factor management still faces significant challenges. The "three lows" of hypertensione3lemented prevention and control strategies such asnd cal—remain prominent. In addition, the control rate for diabetes is below 50%, and only 39% of patients with dyslipidemia have achieved target LDL cholesterol levels.

Moving forward, the prevention and control of CVDs and neurodegenerative diseases should be strengthened through a multidisciplinary, collaborative care model. This includes the implementation of Internet of Things-based blood pressure and glucose monitoring at the community level, alongside early risk screening and lifestyle interventions targeted at younger populations. Such strategies are essential to mitigating the dual burden of CVDs and neurodegenerative diseases.

There are several advantages to our study. First, MR analysis was employed to investigate the relationship between neurodegenerative diseases and CVD, which substantially reduces confounding factors typically present in observational studies. Second, the relatively large sample size of the dataset helps compensate for the limitations of traditional studies, making the conclusions more convincing. Third, the MR-PRESSO software package was used to test for horizontal pleiotropy, eliminating SNPs with potential biasing effects and thereby yielding more accurate results.

Concomitantly, certain limitations must be considered when interpreting the findings. First, the data were derived from European populations, which may limit the generalizability of our results to other ethnic groups. Second, due to restricted access to individual-level data, we were unable to account for potential sample overlap between datasets. Third, actual disease risks are often influenced by environmental exposure and gene–environment interactions. For instance, the consumption of coffee, alcohol, and tea is closely linked to lifestyle factors, and the potential for residual confounding or pleiotropy remains. Therefore, future research should aim to incorporate these interactions into the analytical framework. Finally, although MR analysis minimizes the impact of confounders on causal inference, it cannot fully exclude the influence of other pathogenic factors on CVD. MR primarily addresses genetic-level causal relationships; however, a more comprehensive understanding of disease mechanisms would benefit from integration with additional omics layers such as transcriptomics, metabolomics, and epigenetics. Such multi-omics approaches could elucidate intermediate molecular pathways and enhance the biological interpretation of MR findings. These represent key directions for our future research.

5. Conclusion

AD was negatively associated with pulmonary embolism, heart failure, type 2 diabetes, systolic blood pressure, BMI, and triglycerides, and was positively associated with LDL. PD was positively associated with hypertension, ischemic stroke, and fasting blood glucose. In addition, the findings revealed a positive association between ALS and both AF and total cholesterol, and a negative association with peripheral artery disease. Moreover, coffee intake was positively associated with coronary heart disease, peripheral arterial disease, type 2 diabetes, BMI, and HDL, and negatively associated with diastolic blood pressure. Similarly, alcohol intake was positively associated with coronary heart disease, hypertension, AF, heart failure, myocardial infarction, type 2 diabetes, BMI, and triglycerides. In contrast, tea intake was negatively associated with coronary heart disease and heart failure. These associations provide valuable insights into the complex interplay between neurodegenerative diseases and CVDs, suggesting that CVDs are interlinked with broader neurological disorders.

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Conflict of interest

The authors declared that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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Ethics approval and consent to participate

All genomic data analyzed in this study are sourced from the GWAS public database, which has obtained ethical approval. This database explicitly requires users to assume full responsibility for any materials or content uploaded to the EMBL-EBI data resources and tools.

Consent for publication

This study uses large-scale GWAS summary datasets where all participants gave informed consent in their respective original studies. As we only rely on summary-level statistics, no additional informed consent is required.

Availability of data

Publicly available datasets were analyzed in this study and can be accessed at https://gwas.mrcieu.ac.uk. Supplementary data are available on the Zenodo platform under the DOI: 10.5281/zenodo.16552628.

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