Casual association between plasma CoQ10 levels and stroke: a mendelian randomization study

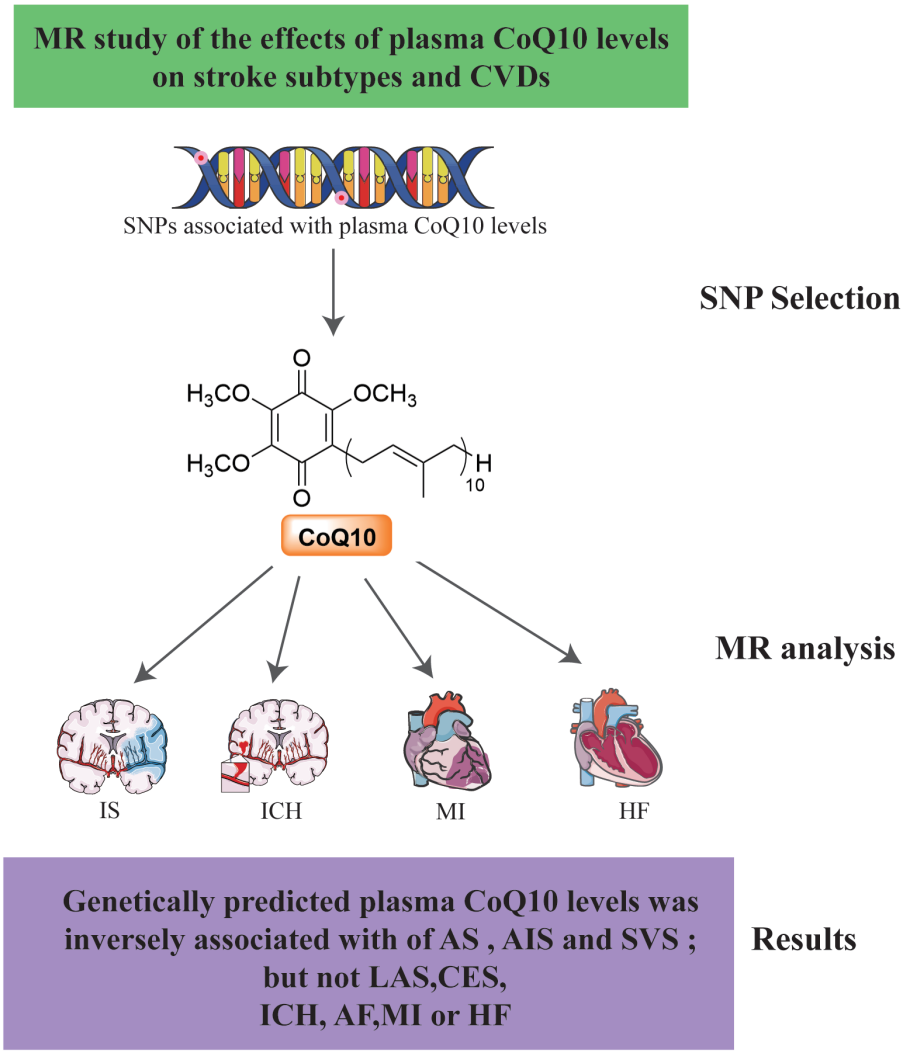
Authors

Xuyang Liu, Yuyuan Gao, Xiaojing Yao, Xu Li, Yuming Xu

Correspondence

xuyuming@zzu.edu.cn (Y. Xu)

Graphical Abstract



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Research Article Brain Conflux

Casual association between plasma CoQ10 levels and stroke: a mendelian randomization study

Xuyang Liu [1], Yuyuan Gao [1], Xiaojing Yao [4], Xu Li [3], Yuming Xu [1,2*]

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Abstract

Background: Coenzyme Q10, a crucial mitochondrial compound and antioxidant, declines with age and statin use. While lower CoQ10 levels are associated with cardiovascular diseases and stroke, and supplementation shows protective effects in some heart conditions, the causal relationship between CoQ10 and stroke or cardiovascular diseases remains unclear. The aim of this study is to investigate the causal relationship between plasma Coenzyme Q10 (CoQ10) levels and stroke, as well as some cardiovascular diseases, using Mendelian randomization methods.
Methods: Causal links were investigated through two-sample Mendelian randomization (MR) analysis. We identified genetic variants that showed significant associations with plasma CoQ10 levels. The inverse variance weighted (IVW) method was employed to estimate the effects. Additionally, sensitivity analysis was used to assess heterogeneity or pleiotropy.
Results: Our MR analysis revealed that genetically predicted plasma CoQ10 levels was inversely associated with of any stroke (AS, OR = 0.803, 95% CI: 0.659–0.978, p=0.029), any ischemic stroke (AIS, OR = 0.792, 95% CI 0.651–0.964, p = 0.020) and small vessel stroke (SVS, OR = 0.512, 95% CI 0.294-0.892, p = 0.018). However, no associations were observed between genetically predicted plasma CoQ10 and large artery stroke (LAS), cardioembolic stroke (CES), intracranial hemorrhage (ICH), atrial fibrillation (AF), myocardial infarction (MI) or heart failure (HF).
Conclusions: Our MR analysis implies a protective effect between higher plasma CoQ10 levels and AS, AIS or SVS. The results and the underlying pathways or mechanisms between plasma CoQ10 levels and stroke needs further investigation.
Keywords: Plasma CoQ10, Stroke, Mendelian Randomization, Cardiovascular Diseases.

Introduction

CoQ10, also known as ubiquinone, is a naturally occurring fat-soluble compound with vitamin-like properties found in mitochondria, cell membranes, and blood [1]. Within mitochondria, CoQ10 plays a crucial role in the electron transport chain, facilitating the transfer of electrons from complexes I and II to complex III [2]. Outside mitochondria, CoQ10 is primarily distributed across various membrane structures and possesses antioxidant properties that mitigate oxidative stress damage [3, 4]. However, with the aging process, the levels of CoQ10 in both plasma and tissues decline significantly [5, 6]. At the same time, the intake of certain medications, such as statins, can also impact the synthesis of CoQ10, leading to a reduction in its content [7]. Previous studies have indicated that supplementing CoQ10 has a certain protective effect against ischemic heart disease [8, 9], hypertension [10, 11], and heart failure [12, 13]. Some studies have found a decrease in plasma CoQ10 levels in stroke patients [14], and this decrease is correlated with the deterioration of neurological function induced by stroke [15]. Nevertheless, there is still a lack of reliable randomized controlled trial (RCT) research on the relationship between CoQ10 supplement and cerebrovascular diseases such as stroke. In addition, it is unclear whether lower plasma CoQ10 levels is a potential cause or an accompanying phenomenon of stroke and main cerebrovascular diseases.
Mendelian randomization analysis stands as a genetic epidemiological method for inferring causality. It utilizes genetic variants derived from summary-level genome-wide association study (GWAS) data as instrumental variables (IVs), effectively minimizing sampling errors and confounding factors [16]. The objective of this MR study is to assess the causal relationships between genetically predicted plasma CoQ10 levels and the susceptibility to stroke and main cardiovascular diseases.

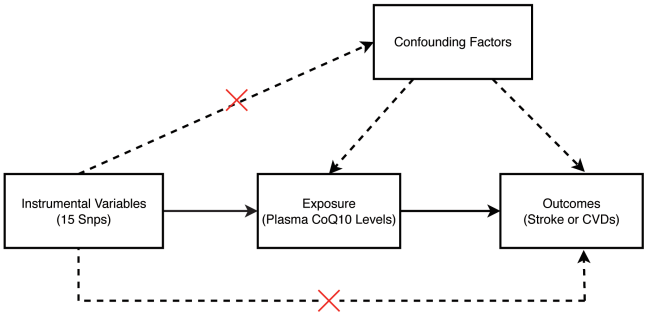
1 Department of Neurology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou University, Zhengzhou, China.
2 Henan Key Laboratory of Cerebrovascular Diseases, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China.
3 Department of Endovascular Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China.
4 The Third Affiliated Hospital of Zhengzhou University, Zhengzhou, China
* Corresponding Author.

Methods

MR assumptions

The current MR analysis relies on three primary assumptions. Firstly, the IVs are associated with the plasma CoQ10 levels at genome-wide significance; secondly, the IVs show no correlation with any potential confounding factors; thirdly, the IVs have no direct impact on stroke or cardiovascular diseases (CVDs), potentially influencing them only indirectly through plasma CoQ10 levels. The design of the present MR study is visually presented in Figure 1.

Figure 1. The main assumptions of the present Mendelian randomization study of plasma CoQ10 levels and stroke or CVDs. A total of 15 SNPs were selected as instrumental variables. CVDs, cardiovascular diseases; SNP, single nucleotide polymorphism



Plasma CoQ10 levels GWAS summary dataset

Our main analysis workflow is presented in Figure 2. We obtained genetic variants linked to plasma CoQ10 levels from a GWAS summary dataset of a 1300 cross-sectional German cohort [17], which includes 846 participants from the PopGen cohort and 454 participants from the FoCus cohort, all European ancestry [18]. This GWAS meta-analysis was adjusted for age, sex and study center. Initially, we selected 18 SNPs that met the criterion of p < 5e-6. Subsequently, SNPs with an R2 > 0.001 within a 10,000 kb window were excluded after conducting a linkage disequilibrium test [19]. We calculated the F statistic for each SNP following the previously described method [20]. Then, SNPs with an F statistic less than 10, indicating a weak instrumental variable, were also excluded. As a result, we identified 15 SNPs that emerged as predictors for plasma CoQ10 levels (Table 1).

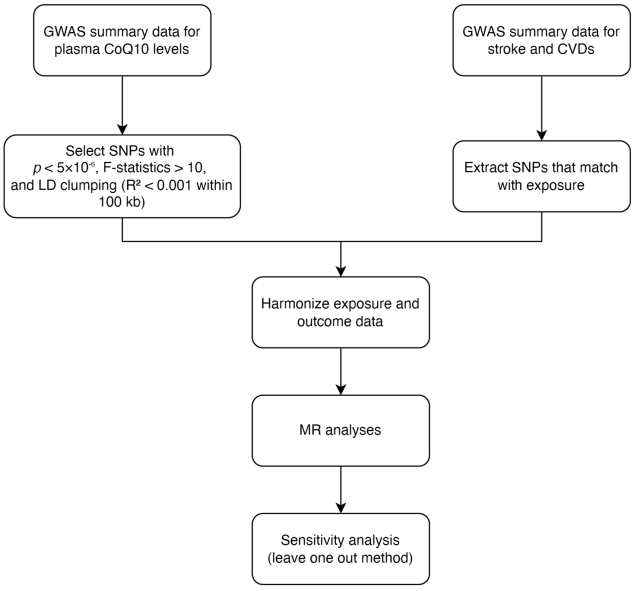
Stroke and CVDs GWAS datasets

We acquired genetic variants for the outcomes from comprehensive GWAS datasets that encompassed main stroke subtypes and CVDs. Specifically, from the MEGASTROKE consortium, we obtained stroke-associated GWAS datasets [21]. The MEGASTROKE study included 40,585 stroke cases and 406,111 controls, categorized as follows: 34,217 cases of ischemic stroke, 4,373 cases of large vessel stroke, 7,193 cases of cardioembolic stroke, and 5,386 cases of small vessel stroke. Additionally, we obtained GWAS summary datasets for ICH, MI, HF, and AF from the FinnGen group [22], CARDIoGRAM consortium [23], HERMES consortium [23], and Nielsen et al. [24], respectively. Supplementary Table 1 provides detailed information about these datasets. All individuals included in these datasets for our MR study were of European ancestry.

Statistical analysis

We employed the IVW method as the primary tool for causal effect analysis and utilized other analytical methods [25], such as the weighted median, weighted mode, simple median, and simple mode, as supplementary analyses. We conducted heterogeneity and pleiotropy analyses using MR-Egger, MR-PRESSO, Cochrane's Q test, and leave-one-out analysis [26, 27]. All the analyses were performed using the TwoSampleMR package.

Figure 2. The study design of the present Mendelian randomization study of plasma CoQ10 levels and stroke or CVDs. A total of 15 SNPs were selected as instrumental variables. CVDs, cardiovascular diseases; SNP, single nucleotide polymorphism



Results

Genetically predicted plasma CoQ10 levels and risk of stroke

The IVW method revealed that genetically predicted plasma CoQ10 levels was linked to a reduced risk of stroke (OR = 0.803, 95% CI: 0.659–0.978, p = 0.029) (Figure 3 and Supplementary Figure 1,2). Subsequent analysis categorized stroke into hemorrhagic or ischemic types, we found genetically predicted plasma CoQ10 levels were inversely associated with AIS (OR = 0.792, 95% CI 0.651–0.964, p = 0.020) but not ICH (OR = 1.002, 95% CI 0.722–1.389, p = 0.992) (Figure 3 and Supplementary Figure 1,2). Further exploring the etiology of ischemic stroke indicated that genetically predicted plasma CoQ10 levels were linked to a reduced risk of SVS (OR = 0.512, 95% CI 0.294-0.892, p = 0.018) (Figure 3 and Supplementary Figure 1,2). However, no causal links were observed between genetically predicted plasma CoQ10 levels and the risk of LAS (OR = 0.917, 95% CI 0.551– 1.525, p = 0.737) or CES (OR = 1.043, 95% CI 0.715–1.523, p = 0.826) (Figure 3 and Supplementary Figure 1,2). Further details regarding the estimated effects of each SNP on stroke and its subtypes can be found in Supplementary Table 2. Our sensitivity analysis revealed no evidence of heterogeneities (all pval > 0.05) or pleiotropies (all pval > 0.05) in the estimated effects of plasma CoQ10 levels on stroke or its sub-

types. (Supplementary Table 4). Furthermore, the leave-one-out analysis demonstrated the robustness of the MR estimated effects, as no single SNP had a substantial impact on the overall results (Figure 4).

In summary, our MR analysis indicates that genetically predicted plasma CoQ10 levels are inversely associated with the risk of AS, showing a 20% decrease in AS risk for each one standard deviation increase in plasma CoQ10 levels. Additionally, we observed a potential link between genetically predicted plasma CoQ10 levels and AIS or SVS, with a one standard deviation increase in quantile-normalized plasma CoQ10 levels corresponding to a 21% decreased risk of AIS and a 49% decreased risk of SVS in stroke subtypes.

Genetically predicted plasma CoQ10 levels and risk of CVDs

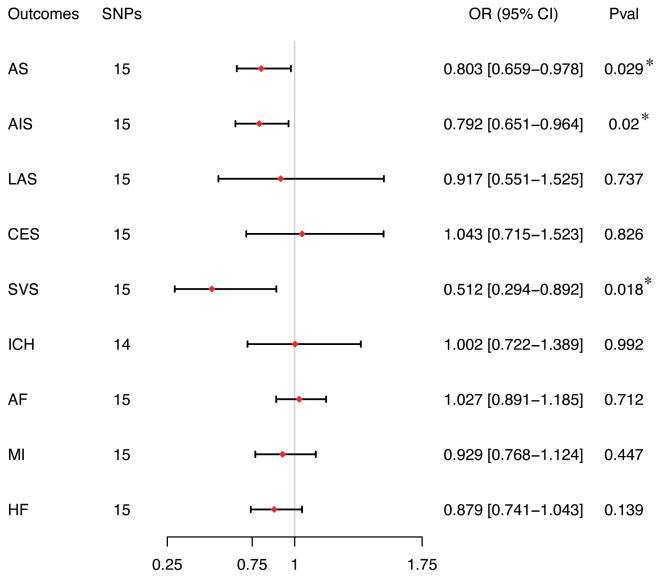
In general, our analysis revealed suggestive (but not statistically significant) evidence of an inverse association between genetically predicted plasma CoQ10 levels and HF risk (OR=0.879, 95% CI 0.741–1.043, p = 0.139). No significant causal link was found between genetically predicted plasma CoQ10 levels and the risk of AF (OR = 1.027, 95% CI 0.891–1.895, p = 0.712) or MI (OR = 0.929, 95% CI 0.768–1.124, p = 0.447) (Figure 3). Supplementary Table 3 provides more details regarding the estimated effects of each SNP on CVDs. Sensitivity analysis demonstrated no heterogeneities (all p > 0.05) or pleiotropies (all p > 0.05) in the estimated effects of plasma CoQ10 levels on CVDs (Supplementary Table 4). Additionally, the leave-one-out analysis indicated that the associations between plasma CoQ10 levels and CVDs were not primarily driven by any individual SNP (Figure 4).

Table 1. Genetic variants significantly associated with the plasma CoQ10 levels.

ID	Chr	OA	EA	EAF	β	SE	p	F statistic
rs9952641	18	G	A	0.10	0.063	0.011	1.31×10^{-8}	38.40
rs933585	2	G	A	0.43	-0.034	0.006	3.64×10^{-8}	105.08
rs686030	9	C	A	0.87	-0.044	0.009	1.39×10^{-6}	40.58
rs35996509	11	C	T	0.23	0.037	0.008	1.92×10^{-6}	63.82
rs150057671	6	G	A	0.32	0.034	0.007	2.44×10^{-6}	78.72
rs12480807	20	A	G	0.27	-0.033	0.007	2.66×10^{-6}	70.82
rs41313321	9	G	A	0.14	0.045	0.010	2.70×10^{-6}	42.05
rs17769758	12	G	A	0.11	-0.049	0.010	3.61×10^{-6}	33.03
rs9426691	1	A	G	0.27	-0.032	0.007	3.85×10^{-6}	69.28
rs61745943	12	A	T	0.04	0.071	0.015	3.93×10^{-6}	11.89
rs11591201	1	G	A	0.27	-0.034	0.007	4.02×10^{-6}	69.30
rs7141874	14	G	A	0.92	-0.057	0.012	4.02×10^{-6}	24.46
rs1462324	3	G	A	0.93	0.052	0.011	4.24×10^{-6}	21.80
rs283228	6	A	C	0.31	-0.030	0.007	4.77×10^{-6}	74.65
rs898838	2	T	C	0.47	0.028	0.006	4.84×10^{-6}	87.48

Abbreviations: Chr, chromosome; EA, effect allele; EAF, effect allele frequency; OA, other allele; SE, standard error; SNP, single nucleotide polymorphism.

Figure 3. Two-sample mendelian randomization analysis between plasma CoQ10 levels and stroke or cardiovascular diseases by IVW method. AF: atrial fibrillation; AS: any stroke; CES: cardio-embolic stroke; CI: confidence interval; HF: heart failure; ICH: intracranial hemorrhage; IS: ischemic stroke; IVW: inverse variance weighted; LAS: large artery atherosclerosis stroke; MI: myocardial infarction; OR: odds ratio; SNP: single nucleotide polymorphism; SVS: small vessel occlusion stroke.



Discussion

CoQ10, as a dietary supplement, has been widely used in the prevention and treatment of various CVDs. This study represents the first systematic exploration of the causal relationship between plasma CoQ10 levels and stroke or CVDs.

In this study, we utilized genetic variations associated with plasma CoQ10 levels as instrumental variables and employed MR to systematically analyze the causal relationship between plasma CoQ10 levels and stroke, as well as other CVDs. Our results show that (1) genetically predicted plasma CoQ10 levels were inversely associated with risk of AS and AIS; (2) regarding the etiology of ischemic stroke, genetically predicted plasma CoQ10 levels were associated with a lower risk of SAS, but not CES or LAS; (3) no causal links were identified between genetically predicted plasma CoQ10 levels and the risk of ICH, AF, MI and HF.

Our MR analysis revealed a significant protective association between genetically predicted plasma CoQ10 levels and SVS (OR=0.512, 95% CI=0.294–0.892, P=0.018), but not with CES. The relatively wide confidence interval may reflect:(1) Limited sample size of the SVS subgroup (n=6,399 cases) reducing estimate precision;(2) Effect heterogeneity in SVS pathophysiology (e.g., diverse small vessel pathologies such as arteriolosclerosis or CAA) potentially diluting IV strength;(3) Influence of outliers in the genetic instrument-exposure association. Despite the wide CI, the significant protective effect (OR<1, P<0.05) is consistent across sensitivity analyses, supporting further validation in larger cohorts.

Notwithstanding these statistical considerations, the observed subtype-specific protective effect for SVS warrants mechanistic interpretation. This specificity may stem from distinct pathophysiological mechanisms across stroke subtypes. SVS is primarily characterized by cerebral small vessel endothelial dysfunction and blood-brain barrier disruption, where oxidative stress plays a central role. CoQ10, as a potent mitochondrial electron transporter and lipid-soluble antioxidant, may mitigate oxidative damage in small vessel endothelial cells more effectively than in larger vessels. Small vessels exhibit higher mitochondrial density and metabolic activity, rendering their endothelium particularly vulnerable to reactive oxygen species (ROS)-induced injury. The observed protective effect could thus reflect CoQ10's ability to stabilize endothelial function and reduce oxidative stress in microvasculature, aligning with its known role in suppressing ROS generation and preserving nitric oxide (NO) bioavailability.

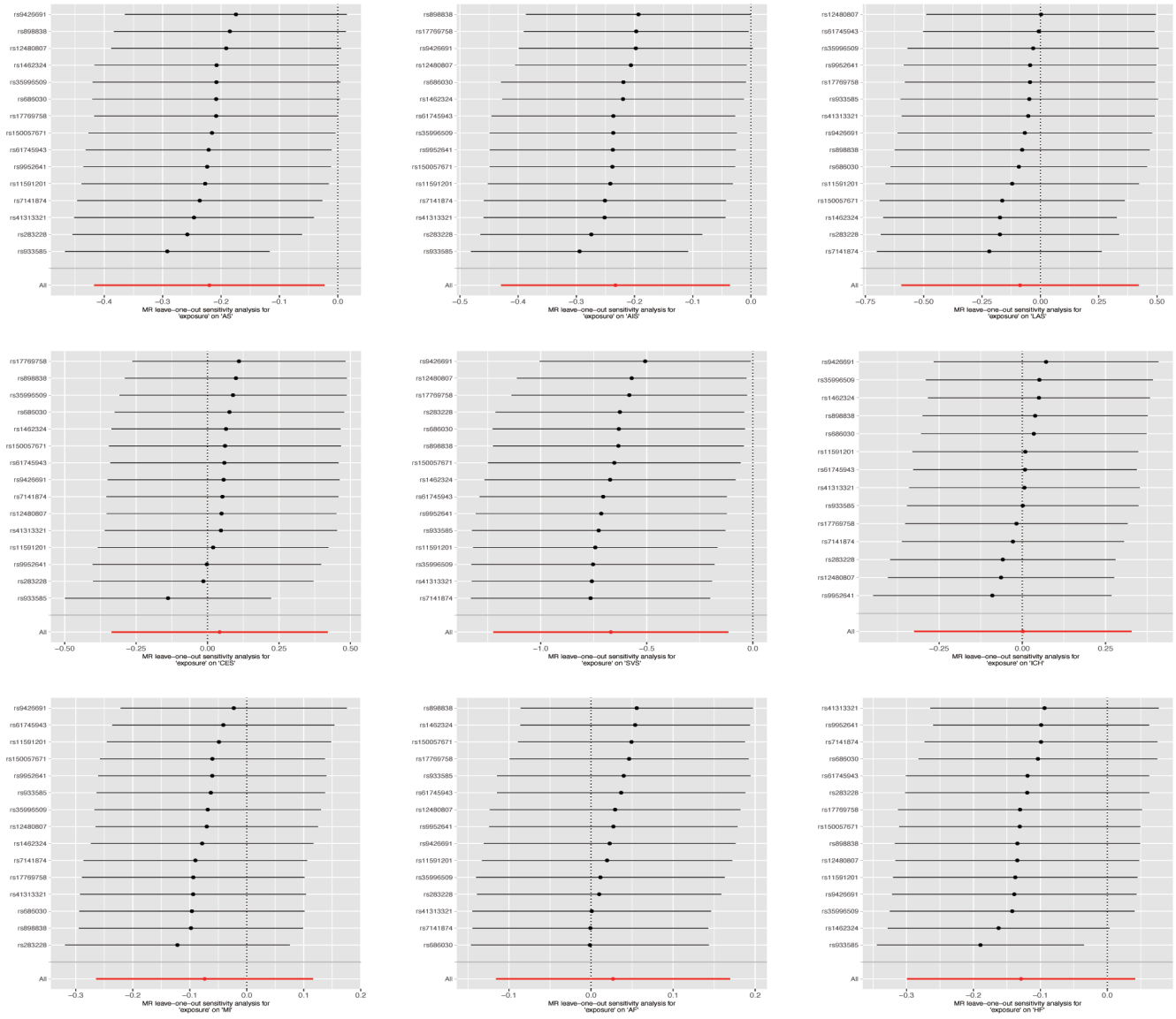
In contrast, LAS and CES involve thromboembolic mechanisms (e.g., atherosclerotic plaque rupture or atrial fibrillation-related clots) where oxidative stress may be less dominant. Additionally, the null association with intracranial hemorrhage (ICH) (OR=1.002, p=0.992) suggests CoQ10's effects are specific to ischemic pathways rather than hemorrhagic pathophysiology.

The absence of causal links between CoQ10 and cardiovascular outcomes like AF, MI, HF may reflect disease-specific mechanisms. For AF, electrical remodeling and fibrosis are driven more by ion channel dysfunction and inflammation than mitochondrial oxidative stress. Similarly, MI pathogenesis centers on acute plaque rupture and thrombosis, where CoQ10's antioxidant properties may not sufficiently counteract abrupt thrombotic events. Although prior RCTs suggest CoQ10 supplementation benefits HF patients, our null genetic association (OR=0.879, p=0.139) implies that plasma CoQ10 levels alone may not modulate HF risk through the pathways captured by our instrumental variables. This discrepancy could arise from differences in study design (e.g., MR assesses lifelong exposure vs. RCTs examining short-term supplementation).

Previous studies have reported associations between CoQ10 and stroke. It was found that stroke patients have lower plasma CoQ10 levels compared to the normal control group [14]. Additionally, early supplementation of CoQ10 in patients after acute ischemic stroke can improve neurological function scores, as measured by the National Institute of Health Stroke Scale (NIHSS) [15]. Our research further indicates a potential association between the plasma CoQ10 levels and the occurrence of stroke. This effect may be related to the significant antioxidant effect of CoQ10, which protects the vascular endothelium, prevents dysfunction of endothelial cells, and helps in the prevention of stroke [28, 29]. Due to the gradual decline in CoQ10 levels with increasing age, this decrease may become an important contributing factor to the occurrence of strokes in the elderly population. Previous studies have already demonstrated the supplemental role of CoQ10 in the adjunctive treatment of cardiovascular diseases such as hypertension and heart failure. This study further suggests that moderate supplementation of CoQ10 in the elderly population may provide a certain protective effect against the occurrence of strokes.

This study also has certain limitations. Due to the lack of large-scale GWAS results on plasma CoQ10, there may be a presence of weak instrument bias. However, F statistics for these exposures were well over 10, meaning that the magnitude of bias is likely to be small. Lastly, only people of European

Figure 4. Sensitivity analysis of the association between genetically predicted plasma CoQ10 levels and risk of (A) AS, (B) AIS, (C) SVS, (D) LAS, (E) CES, (F) MI, (G) HF, (H) ICH, (I) AF by leave-one-out method.



ancestry were included in the MR analysis, which limited the generalizability of the findings of the present MR study. The proportions of stroke etiologies vary based on race or ethnicity.

Conclusions

We found genetically predicted plasma CoQ10 levels to be inversely associated with AS, AIS and SVS. Our analysis did not identify any causal associations between genetically predicted plasma CoQ10 levels and CES, LAS, AF, MI and HF.

Author Contribution

Xuyang Liu conceived the analysis and drafted this manuscript. Yuyuan Gao and Xu Li were responsible for data collection. Xiaojing Yao executed data analysis. Yuming Xu contributed to the study concept and supervision. All authors have given their approval for the submitted version.

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Ethics Approval and Consent to Participate

The present study was based on the secondary analysis of data publicly available and ethics consent was not required.

Competing Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data Availability

The data that support the findings of this study are available from the corresponding author upon request. Codes used in current study are available from the corresponding author on reasonable request.

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