Assessing the role of blood pressure in amyotrophic lateral sclerosis: a Mendelian randomization study

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Abstract

Background

Observational studies have suggested a close but controversial relationship between blood pressure (BP) and amyotrophic lateral sclerosis (ALS). However, it remains unclear whether this association is causal. The authors employed a bidirectional two-sample Mendelian randomization (MR) approach to investigate whether there is a causal relationship between BP and ALS. Genetic proxies for systolic blood pressure (SBP), diastolic blood pressure (DBP), antihypertension drugs (AHDs), ALS, and their corresponding genome-wide association studies (GWAS) summary datasets were obtained from the updated largest studies. Inverse variance weighted (IVW) method was adopted as the main approach to examine the effect of BP on ALS and four other MR methods for sensitivity analyses. To exclude the interference between SBP and DBP, multivariable MR was used.

Results

We found that genetically determined increased DBP was a protective factor for ALS (OR = 0.978, 95% CI 0.960–0.996, P = 0.017), and increased SBP was an independent risk factor for ALS (OR = 1.014, 95% CI 1.003–1.025, P = 0.015). The high level of targeted protein of Calcium channel blocker (CCB) showed a causative relationship with ALS (OR = 0.985, 95% CI 0.971-1.000, P = 0.049). No evidence was revealed that ALS caused results change of BP measurements.

Conclusions

This study demonstrated that an increase in DBP is a protective factor for ALS, and increased SBP is independently risk for ALS, which may be related to sympathetic excitability. Blood pressure management is important in ALS, in which CCB may be a promising candidate.

Background

Amyotrophic lateral sclerosis (ALS) is a rarely fatal neurodegenerative disorder with unknown etiology[1]. The specifically grievous loss of motor neurons results in unrecoverable weakness and atrophy in muscles, even the respiratory and swallowing muscles are involved. The poor prognosis of ALS has brought a huge burden to social and economic development; therefore, it is urgent to find possible causes and corresponding early preventions for the disease. Recently, an increasing number of nonmotor symptoms have been reported in individuals with ALS, including impaired cognitive function[2] and pain[3]. That was largely neglected by doctors and recalled by more than 60% of patients, providing a new perspective to further investigation.

Hypertension is one of the most important risk factors for cardiovascular events and chronic kidney disease and the largest contributor to the global burden of disease[4], with a heritability of approximately 50%[5]. Current epidemiological studies revealed that the presence of premorbid hypertension is not related to ALS phenotypes and prognosis after adjusting for age[6]. For ALS patients, the incidence of hypertension is significantly lower than that in the general population (31.5% vs. 47.2%), and the presence of which does not affect the disease progression or survival of ALS[7, 8]. However, a study nominated hypertension as a risk factor for ALS because the duration of hypertension was associated with poorer ALS survival in univariate analysis[9]. Some studies have suggested that hypertension is a protective factor for ALS[10, 11]. Hypertension was reported to be associated with older ALS onset age[10]. A case-control study involving 123 Chinese ALS patients noted that hypertension could reduce the risk of ALS with Odds ratio (OR) equaling 0.526 (P = 0.015)[11]. Due to these inconsistent observational studies are susceptible to the influence of confounders, selection biases and potentially reverse causality, the causality between the results of blood pressure measurement and ALS remains largely ambiguous.

Mendelian randomization (MR) is a method for analyzing the causal relationship between exposure and an outcome by using genetic variations as instrumental variables (IVs) for exposure [12]. It is a promising statistical approach to overcome the limitations of observational studies and is similar to randomized controlled trials, in which risk alleles are naturally grouped to make powerful controls for reverse causality and confounders [13]. Therefore, in present study, we employed to a bidirectional two-sample MR study with the latest genome-wide association studies (GWASs) summary data to investigate the causal association between blood pressure and ALS.

Methods And Materials

Data sources

GWAS summary data collection

To assess blood pressure as comprehensively as possible and diminish false results, we regarded blood pressure as a continuous variable instead of a binary variable considering the presence of hypertension or not[14]. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were included as exposures separately, in order to reduce the impact of stratification. We obtained their summary-level data from the latest and largest GWASs involving more than 757600 European individuals, which performed a meta-analysis on the data from the UK Biobank and ICBP after adjusting for age, sex[15]. Blood pressure was measured by automated measurement or manual measurement. The mean SBP was 141.1 mmHg (standard deviation (SD) = 20.7), and the mean DBP was 84.3 mmHg (SD = 11.3).

We further included the targeted proteins of antihypertension drugs to mimic the effect of corresponding drugs on ALS. Proxies for the common classes of drugs that lower SBP (including angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), β-blockers (BBs), and calcium channel blocker (CCB)) based on DrugBank (https://www.drugbank.ca/) and GeneCards (https://www.genecards.org/).

ALS GWAS summary data available online were retrieved from a study by Nicolas, A. *et al* with 80610 European individuals, in whom the proportion of cases was 0.258[16]. All the patients had disease onset after 18 years of age and were diagnosed at probable or definite levels according to the El Escorial criteria.

Genetic variants selection

We estimated causal relationship between exposures and outcome by genetic instrumental variables (IVs) adequately related to exposure. SNPs independently ($r^2 < 0.001$) associated with blood pressure at the genome-wide significance level ($P < 5E-8$) were strictly selected. IVs for antihypertension drugs were all significantly associated with SBP ($P < 5E-8$) and in a relatively modest linkage disequilibrium (LD) correlation ($r^2 < 0.4$), which increased the variance explained proportion and statistical power, as described in detail elsewhere[17]. The genetic contribution of each allele changes in 1 SD SBP and DBP were 0.016 and 0.025, respectively.

IVs absent in the ALS dataset were replaced with proxies in strong LD ($r^2 > 0.9$) by searching in the SNiPA (http://snipa.helmholtz-muenchen.de/snipa3/). Those without reported proxies were removed from downstream MR analysis. Because of the calculation requirements, an exposure would be excluded when its available IVs were less than two. Altogether, 400 SNPs were identified as IVs for SBP, 397 SNPs were identified as IVs for DBP, 47 SNPs were identified as IVs for CCB, and 5 SNPs were identified as IVs for ALS in reverse MR estimates. An additional table shows this in more detail [see Additional file 1]. ACEI, ARB and BB were deleted due to insufficient IVs. In multivariable MR (MVMR) analysis (see below), 62 SNPs of SBP and 30 SNPs of DBP were excluded because they were palindromic with intermediate allele frequencies.

Two-sample MR

The theoretical basis of MR research relies on three assumptions: *assumption 1 exclusion restriction*, the selected genetic variations are not associated with other confounders; *assumption 2 relevance*, the selected genetic variations are significantly associated with exposure; and *assumption 3 independence pathway*, the selected genetic variations are significantly associated with the risk of outcome only through the pathway from exposure[18]. The strict selection of IVs satisfied assumption 1. Assumptions 2 and 3 were met through MR approaches.

We implemented the multiplicative random effects inverse variance weighted (IVW) method as the main approach to examine the overall causal relationship between exposure and ALS based on the effect of SNPs on blood pressure and the effect of SNPs on ALS[19]. To validate the results from the IVW method, we applied the weighted median method, simple median method [20], MR Egger method [21] and MR-PRESSO method as sensitivity analyses. To test potential pleiotropy, the MR Egger method, which reminds the presence of pleiotropy when the intercept significantly deviates from the origin, and MR-PRESSO analysis, which was used to detect the influence of outliers [22], were employed. The heterogeneity of SNPs used in IVW estimates was tested by Cochran's Q test, which suggests the

presence of heterogeneity when it is lower than the significant P value. Leave-one-out analysis and single SNP analysis were employed to evaluate the robustness of the significant results and the possibility of results being driven by a single SNP. We also calculated F statistics for IVs to demonstrate their strength. Given the close correlation between SBP and DBP, we employed multivariable MR (MVMR) to diminish the influence of the other result of blood pressure measurement and assess the causal association between SBP and ALS with regarding DBP as a covariate and the association between DBP and ALS with regarding SBP as a covariate. Additionally, we investigated reverse causality between blood pressure and ALS by bidirectional MR, which made ALS as an exposure and SBP and DBP as the outcomes. The process was shown in Fig. 1.

P values less than 0.05/3 were considered significant with Bonferroni correction. A P value between 0.017 and 0.05 was regarded as a suggestive significance level. All analyses were performed by “TwoSampleMR” package (version 0.5.6) in R software (version 3.6.3).

Results

In our study, proxies related to SBP, DBP and CCB were utilized to investigate the relationship between blood pressure and ALS first separately using 5 MR methods. To explore the possible reverse causality, the genetic proxies for ALS were also included in the bidirectional framework. The detailed results are shown in Table 1, Table 2 and the main results are visualized in Figs. 2 and 3.

Table 1
Summary of the causal effects of each trait on ALS via different MR methods

		DBP	SBP	CCB
N SNPs		397	400	47
F statistics		31000	29400	3180
Cochran's Q	Q	446.29	431.44	40.60
	p value	0.04	0.13	0.70
Simple median	OR (95% CI)	0.99 (0.98, 1.00)	1.01 (0.99, 1.02)	0.99 (0.96, 1.01)
	P value	0.18	0.62	0.25
Weighted median	OR (95% CI)	0.99 (0.98, 1.01)	1.01 (0.99, 1.02)	0.99 (0.96, 1.01)
	P value	0.25	0.59	0.28
MR Egger	OR (95% CI)	0.98 (0.96, 1.01)	1.01 (0.99, 1.03)	1.02 (0.97, 1.07)
	P value	0.17	0.16	0.49
Inverse variance weighted-mre	OR (95% CI)	0.99 (0.98, 1.00)	1.01 (1.00, 1.02)	0.99 (0.97, 1.00)
	P value	0.07	0.40	0.05
Inverse variance weighted-fe	OR (95% CI)	0.99 (0.98, 1.00)	1.01 (1.00, 1.01)	0.99 (0.97, 1.00)
	P value	0.06	0.38	0.064
MR Egger	intercept	0.002	-0.003	-0.01
	P value	0.46	0.25	0.17
MR-PRESSO	outlier-corrected	NA	NA	NA
	global test P value	0.04	0.14	0.72
	distortion test	NA	NA	NA
multivariable MR	OR (95% CI)	0.98 (0.96, 1.00)	1.01 (1.00, 1.03)	
	P value	0.017	0.015	

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure; ALS, amyotrophic lateral sclerosis; CCB, calcium channel blocker; OR, odds ratio; CI, confidence interval; MR, Mendelian randomization; SNP, single nucleotide polymorphism.

Table 2
Summary of the causal effects of ALS on blood pressure via MR methods

		DBP	SBP
N SNPs		5	5
Cochran's Q	Q	7.525	7.002
	p value	0.111	0.136
Simple median	OR (95% CI)	1.069 (0.877, 1.302)	1.22 (0.863, 1.726)
	P value	0.511	0.26
Weighted median	OR (95% CI)	1.094 (0.922, 1.297)	1.265 (0.934, 1.713)
	P value	0.304	0.129
MR Egger	OR (95% CI)	1.349 (0.863, 2.108)	1.686 (0.755, 3.765)
	P value	0.280	0.292
Inverse variance weighted-mre	OR (95% CI)	1.024 (0.841, 1.246)	1.126 (0.809, 1.566)
	P value	0.815	0.482
MR Egger	intercept	-0.045	-0.066
	P value	0.278	0.360
MR-PRESSO	outlier-corrected	NA	NA
	global test P value	0.203	0.223
	distortion test	NA	NA

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure; ALS, amyotrophic lateral sclerosis; CCB, calcium channel blocker; OR, odds ratio; CI, confidence interval; MR, Mendelian randomization; SNP, single nucleotide polymorphism.

We calculated that increased DBP had a potential protective effect on ALS (IVW, OR = 0.991, 95% confidence interval (CI) 0.982–1.001, P = 0.074) (Table 1, Fig. 2). The results of the simple median method (OR = 0.990, 95% CI 0.977–1.004, P = 0.178) and the MR Egger method (OR = 0.983, 95% CI 0.961–1.007, P = 0.165) are in the similar direction with wider CI and less precision. No influence of outliers in IVs was detected. The MR PRESSO global test provided a suggestive horizontal pleiotropy for IVs (P = 0.042), which is not supported by the MR Egger intercept (intercept = 0.002, P = 0.461). A slight heterogeneity of IVs was observed by Cochran's Q test (Q = 446.290, P = 0.041). When we adjusted SBP, the direct effect of DBP on ALS was enhanced. The risk of ALS was alleviated by 2.2% (OR = 0.978, 95% CI 0.960–0.996, P = 0.017) by per genetically predicted SD increasing in DBP (approximately 11 mmHg). In the bidirectional causal relationship exploration, no evidence noted that ALS caused changed estimated of DBP (IVW, OR = 1.024, 95% CI 0.841–1.246, P = 0.815) (Table 2).

In the initial analysis, SBP was calculated to be in null genetic relationship with ALS (IVW, OR = 1.006; 95% CI 0.998–1.015; P = 0.135) (Table 1, Fig. 2). Sensitivity analyses generated analogical results. We monitored no obvious horizontal pleiotropy of the IVs with the MR Egger method (intercept=-0.003, P = 0.246). No effect of the outliers existed, and no heterogeneity was detected in Cochran's Q test. Nevertheless, the effect of SBP on ALS was distinct after DBP was adjusted, which elevated the risk of ALS by 1.4% per genetically predicted SD unit increase in SBP (OR = 1.014, 95% CI 1.003–1.025, P = 0.015). No effect of ALS on SBP was manifested (OR, 1.126, 95% CI 0.809–1.567, P = 0.482) (Table 2).

Taking the deleterious effect of higher SBP on ALS into consideration, we probed the role of antihypertension drugs in ALS (Table 1, Fig. 3). Because of the limited IVs, ACEIs, ARBs and BBs were excluded from the downstream analyses. CCB indicated a suggestive protective role in ALS (IVW, OR = 0.985; 95% CI 0.971-1.000; P = 0.049), which was not replicated in additional MR analyses. No influence of the outliers, no heterogeneity and no horizontal pleiotropy were detected.

Discussion

Based on large-scale blood pressure GWASs and ALS GWAS, we conducted a two-sample MR analysis and found that an increased DBP may be a protective factor for ALS, while SBP may be a risk factor for ALS in the European population. The effects were more obvious after adjusting for the other result of blood pressure measurement, shedding light on the pathogenesis of ALS outside of the motor system. Furthermore, CCB was a common antihypertension drug indicated to have a protective effect on ALS in our study, perhaps to play a potential role in ALS management.

Our study declared the role of blood pressure in ALS in detail, in which DBP may play a leading role in protection, while SBP may play a role in the risk aspect. The combination of low DBP and high SBP is an indicator of increased large arterial stiffness and widely observed in elderly people, which reconciles our results. Although Bandres-Ciga *et al*. reported a contrary conclusion to ours[23, 24], we carefully stated the causative relationship between blood pressure and ALS by doubling the sample size. Currently, SBP is the main target in blood pressure management[25], because elevation of which is more common and has a greater effect on cardiovascular outcomes[26]; therefore, we focused more on the risk effect of SBP, which supports previous study identifying hypertension as a risk factor for ALS[6, 9]. We investigated the effect of antihypertension drugs on ALS in consideration of the detrimental effect of SBP on ALS and hope to find a potential drug target for ALS, in which CCB suggests a protective role for ALS. The protective effect of ACEI on ALS was also nominated in the year 2015[27], but we can’t verify which due to the limited IVs. Additionally, observational evidence indicated the presence of hypertension in ALS patients was not consistent with that in healthy controls[7, 8] and the blood pressure of SOD1 G93A mice was lower than that of their wild-type siblings[28]. Aiming to clarify whether the difference in blood pressure of ALS individuals and healthy controls is a symptom caused by the disease or not, we performed a reverse direction MR to determine the effect of ALS on blood pressure. No result supported the view that ALS caused observed value changes in DBP or SBP.

The underlying biological mechanism needs to be studied further. Results generated with high-resolution magnetic resonance imaging suggested the link between low DBP, high SBP and cerebral hypoperfusion[29], and this hypoperfusion precedes the neurodegenerative pathological changes[30]. It brings insufficient energy to neurons and triggers neuroinflammation and blood-brain barrier disruption, which can serve as a pathological feedforward to ALS[31]. Sympathetic excitability enhancement may also play a role in the pathway of SBP to ALS, which increases SBP and aggravates oxygen consumption in ALS. Relatively low oxygen tension promotes the cleavage of reductive bonds in the SOD1 protein and increases the disordered and aggregated SOD1 protein, which intensifies ALS pathological spread[32]. Recently, some sympathetic dysfunctional symptoms have been reported in ALS patients, including decreased heart rate variability, cardiac sympathetic nerve degeneration[33, 34], and decreased norepinephrine levels[35].

The intervention of calcium ion (Ca^{2+}) seems to be a promising target for ALS management. While it should be with caution when explained into the expected pharmacologic efficacy because of the disparity between the genetically predicted lifelong exposure to a biomarker and the short-term intervention. The latent molecular mechanism is traceable. Recently, a study reported an elevated basal intracellular calcium level in mutant TDP43 motor neurons, suggesting Ca^{2+} dyshomeostasis in ALS[36]. Ca^{2+} dysfunction in lysosomes is considered a vital pathological clue to the death of motor neurons in ALS[37]. The abnormal Ca^{2+} level facilitates the functional defects of lysosomes and autophagic flux, which in turn hinders the removal of misfolded toxic proteins such as SOD1, TDP43, and FUS and leads to further development of the disease[38]. Thus, the protection of CCB may partly be led by the clearance of intracellular calcium buildup in neurons[39]. The influence proportion of CCB on ALS via the SBP pathway is still unclear.

Our study is the first to provide insights for the prospective management of blood pressure in ALS as far as we concerned. Our analysis is based on unitary race and the largest current GWASs, ensuring the quality and statistical power of the study. Nevertheless, there are still some shortcomings to declare. The limitations of methodology have been reviewed elsewhere[40]. In addition, some overlapping SNPs were shared by SBP and DBP, which may disturb the results; therefore, we conducted MVMR analysis, sensitivity analysis and horizontal pleiotropy analysis to ensure the reliability of our results. In addition, there may be some mediators between blood pressure and ALS (including body mass index (BMI), low-density lipoprotein, education), and our study did not calculate the proportion of power explained by them separately at present. Moreover, the potential effect of blood pressure on the prognosis of ALS was deduced without verified with MR approaches due to the lack of relevant GWAS data (eg: clinical progression pattern, cognitive impairment, and survival).

Conclusion

This study provides genetic supports for a causal effect of BP and ALS that increased DBP has a protective effect on ALS and increased SBP is risk for ALS, which may be related to sympathetic excitability. Blood pressure management is important in ALS, and CCB may be a promising candidate.

Abbreviations

ALS: amyotrophic lateral sclerosis

BP: blood pressure

MR: Mendelian randomization

SBP: systolic blood pressure

DBP: diastolic blood pressure

AHD: antihypertension drug

GWAS: genome-wide association study

IVW: inverse variance weighted method

CCB: Calcium channel blocker

IV: instrumental variable

SD: standard deviation

ACEI: angiotensin converting enzyme inhibitor

ARB: angiotensin receptor blocker

BB: β-blocker

LD: linkage disequilibrium

MVMR: multivariable MR

CI: confidence interval

Ca2+: calcium ion

BMI: body mass index

SNP: single nucleotide polymorphism

OR: odds ratio

Declarations

Ethics approval and consent to participate

This study was approved in terms of its ethics by the relevant research ethics committee and the Review Committee of Peking University Third Hospital. Consent to participate is not applicable.

Consent for publication

All authors agreed to the publication of this article.

Conflict of Interest

The authors do not have any conflicts of interest to declare.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Code availability

Codes generated or used during the study are available from the corresponding author by request.

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Authors' contributions

Dongsheng Fan designed the study, and Tao Huang supervised the work. Dongsheng Fan and Tao Huang contributed equally to this paper. Kailin Xia analyzed the data and wrote the manuscript. Lu Tang revised the draft. Linjing Zhang and Tao Huang supervised data analysis.

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Figures

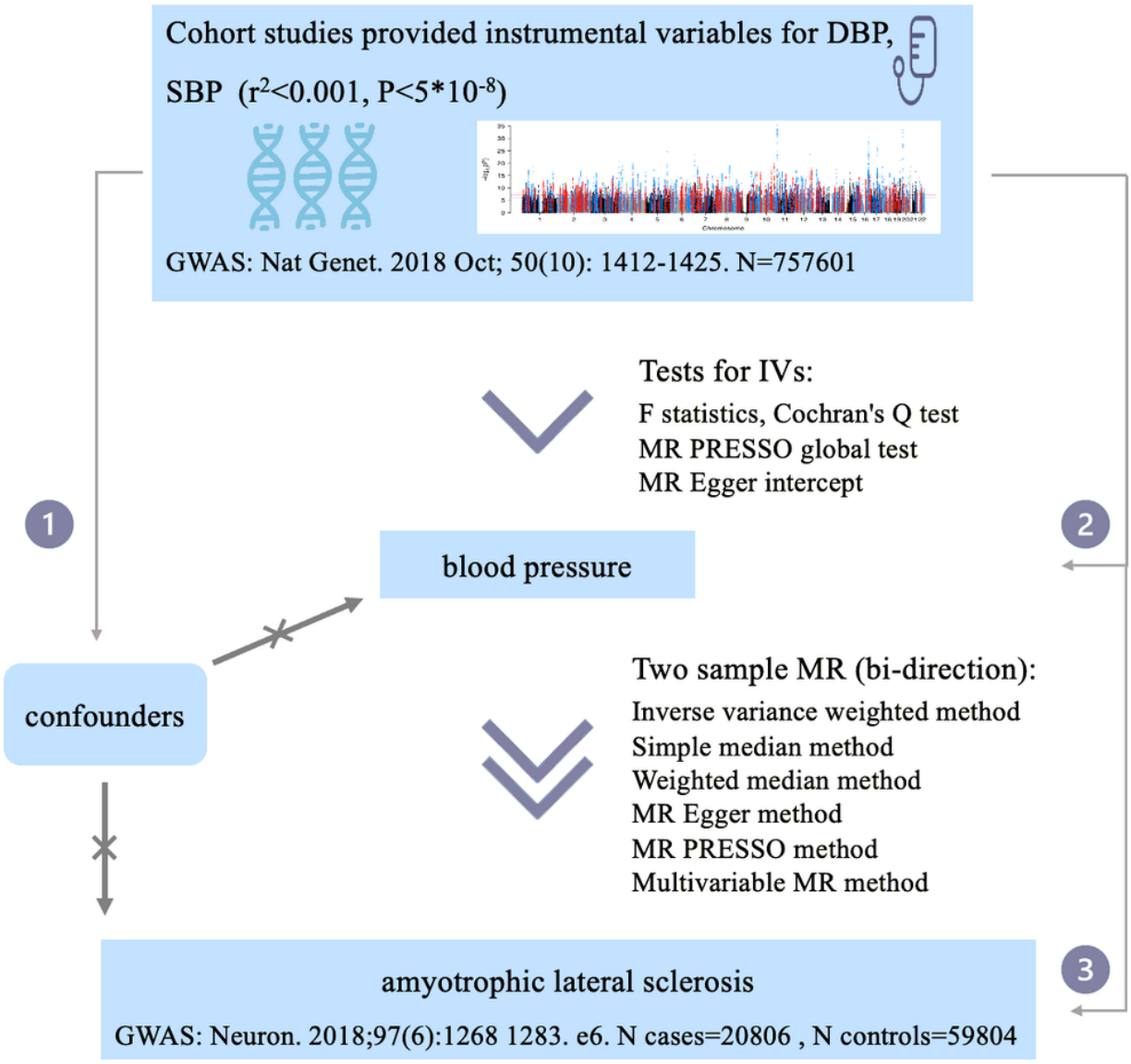

Figure 1

Flow chart showing the process for the Mendelian randomization analyses. The number in the line indicates 3 key assumptions for MR. Assumption 1: The selected genetic variations are not associated with other confounders. Assumption 2: The selected genetic variations are significantly associated with the exposure. Assumption 3: The selected genetic variations are significantly associated with the risk of the outcome only through the pathway from exposure. GWAS, genome-wide association studies; MR, Mendelian randomization; SNP, single nucleotide polymorphism; DBP, diastolic blood pressure; SBP, systolic blood pressure.

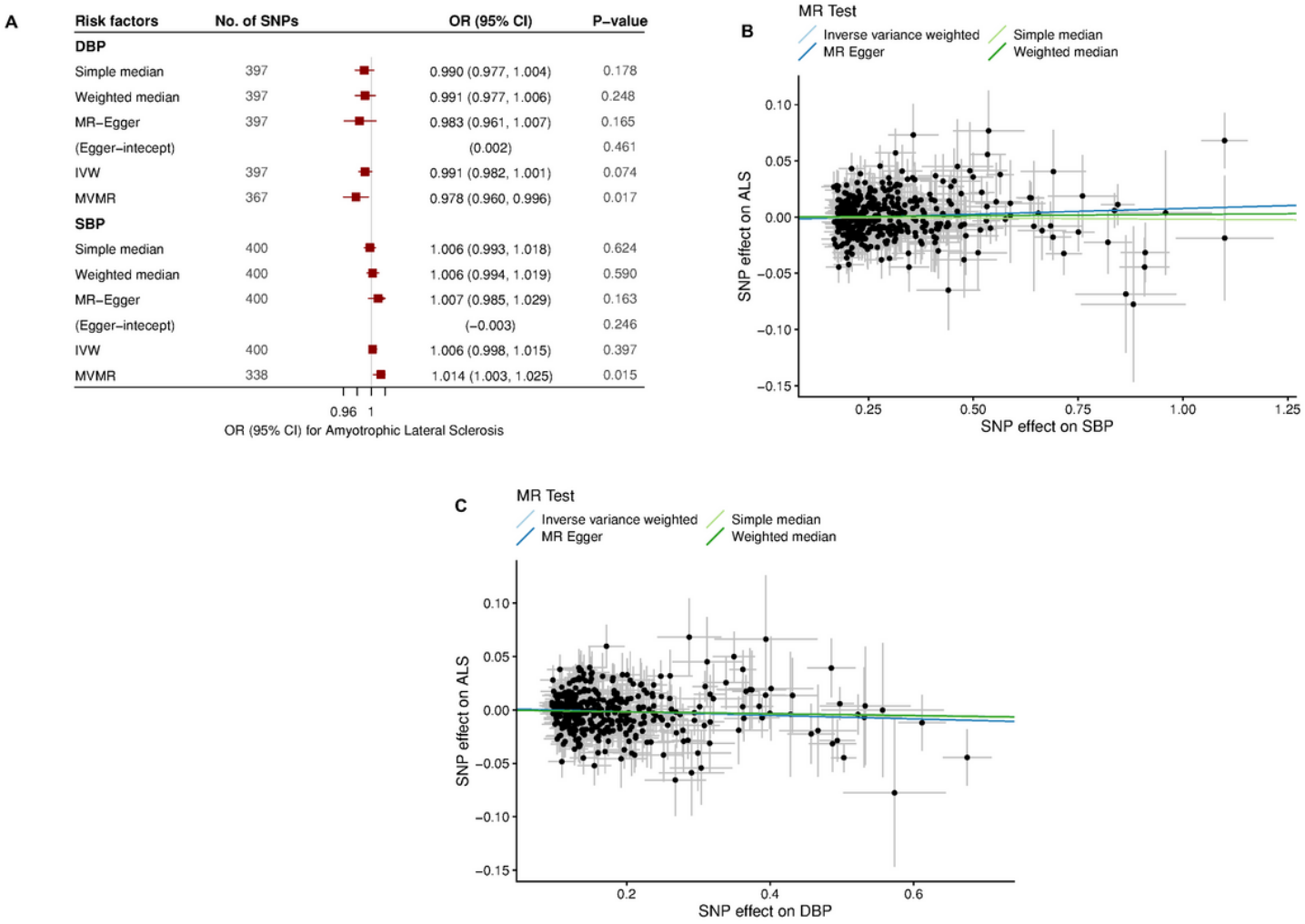

Figure 2

Flow chart showing the process for the Mendelian randomization analyses. The number in the line indicates 3 key assumptions for MR. Assumption 1: The selected genetic variations are not associated with other confounders. Assumption 2: The selected genetic variations are significantly associated with the exposure. Assumption 3: The selected genetic variations are significantly associated with the risk of the outcome only through the pathway from exposure. GWAS, genome-wide association studies; MR, Mendelian randomization; SNP, single nucleotide polymorphism; DBP, diastolic blood pressure; SBP, systolic blood pressure.

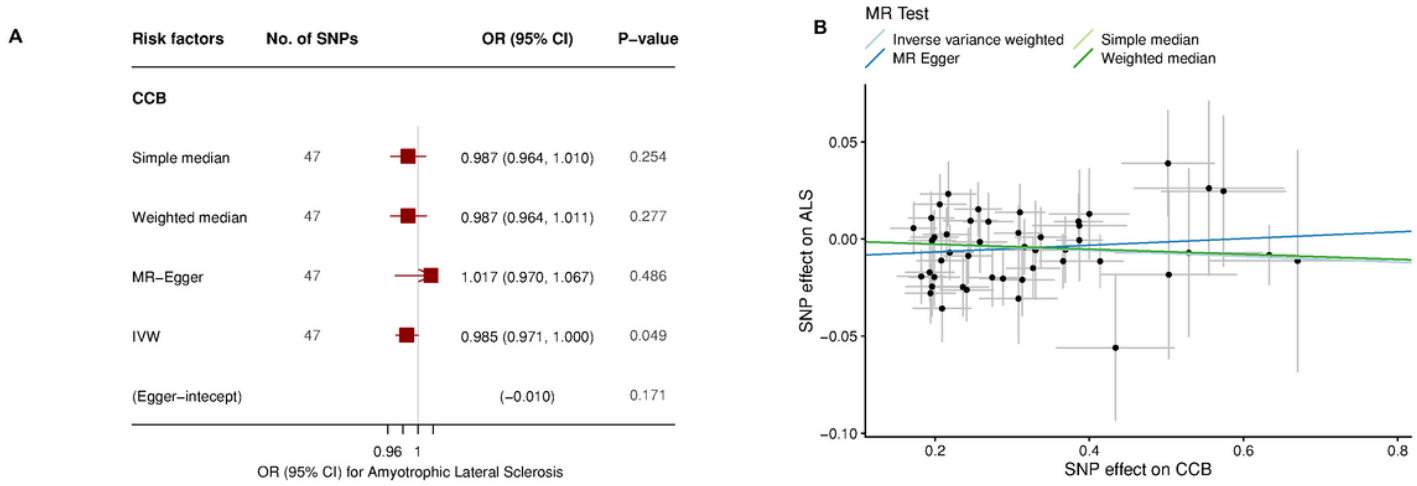

Figure 3

The relationship between CCB and ALS. A. The main results of the effects of genetically predicted CCB on ALS via MR approaches. B. Scatter plot of the SNP effects on CCB versus ALS, with the slope of each line corresponding to the estimated MR effect per method. OR, odds ratio; CI, confidence interval; MR, Mendelian randomization; SNP, single nucleotide polymorphism; CCB, calcium channel blocker; ALS, amyotrophic lateral sclerosis.

Supplementary Files

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- additionalfile1.docx