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Association of plasma C-reactive protein with ischemic stroke: A Mendelian randomization study

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Running title: Association of plasma C-reactive protein with Ischemic Stroke

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Background and purpose: Elevated C-reactive protein (CRP) is associated with an increased risk of ischemic stroke (IS). However, the causality of this association is uncertain. We aim to investigate whether genetically raised plasma CRP concentration levels are associated with the IS based on the Mendelian randomization (MR) method.

Methods: Based on the National Center for Biotechnology Information SNP database, the Chinese online genetic database as well as previously published studies, four CRP-associated SNPs alleles (rs1130864, rs1205, rs876537 and rs3093059) with minor allele frequency (MAF) ≥ 0.15 were selected and the concentration levels of CRP were measured in 378 first-ever IS patients and 613 healthy controls.

Results: Three SNPs were chosen and used as instrumental variables. The adjusted odds ratios (ORs) (95% confidence interval (95% CI)) of IS per addition of the modelled allele were 1.07 (0.79-1.45) for rs876537, 0.99 (0.73-1.35) for rs1205 and 1.08 (0.71-1.65) for rs3093059. The OR (95% CI) of IS for the plasma CRP ≥ 2.0 mg/L was 2.19 (1.06-4.53) as compared with < 2.0 mg/L. The adjusted OR (95% CI) of IS per genetically predicted 10% higher CRP concentration, based on the three SNPs as the instruments, was 1.02 (0.94-1.11). Furthermore, the similar results were obtained with the adjusted ORs (95% CI) of 1.00 (0.88-1.13) and 1.04 (0.93-1.16), respectively, for large-artery atherosclerosis and small-artery occlusion per genetically predicted 10% higher CRP concentration.

Conclusions: This MR study provides no clear support that elevated CRP concentration is causally associated with the risk of IS.

Keywords: C-reactive protein; SNP; ischemic stroke; Mendelian randomization; Odds ratio

Introduction

Ischemic stroke (IS) is the most common type of stroke and accounts for about 80%-85% of stroke cases [1]. Over the last few decades, inflammation has been proposed to play an important role in the pathogenesis of IS [2, 3]. C-reactive protein (CRP) is deemed to be the most extensively studied marker of inflammation and atherosclerosis [4]. Previously, some conventional studies have reported the direct association between the raised levels of CRP and the enhanced risk of IS [5, 6] and are susceptible to confounding and reverse causation bias. Mendelian randomization (MR) approach uses the genetic variants associated with the phenotype to determine the causal association between the phenotype and disease risk [7, 8]. Some previous MR studies provide no evidence in European ancestry individuals that the CRP concentration plays a major role in the development of IS [9, 10]. It remains unclear, however, whether the associations are causal in the Chinese population. Therefore, we implemented a MR approach to investigate the effect of CRP level on IS based on a case-control study of the Chinese population.

Methods

Study Population

A total of 851 first-ever IS patients were recruited from Beijing Tiantan Hospital, Capital Medical University during 2009-2010. IS was diagnosed in accordance with the World Health Organization criteria [11]. According to the TOAST criteria, all IS patients were further classified into different stroke subtypes: large-artery atherosclerosis (LAA), small-artery occlusion (SAO), cardioembolism, other determined etiology (SODE), and undetermined etiology (SUE) [12], which was conducted by two unified training neurologists. The exclusion criteria included head trauma, primary and metastatic neoplasms, post-seizure paralysis, previous history of stroke, intracerebral hemorrhage, or infectious diseases. Healthy controls were recruited from the physical examination population in Xuanwu Hospital, Capital Medical University during the same period. A total of 378 patients with IS and 613 healthy subjects were included in the final analysis (Figure 1 (A)). Based on the allele proportion for associated SNPs-CRP of previous study [13], the sample size of this study is larger than the ones needed under the condition of type-I error being 0.05 and

power being 0.80. This study was approved by the Institutional Review Board of Capital Medical University and was in accordance with the principle of Declaration of Helsinki. Written informed consent provided by all participants prior to the participation.

Genotyping

SNPs were selected within the *CRP* gene from National Center for Biotechnology Information SNP database (http://www.ncbi.nlm.nih.gov/SNP) and the Chinese dataset of an online genetic database (http://www.ensembl.org) according to reported associations with IS [14, 15] and minor allele frequency (MAF) $\geq$ 0.15. At last, four SNP alleles (rs1130864, rs876536, rs1205, and rs3093059) were selected for analysis. Genomic DNA was extracted from peripheral white blood cells using blood genome DNA extraction kits (BioTeke, Beijing, China). Genotype sampling was performed on the SNP's of interest by using the Mass ARRAY system (Sequenom, Inc., San Diego, CA, USA).

Biochemical Analyses and Other Covariates

Venous blood samples were collected on the next morning of overnight fasting after admission of each inpatient. Plasma high-sensitivity CRP (hs-CRP) levels were measured using the ELISA kits (DuoSet, R&D). Weight and height were measured using the standard procedures, from which body mass index (BMI) was calculated. Clinical data including systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were all tested via standard methods in the clinical laboratory of Beijing Tiantan Hospital [16].

Statistical Analysis

Demographic and clinical characteristics were repesented as frequencies (%) for categorical data and mean ± standard deviation (SD) for continuous variables underlying the normal distribution, otherwise the medians (interquartile ranges) were used. The *Chi*-square test was also used to test Hardy-Weinberg equilibrium (HWE). According to the method of avoiding the potential for

established disease to influence the size of the genotype–phenotype correlation in some previous studies [17, 18], we evaluated the association between SNP and CRP based on the data of healthy participants. A linear regression model was fitted for each SNP, with natural log-transformed CRP as the dependent variable and adjusted for age, sex, BMI, blood pressure, FPG, TC, TG, HDL-C and LDL-C. The β coefficients were obtained from the linear regression model with natural log-transformed CRP concentration. The percentage difference in CRP concentration per modelled allele was obtained from the expression $(\exp[\beta]-1)\times 100$.

In the main analyses, we summarized the ratio estimates for the individual genetic variants by using the conventional fixed-effect inverse variance weighted (IVW) method. In addition, sensitivity analyses were conducted by using the weighted median (WM), penalized weighted median (PWM), and MR-Egger regression methods. Pleiotropy was evaluated based on the intercept obtained from the MR-Egger analysis [19, 20]. All results were presented as the odds ratio (OR) of IS (or different subtypes of IS) per 10% increase in the CRP concentration.

For all analyses, a two-tailed P value < 0.05 was considered to be statistically significant. All statistical analyses were performed using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) and IBM SPSS Statistics for Windows version 25.0 (IBM Corp., Armonk, NY, USA).

Results

The clinical characteristics are described in Table 1. The IS patients were more likely to be older males with higher BMI, SBP, DBP, FPG and CRP levels and lower TC, HDL-C and LDL-C levels (Table 1 and Figure 1 (B)).

For four *CRP* polymorphisms, rs1130864, rs876537, rs1205 and rs3093059, the genotypic distribution, among the healthy controls, was in accordance with the HWE (P values = 0.331, 0.801, 0.413 and 0.449, respectively). Of the four SNPs, three (rs876537, rs1205 and rs3093059) were significantly associated with plasma CRP levels. For the polymorphism rs876537, the C allele was associated with increased CRP levels of 20.20% as compared with T allele (Table 2). Significant differences in the plasma CRP levels were also associated with the rs1205

polymorphism (C allele *vs.* T allele, 21.17% increase) as well as the rs3093059 polymorphism (G allele *vs.* A allele, 29.82% increase).

For the three *CRP*-associated SNPs, none was associated with the IS risk (Table 3), and the adjusted ORs (95% CI) for IS per addition of the modelled allele were 1.07 (0.79-1.45) for rs876537, 0.99 (0.73-1.35) for rs1205 and 1.08 (0.71-1.65) for rs3093059 after adjusting age, sex, BMI, blood pressure, TC, TG, HDL-C and LDL-C. Moreover, there was also no association between LAA or MAO and the three SNPs (Table 3).

Plasma CRP was not associated with IS when CRP levels were plugged in the logistic regression (Model 1 in Figure 2 (A)) after adjustment for age, sex, BMI, blood pressure, FPG, TC, TG, HDL-C and LDL-C. CRP ≥ 2.0 mg/L versus < 2.0 mg/L was associated with an OR (95% CI) of 2.19 (1.06-4.53) for IS (Model 2 in Figure 2 (A)), and CRP ≥ 2.0 mg/L was also associated with an OR (95% CI) of 2.24 (1.08-4.67) for IS compared with CRP < 1.0 mg/L (Model 3 in Figure 2 (A)).

With the instrumental variable approach, we noted null association between CRP concentration and risk of IS. The OR (95% CI) of IS per genetically predicted 10% higher CRP concentration conferred by the three CRP-elevating alleles was 1.02 (0.94-1.11, *P* value = 0.676) by performing IVW method (Figure 2 (B)). Two sensitivity analyses performed by the WM and PWM methods yielded similar results (Figure 2 (B)). In the MR-Egger analysis, there was no clear evidence of pleiotropy (intercept is −0.064 and *P* value = 0.915) and causal effect (*P* value = 0.862) (Figure 2 (B)).

Furthermore, the ORs (95% CIs) of LAA and SAO per genetically predicted 10% higher CRP concentration was 1.00 (0.88-1.13) and 1.04 (0.93-1.16) by applying IVW method. In the WM and PWM analyzes for the two subtypes of strokes, there was also no causal effect (*P* values = 0.857 and 0.866, respectively for LAA and SAO) (Figure 3).

Discussion

Our results show no causal association between the genetically raised CRP concentration and IS. Thus, our study demonstrates a decreased probability of that the CRP levels have a clinical

significant impact on the risk of IS.

Elevated plasma CRP has been regarded as a significant risk factor for the IS and coronary ischemic disease [5, 21, 22]. In one meta-analysis, the adjusted relative risk (95% CI) for IS was 1.27 (1.15-1.40) [23]. In another meta-analysis study, 1-SD increment in CRP was also associated with a 46% (95% CI: 27%-67%) increased risk of IS [24]. The associations are possibly explained by reverse causation bias or confounding from atherosclerosis, influenza or common cold. Possible mechanisms can explain the prognostic value of CRP in IS which is known to be caused by atherosclerosis, whereas inflammation is directly related to the development of atherosclerotic lesions [25] and thus, instability of the atheroma [26].

Our findings corroborate the results from a case-control study of serum CRP concentration and genotype in relation to IS [27]. Consistent with our results, that study showed the similar results with possible association between four genetic variants of the *CRP* gene with CRP levels and no association of the latter with the IS [27]. However, the causal effect of CRP on IS was not studied in that study. Our results also agree with those from previous studies, including the null findings of in vivo studies of atherosclerosis which have involved either injection of CRP in different species or transgenic expression of CRP in mice and rabbits [28, 29]. Previous MR studies have assessed that elevated CRP was not associated with coronary heart disease [30], COPD [31] or components of metabolic syndrome [32]. In terms of instrumental variable analysis, it suggests that studies seeking to test the inflammation hypothesis in IS should examine the inflammatory mediators other than CRP.

This study has several major strengths. To the best of our knowledge, this is the first MR study assessing the plasma CRP levels in relation to the risk of IS and different subtypes of IS in a Chinese population. Furthermore, healthy controls were randomly recruited from the general population in the same geographical areas, which could reduce the selection bias of results. Moreover, we carefully selected specific polymorphisms to capture the range of common variability in the *CRP* gene which were more exclusively associated with CRP than the other variants. Furthermore, there were no pleiotropic effects of the four genetic variants of interest.

Lastly, in order to evaluate with high credibility, four methods including the conventional IVW, WM, PWM, and MR-Egger methods were jointly performed.

This study also has some limitations. First, we used a relatively small sample size to explore the causal relationship between CRP and IS with the power less than 0.90. Furthermore, neither of MRs for LAA and SAO is effective with the power larger than 0.80. Further validation of the results in larger independent populations is necessary in our future work. Second, there is a possibility of residual confounding by unrecognized effects of genotypes on other risk factors and by adaptation during early life to compensate for genetically raised CRP concentrations, though there is no evidence of their impact in the current context. Third, our analyses only involved the Chinese IS patients and healthy subjects, so the results obtained may not be translatable to non-Chinese populations.

In summary, our results show that SNPs related to CRP are not associated with the risk of IS. This MR study provides no evidence that the circulating CRP concentration plays a major role in the development of IS in the individuals of Chinese ancestry.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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Figure Legends

Figure 1. Profile of the ischemic stroke cases and the healthy controls. **(A)**. Ischemic stroke cases identified from patients and the healthy controls recruited from an examination population during 2009-2010. **(B)**. The bar plot of mean with standard error comparing the CRP levels in the ischemic stroke cases with the healthy controls.

Figure 2. Odds ratios of IS according to levels of plasma CRP adjusted for main characteristics including age, sex, BMI, blood pressure, FPG, TC, TG, HDL-C and LDL-C. **(A)**. Logistic regression analysis with the CRP levels. **(B)**. Mendelian randomization analysis by using the three significant SNPs as the instruments.

Figure 3. Mendelian randomization analysis of two subtypes of IS according to levels of plasma CRP adjusted for main characteristics including age, sex, BMI, blood pressure, FPG, TC, TG, HDL-C and LDL-C. **(A).** Large-artery atherosclerosis. **(B).** Small-artery occlusion.

Table 1 Clinical characteristics of the participants

Variables	Cases (n=378)	Controls (n=613)	*P* value
Age, years	55.92 (13.25)	47.90 (5.51)	< 0.001
Male	284 (75.1)	196 (32.0)	< 0.001
BMI, kg/m^2	25.94 (4.91)	24.60 (3.17)	< 0.001
SBP, mmHg	143.86 (22.53)	117.82 (14.74)	< 0.001
DBP, mmHg	85.67 (13.48)	79.12 (10.47)	< 0.001
FPG, mmol/L	5.79 (2.17)	5.36 (0.85)	< 0.001
TC, mmol/L	4.02 (1.06)	5.14 (0.92)	< 0.001
TG, mmol/L	1.60 (1.20)	1.56 (1.41)	< 0.001
HDL-C, mmol/L	1.08 (0.62)	1.63 (0.35)	< 0.001
LDL-C, mmol/L	2.43 (0.88)	2.81 (0.72)	< 0.001
CRP, mg/L	1.03 (1.33)	0.71 (1.39)	< 0.001
Subtype, n(%)		-	-
LAA	133 (35.2)	-	-
SAO	197 (52.1)	-	-
CE	25 (6.6)	-	-
SODE or SUE	23 (6.1)	-	-

Data are shown as the mean (SD) or n (%); BMI: body mass index; CRP: C-reactive protein; DBP: diastolic blood pressure; FPG: fasting plasma glucose; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides; LAA: large-artery atherosclerosis; SAO: small-artery occlusion; CE: Cardioembolism; SODE: stroke of other determined etiology; SUE: stroke of undetermined etiology

Table 2 Association of CRP concentration with the tag SNP variants

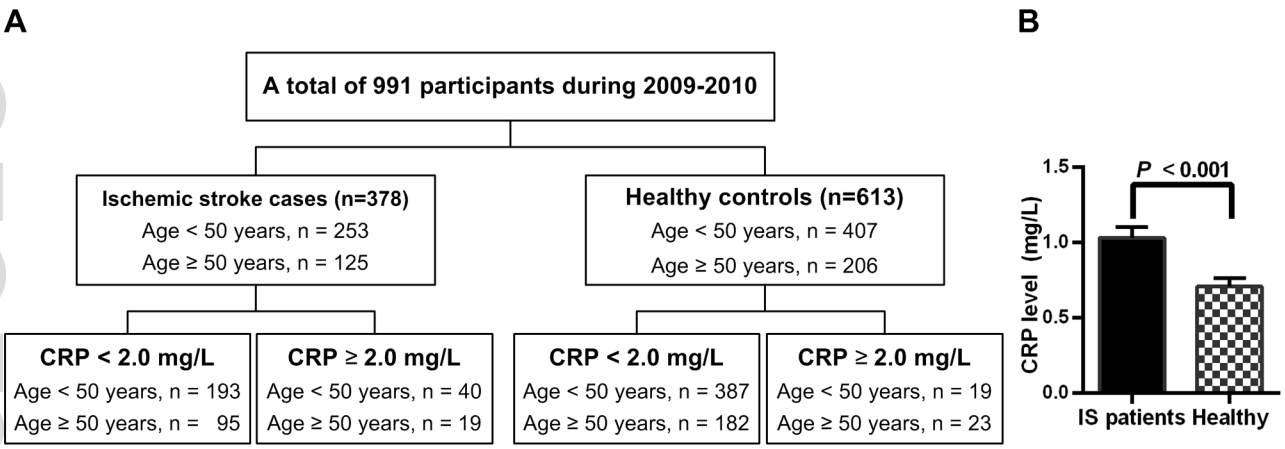
CRP SNPs	minor allele frequency (MAF)	Modelled allele	Change of CRP level for modelled allele (%)	*P* value*
rs1130864	A (0.09)	A	-3.05	0.852
rs876537	C (0.41)	C	20.20	**0.023**
rs1205	C (0.41)	C	21.17	**0.018**
rs3093059	G (0.16)	G	29.82	**0.016**

*Adjusted for age, sex, BMI, blood pressure, TC, TG, HDL-C and LDL-C.

Table 3 Association of ischemic stroke and two subtypes of ischemic stroke with the tag SNP variants

CRP SNPs	Modelled allele	OR (95% CI) of IS per modelled allele	*P* value*
Ischemic stroke			
rs876537	C	1.07 (0.79-1.45)	0.684
rs1205	C	0.99 (0.73-1.35)	0.964
rs3093059	G	1.08 (0.71-1.65)	0.713
Large-artery atherosclerosis			
rs876537	C	1.15 (0.73-1.79)	0.552
rs1205	C	0.88 (0.56-1.38)	0.563
rs3093059	G	0.97 (0.52-1.81)	0929
Small-artery occlusion			
rs876537	C	1.17 (0.80-1.73)	0.414
rs1205	C	1.04 (0.71-1.53)	0.828
rs3093059	G	1.07 (0.62-1.83)	0.814

*Adjusted for age, sex, BMI, blood pressure, TC, TG, HDL-C and LDL-C.



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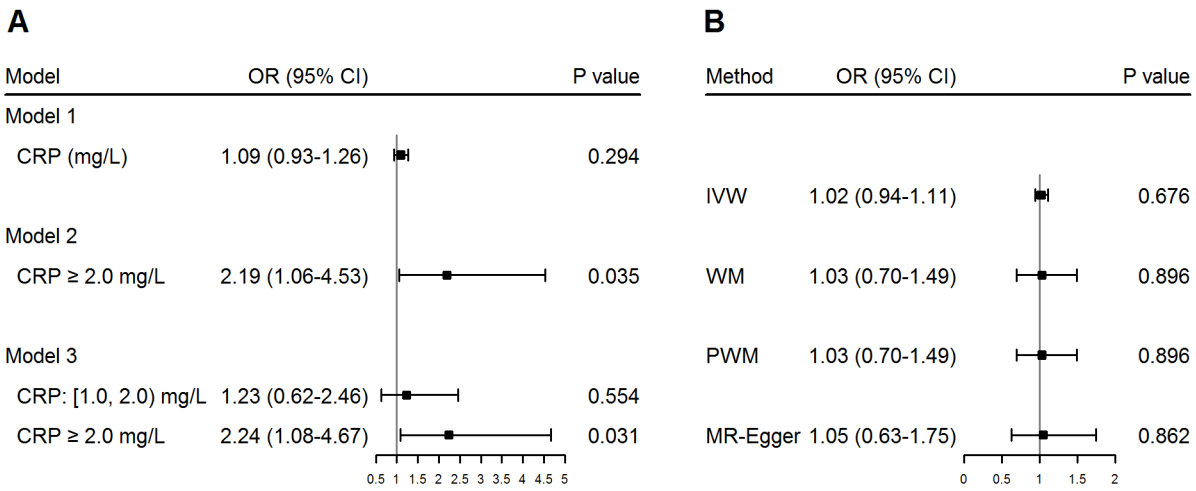

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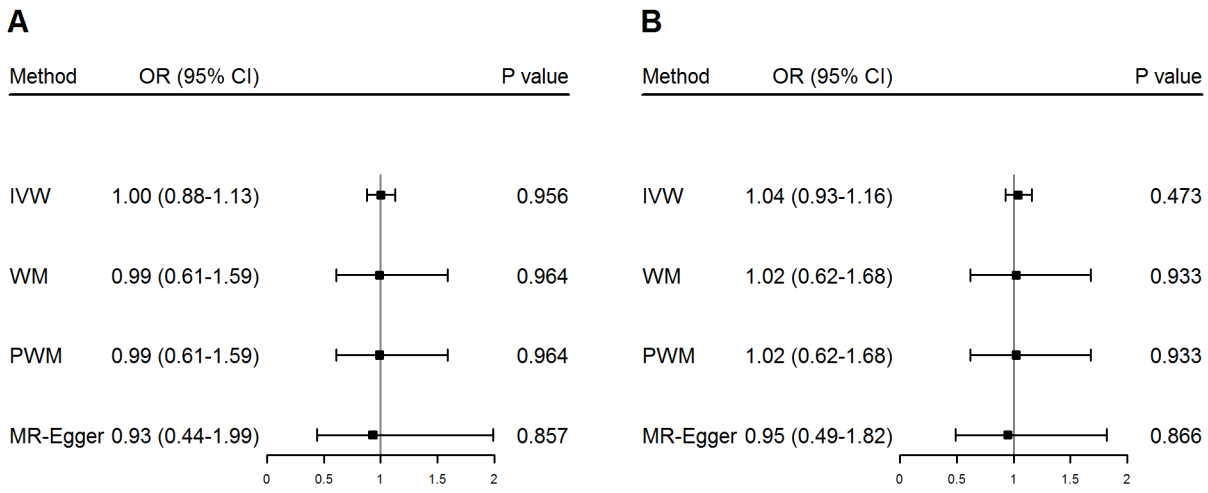

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