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CLINICAL STUDY

Genetic insights into blood urea nitrogen as a risk factor for coronary artery disease: a Mendelian randomization study in East Asians

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ABSTRACT

Background: Previous studies have reported the association between blood urea nitrogen (BUN) and cardiovascular diseases (CVDs) but the causality has not yet been proved. Our study aimed to assess the causal effect of BUN levels on several CVDs using the two-sample Mendelian randomization (MR) method. This is the first MR study examining causal relationships between BUN and multiple cardiovascular diseases.

Methods: Using data from genome-wide association studies (GWAS) of East Asians, we identified single nucleotide polymorphisms (SNPs) associated with BUN levels as instrumental variables. Specifically, SNPs reaching genome-wide significance ($p < 5 \times 10^{-8}$) were selected from a large-scale BUN dataset comprising ($n = 148{,}767$). To ensure robustness, multiple MR methods, including MR-Egger, weighted median, inverse variance weighting (IVW), simple mode, and weighted mode, were employed to evaluate the causal relationship between BUN levels and CVDs. Sensitivity analyses were conducted to assess the reliability and stability of the results.

Result: The IVW approach showed that a higher level of BUN was associated with an increased risk of coronary artery disease (CAD) (OR = 1.42, 95% CI = 1.226 − 1.644, $p = 2.89 \times 10^{-6}$). For atrial fibrillation (OR = 0.868, 95% CI = 0.678 − 1.110, $p = 0.258$), arrhythmia (OR = 0.907, 95% CI = 0.777 − 1.059, $p = 0.216$), and congestive heart failure (OR = 0.924, 95% CI = 0.781 − 1.092, $p = 0.353$), no significant associations were found. Sensitivity analyses indicated the results were robust.

Conclusion: This MR work shows that elevated BUN levels are a potential biomarker for CAD risk but lack causal associations with other CVDs. These findings suggest avenues for risk stratification and CAD prevention strategies, emphasizing the clinical utility of BUN monitoring in at-risk populations.

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Mendelian randomization; blood urea nitrogen levels; atrial fibrillation; arrhythmia; congestive heart failure; coronary artery disease

1. Introduction

Cardiovascular disease (CVD) was the leading cause of death in Asia in 2019, resulting in 10.8 million deaths, accounting for approximately 35% of the total immortality in Asia [1]. Globally, the incidence of CVD raised remarkably in the past 30 years, with the cases almost doubled from 271 million (95% uncertainty interval [UI]: 257 to 285 million) in 1990 to 523 million (95% UI: 497 to 550 million) in 2019 [2]. Besides, number of deaths attributed to CVD also increased nearly 6.5 million in the past three decades. As estimated, annual health care costs for CVD conditions in the United States are forecasted to nearly quadruple from nearly 400 million in 2020 to nearly 1500 million in 2050 [3]. Considering the devasting consequences and the heavy economic burden of CVD, it remains urgent to explore modifiable risk factors for CVD and expand more targets for CVD prevention.

Urea is a nontoxic nitrogen-containing end-product of organic protein metabolism. Under normal circumstances, the plasma urea concentration of human bodies ranges from 3.3 mmol/L to 6.7 mmol/L. Studies have reported that blood urea nitrogen (BUN) is linked to a wide range of human health issues. For instance, in a cross-sectional National Health and Nutrition Examination survey (NHANES) based study, Guo and

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colleagues found that BUN was associated with systemic immune-inflammation index [4]. Similarly, recent research indicates that BUN might be a promising biomarker for CVD predicting and prevention [5–8]. For instance, a cohort study followed up for four years showed that BUN might serve a valuable predictive biomarker for CVD [9]. In detail, among elderly female populations, higher BUN levels (>4.8 mg/dL) were associated with an increase incidence of heart failure but were associated with a decrease incidence in diabetes and metabolic symptoms. In a NHANES study conducted by Hong and colleagues, the results showed that elevated BUN level was correlated with a raised incidence of CVD [10]. However, previous studies have mainly focused on the relationship between BUN levels and CVDs like heart failure, but there have been few studies focusing on the relationship between BNU levels and other common CVDs such as atrial fibrillation, arrhythmia, and coronary artery disease (CAD). Besides, it is inevitable that latent reverse causality and residual confounding are commonly existing in conventional observational studies, making it challenging to reveal causality between the two traits. To date, there is lack of literature to systematically report the causal impact of BUN on CVDs.

The Mendelian randomization (MR) approach, proposed in recent years, has provided a revolutionary technique for causality inference using genetic variants as instrumental variables (IVs). In an MR design, single nucleotide polymorphisms (SNPs) derived from genome wide association studies (GWAS) are used as IVs to proxy exposure of interest. Considering that genetic variants are randomly allocated during gametogenesis and are relatively stable and prior to phenotype generating, MR can largely overcome the confounding and reverse causal issues in traditional observational epidemiological studies [11,12]. In recent years, the MR technology has been widely used in life science to explore risk factors for a wide range of diseases, especially for CVDs. For instance, using the MR method, Cai et al. showed that genetic predisposition toward prescription opioid use was associated with a higher risk of coronary heart disease and myocardial infarction [13]. Ai et al. also found that genetically predicted sleep duration was associated with a decreased risk of atrial fibrillation [14].

In this study, we apply a two-sample MR using summary statistics from large scale GWAS of BUN levels and atrial fibrillation, arrhythmia, congestive heart failure, CAD to reveal the causal effects among them.

2. Materials and methods

2.1. Study design

Based on the GWAS summary data, our study employed the MR approach to explore the causal relationship between BUN levels and several CVDs, including atrial fibrillation, arrhythmia, congestive heart failure, and CAD. As this study reanalyzes previously collected and published data, no additional ethical approval is required. This study strictly follows the three assumptions of MR analysis [15–17]: (1) the IVs selected are related with exposure; (2) the IVs are not related to any confounder factors; (3) the IVs can affect outcomes only through exposure. The overview of the research design is shown in Figure 1.

2.2. GWAS summary data for blood urea nitrogen levels

GWAS summary data of BUN levels were obtained from the Integrative Epidemiology Unit (IEU, website: https://gwas.mrcieu.ac.uk/) [18]. There were 148,767 participants included,

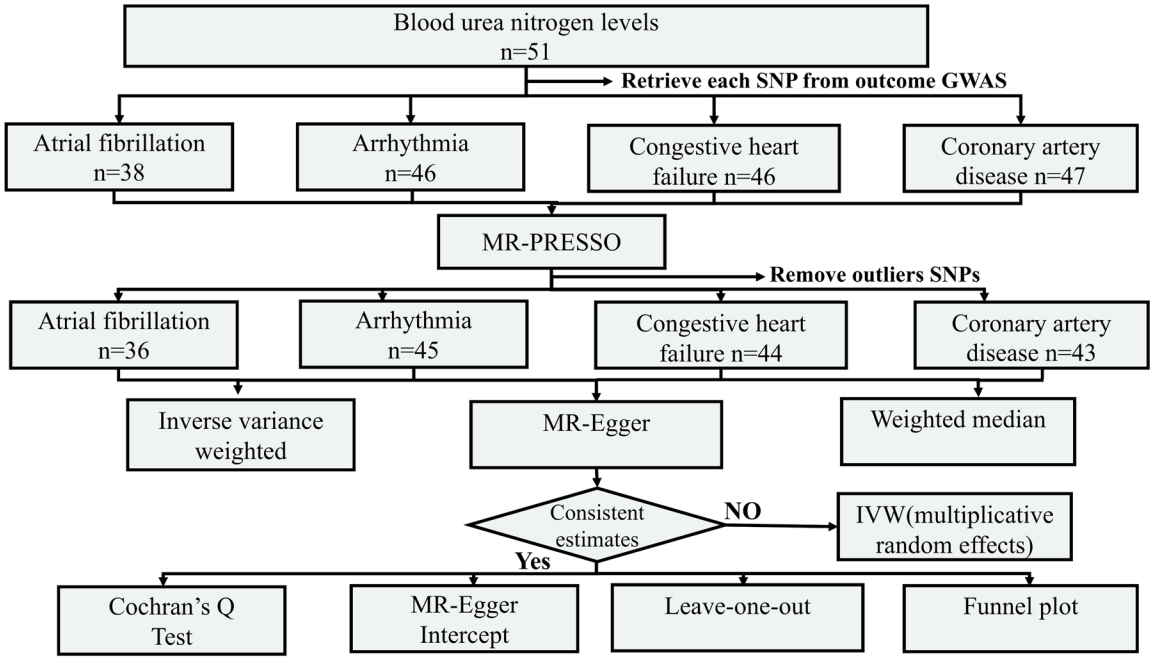


Figure 1. Workflow of mendelian randomization study IVW, inverse variance weighted; MR, mendelian randomization; MR-PRESSO, MR pleiotropy RESidual Sum and Outlier; SNP, single-nucleotide polymorphisms.

and all the individuals were of East Asian heritage. To use eligible IVs to proxy BUN levels, 51 independent SNPs significantly associated with BUN [$p < 5 \times 10^{-8}$, linkage disequilibrium (LD) $r^2 < 0.01$] were extracted from the exposure dataset. To avoid weak tool bias, we used the F-statistic and variance (R^2) to evaluate the strength of IVs for the filtered SNPs [19,20]. The calculation formula for F-statistics used in this study is $F = R^2 (N-k-1)/[k (1-R^2)]$, where R^2 is the cumulative explanatory variance of the selected SNPs on the exposure, k is the number of SNPs analyzed in the final analysis, and N is the sample size of the exposure phenotype. Calculation of R^2 has been described in previous studies [21]. If the F-statistic is greater than 10, it is considered that a strong correlation exists between IVs and exposure. As calculated, the 51 SNPs explained 0.23% of the variability in BUN levels. The F-statistics was 3450, larger than the conventional value of 10, indicating that the instruments had strong potential to predict BUN. The detailed genetic information of the 51 SNPs is listed in Supplementary Table 1.

2.3. GWAS summary data for outcome

For the outcome dataset, GWAS data for atrial fibrillation came from the research performed by Low ed al., and the study included 8,180 cases and 28,612 controls from Japan [22]. The full set of GWAS data was deposited in the IEU website. The summary dataset for arrhythmia was obtained from the IEU consortium and included 9,413 cases and 203,040 controls. The summary dataset for congestive heart failure obtained from the IEU consortium and included 10,540 cases and 168,186 controls The summary dataset for CAD was obtained from the IEU consortium and included 29,319 cases and 183,134 controls. The brief information for the GWAS data included in this MR work is shown in Table 1.

2.4. Statistical analyses

Before formal MR analyses, the exposure SNPs and outcome SNPs were harmonized to align the coding alleles, and eliminate palindromic IVs with moderate frequencies or IVs with incompatible alleles. The harmonized data were presented in Supplemental Tables S2–S5. The MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO) method was also used to assess and correct horizontal pleiotropy [23]. MR-PRESSO includes three major components: (a) detection of horizontal pleiotropy, (b) correction for horizontal pleiotropy *via* outlier removal, and (c) testing of significant differences in the causal estimates before and after correction for outliers. In this work, MR-PRESSO was used to detect and exclude any outliers with potential pleiotropy.

Table 1. The details of the GWAS, all participants were of East Asian.

Consortium	Phenotype	Participants	Web source
IEU	BUN	148767	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90018728/
IEU	CAD	212453	https://gwas.mrcieu.ac.uk/datasets/bbj-a-159/
IEU	Atrial fibrillation	36792	https://gwas.mrcieu.ac.uk/datasets/bbj-a-71/
IEU	Arrhythmia	212453	https://gwas.mrcieu.ac.uk/datasets/bbj-a-86/
IEU	Congestive heart failure	212453	https://gwas.mrcieu.ac.uk/datasets/bbj-a-109/

We used several MR methods to determine the MR estimation of BUN levels on CVDs, including inverse variance weighted (IVW), weighted median, MR egger, simple mode, and weighted mode. The IVW method was applied as the predominant model [24]. The other MR methods are used to complement IVW estimates as these approaches could provide more reliable estimates in a broader set of scenarios. If estimates of these approaches in our study were inconsistent [23].

Sensitivity analysis is pivotal in an MR design to detect underlying pleiotropy and heterogeneity that might potentially violate MR estimates. We used the Cochran's Q test of the IVW model to investigate heterogeneity. Specifically, if there was heterogeneity detected (Cochran's Q derived $p < 0.05$), the random-effects IVW model was applied; otherwise, the fixed-effect IVW model was used. Also, we applied Radial MR to correct the heterogeneity. The intercept obtained from the MR-Egger regression served as an indicator for directional pleiotropy (the intercept derived $p < 0.05$ was considered as the presence of directional pleiotropy) [25]. The leave-one-out analysis was also performed to evaluate whether the MR estimate was driven or biased by any high-influence SNPs [26]. Analyses were implemented by the 'TwoSampleMR' package [27] (version 0.4.25) and 'MRPRESSO' package (version 1.0) in the R program (version 3.6.1). Bonferroni corrected P value (<0.0125) was utilized in this study to define significance.

3. Results

3.1. Overview of IVs

After rigorous SNP selection and outliers removed by MR-PRESSO (Table 2), there were respectively 38, 46, 46, and 47 SNPs remained for atrial fibrillation, arrhythmia, congestive heart failure, and CAD.

3.2. Causal effects of BUN on CVDs

The IVW approach showed that a higher level of BUN was associated with a raised risk of CAD (OR = 1.42, 95% CI = 1.226 − 1.644, $p = 2.89 \times 10^{-6}$). Multiple testing adjusting p was 0.0125. So the results are still solid. Power calculations is 100%. The other four MR models, including weighted median, MR-Egger regression, weighted mode, and simple mode, presented consistent estimates (Figures 2 and 3). Though heterogeneity was detected (Figure 4 and Table 2), the random-effect IVW model was applied to balance heterogeneity. For CAD, we

Table 2. Sensitivity analysis of the MR analysis results of exposures and outcomes.

		Heterogeneity Test		Pleiotropy Test	MR-PRESSO
		Cochran's Q Test (P value)	Rucker's Q Test (P value)	Egger Intercept (P value)	Distortion Test
Exposure	Outcome	IVW	MR-Egger	MR-Egger	outliers
BUN levels	Coronary artery disease	9.05E-76	4.09E-74	0.315	rs10857147, rs11079418, rs2525858, rs916682
	Atrial Fibrillation	0.666	0.620	0.991	rs17663561, rs76273615
	Arrhythmia	0.003	0.002	0.958	rs916682
	Congestive heart failure	0.663	0.634	0.625	rs11642015, rs1275609

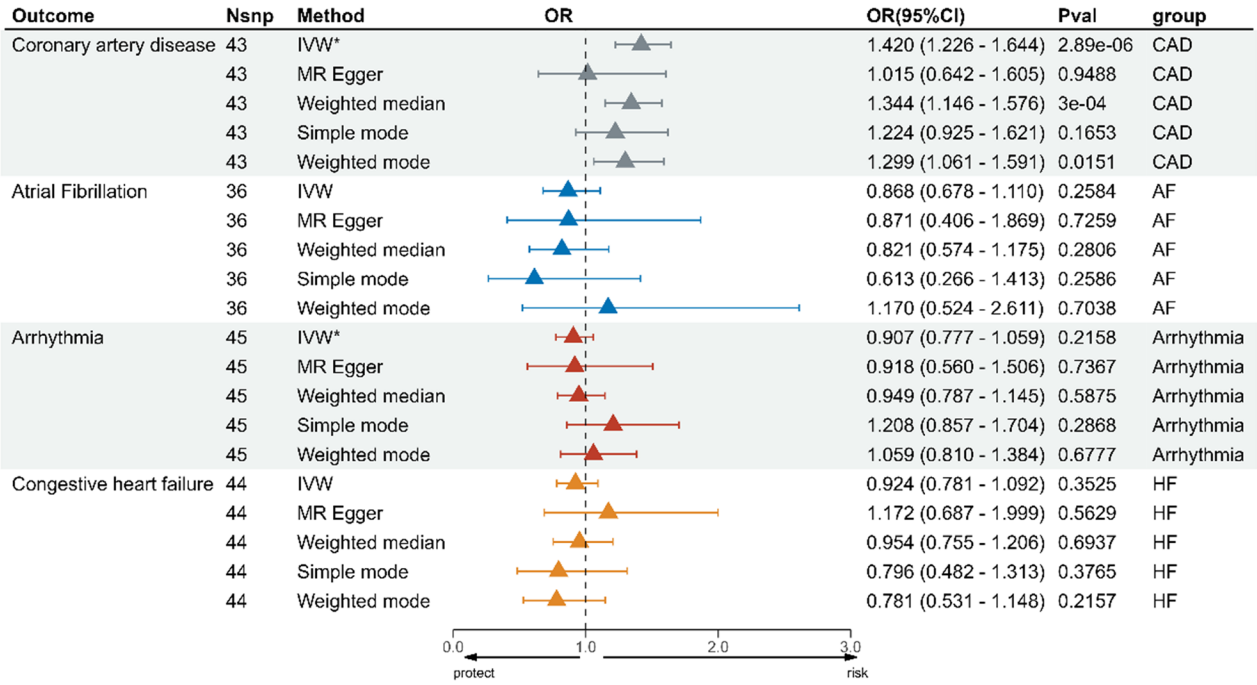


Figure 2. MR analysis between BUN levels and atrial fibrillation, arrhythmia congestive heart failure and CAD five methods: random-effects IVW, MR egger, weighted median, simple mode, and weighted mode.
*Inverse variance weighted (multiplicative random effects)

added Radial MR analyses. Outliers were detected as rs10857147, rs11079418, rs11453704, rs11636220, rs11672660, rs13074774, rs2525858, rs3785888, rs56084563, rs57834988, rs6026579, rs8076417, and rs916682. After removing these outliers, inverse variance weighted P was 1.692527e-07. Cochran's Q Test IVW P-value was 0.781, and Rucker's Q Test MR-Egger P-value was 0.796, supporting our initial findings. Besides, the pleiotropy test showed there was a non-significant intercept derived from the Egger regression, suggesting no horizontal pleiotropy biasing the MR estimates (Table 2). Furthermore, the leave-one-out analysis found no evidence of strong IVs biasing the pooled IVW effect (Figure 5).

For atrial fibrillation (OR = 0.868, 95% CI = 0.678 − 1.110, $p = 0.258$), arrhythmia (OR = 0.907, 95% CI = 0.777 − 1.059, $p = 0.216$), congestive heart failure (OR = 0.924, 95% CI = 0.781 − 1.092, $p = 0.353$), the IVW model found no evidence of the associations of BUN with them. Similar estimates were observed in other MR models (Figures 2 and 3). Though heterogeneity was detected in the association between BUN and arrhythmia (Figure 4), no horizontal pleiotropy was found in the Egger intercept test (Table 2). Similarly, the leave-one-out analysis supported the robustness of the IVW model (Figure 5).

4. Discussion

We used MR for the first time to systematically explore potential causal effects between BUN levels and the risk of atrial fibrillation, arrhythmia, congestive heart failure, and CAD. We found that a higher level of BUN is a risk factor for CAD, but there is no causal relationship between BUN levels and atrial fibrillation, arrhythmia, or congestive heart failure certified in present study. To be more specific, the risk of CAD increases by 1.4 times with each standard error level increase in BUN. When handling patients with elevated BUN, physicians should consider ordering necessary examinations to diagnose CAD.

Urea nitrogen is a metabolite of protein digestion and decomposition, which is converted into urea in the liver through the urea cycle and finally filtered out from the

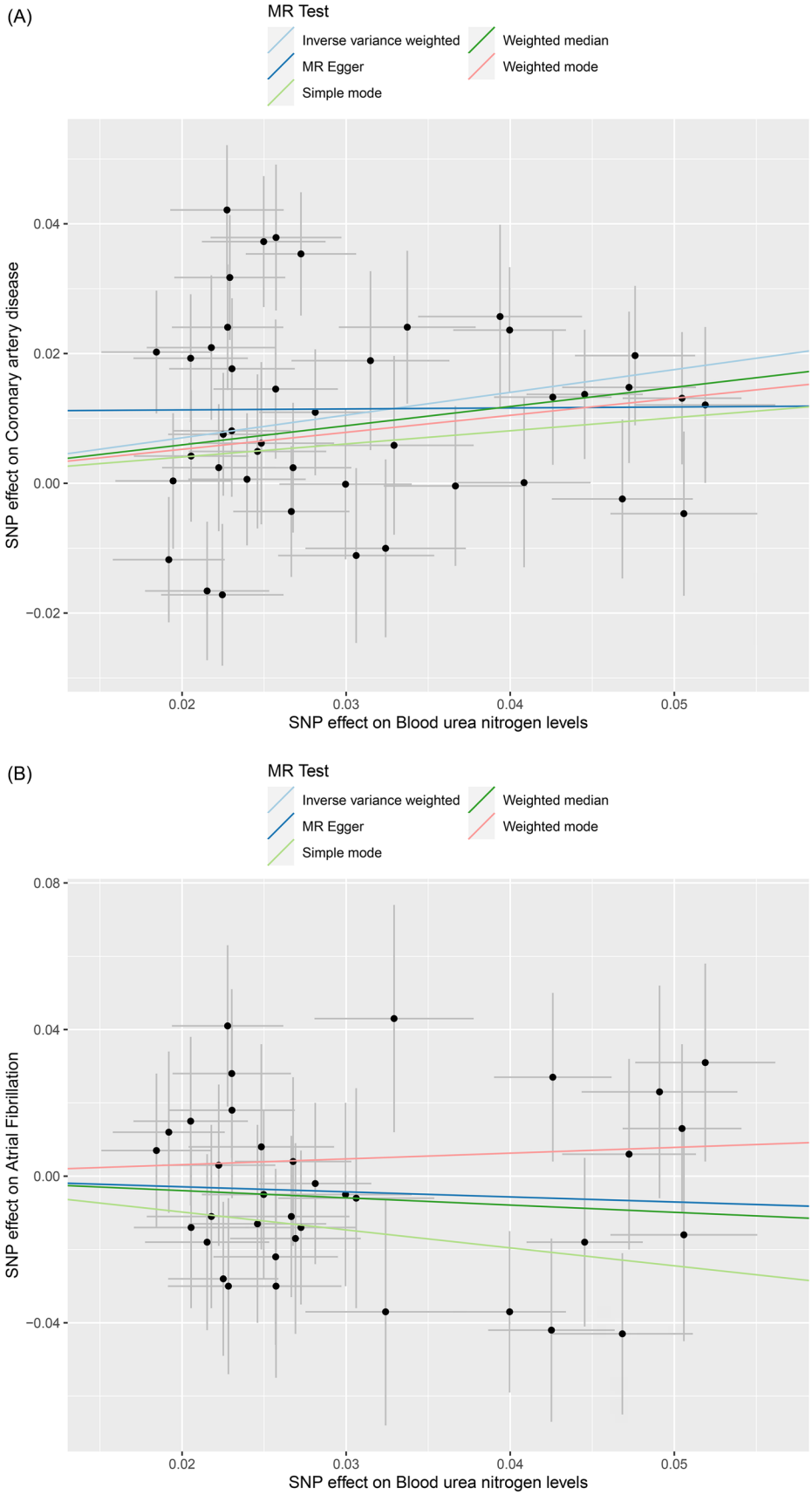


Figure 3. Funnel plot. (A) BUN levels and coronary artery disease; (B) BUN levels and atrial fibrillation; (C)BUN levels and arrhythmia; (D) BUN levels and congestive heart failure.

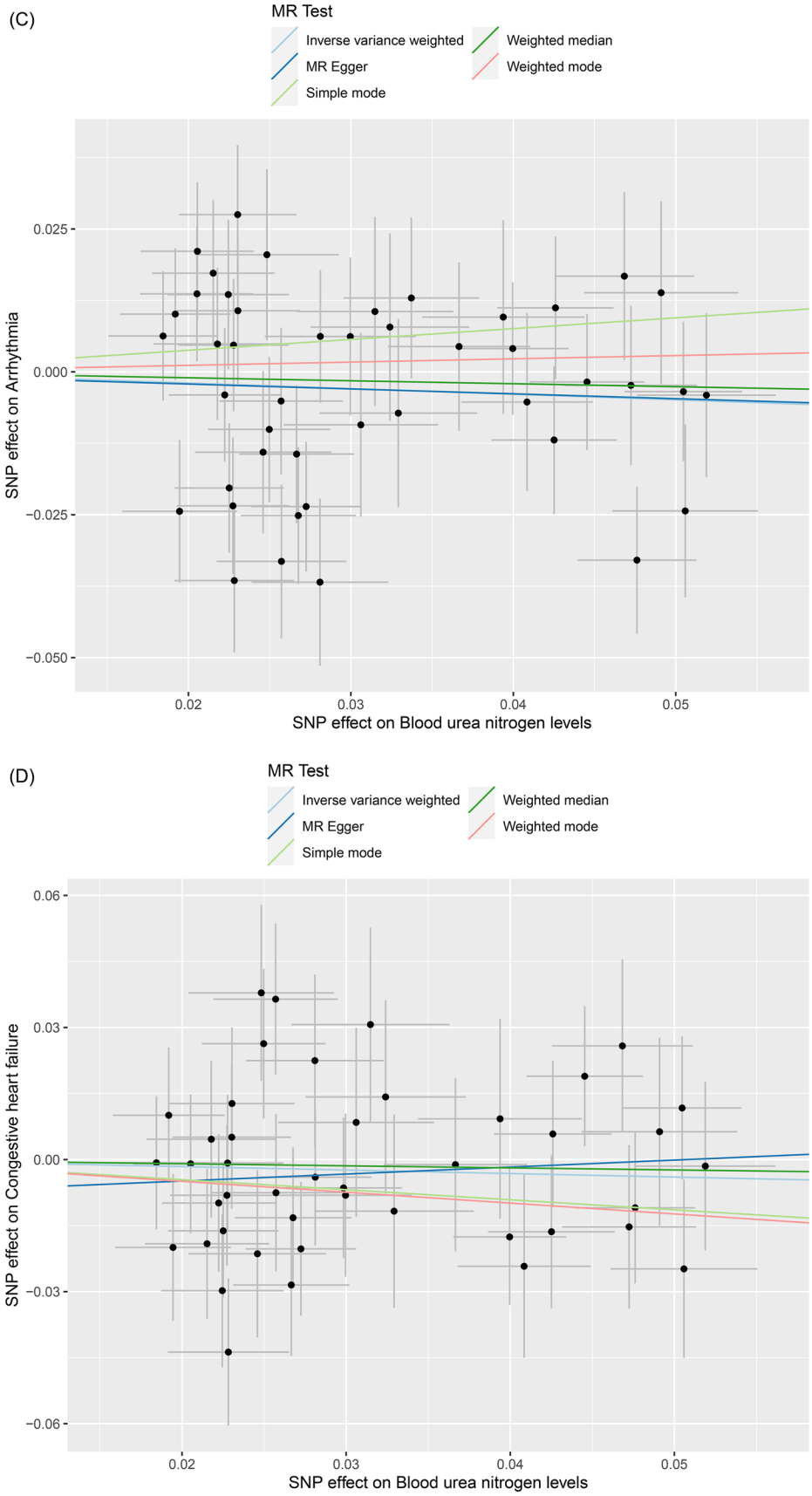


Figure 3. Continued.

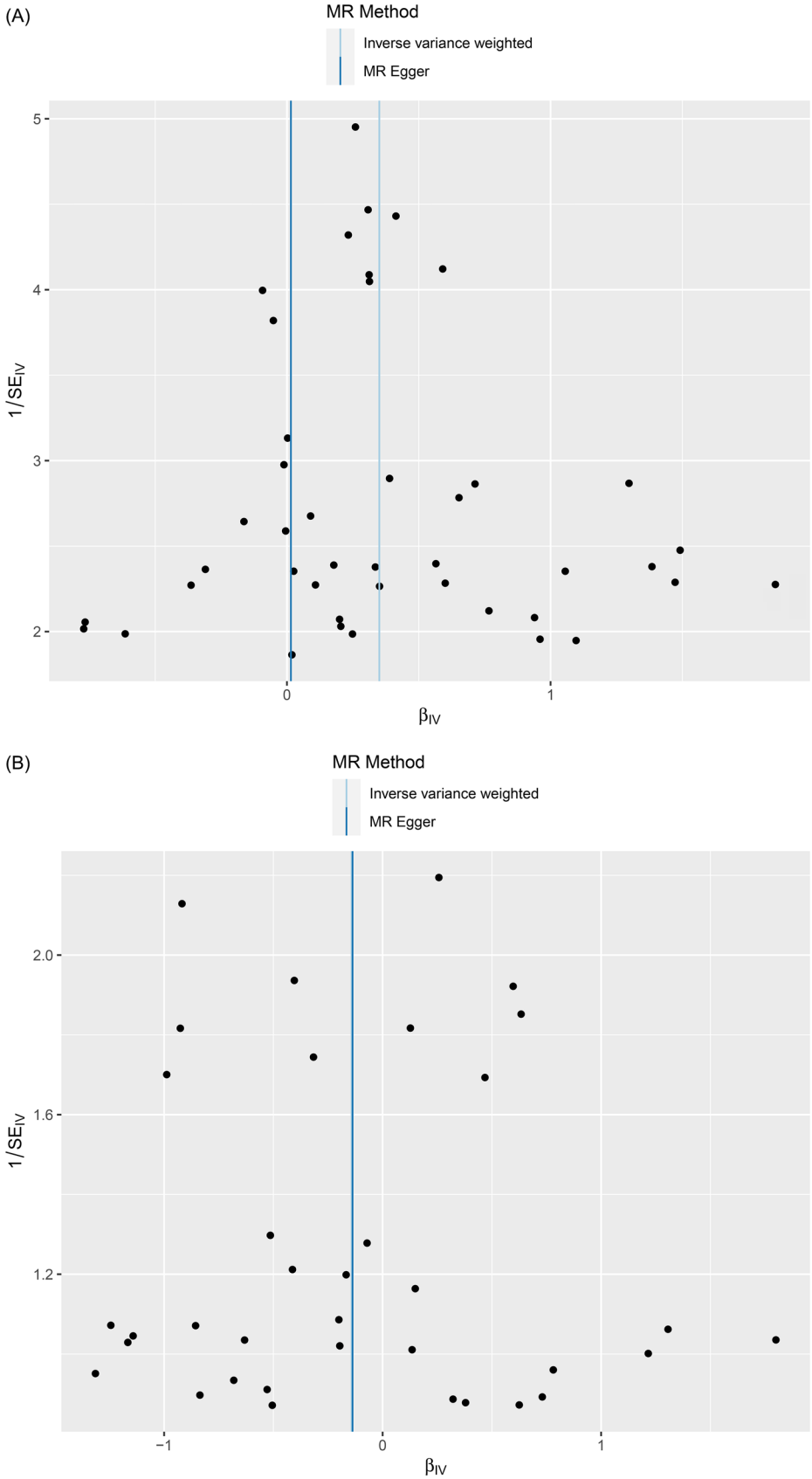
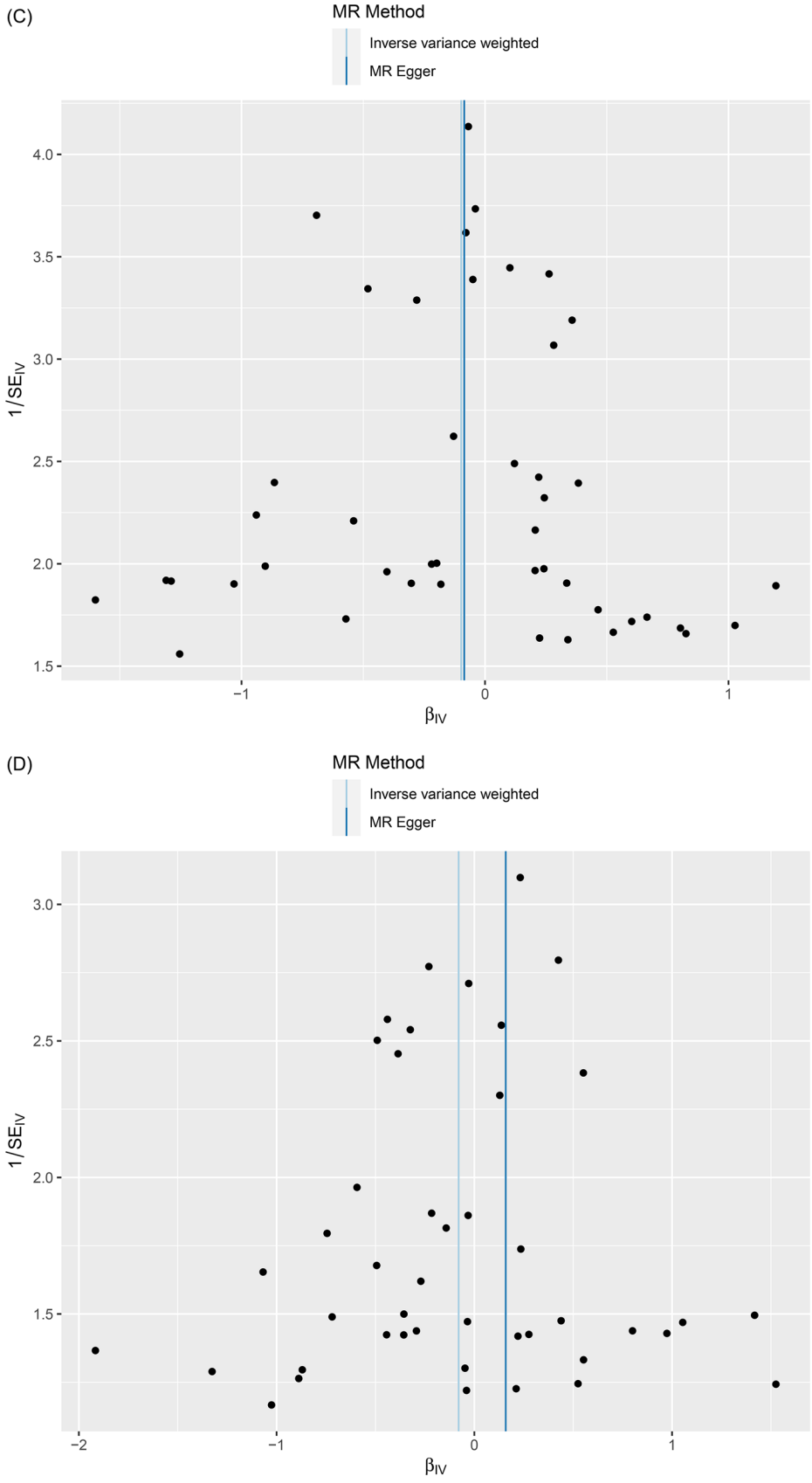


Figure 4. Scatter plot of MR analysis. (A) BUN levels and CAD; (B) BUN levels and atrial fibrillation; (C) BUN levels and arrhythmia; (D) BUN levels and congestive heart failure.



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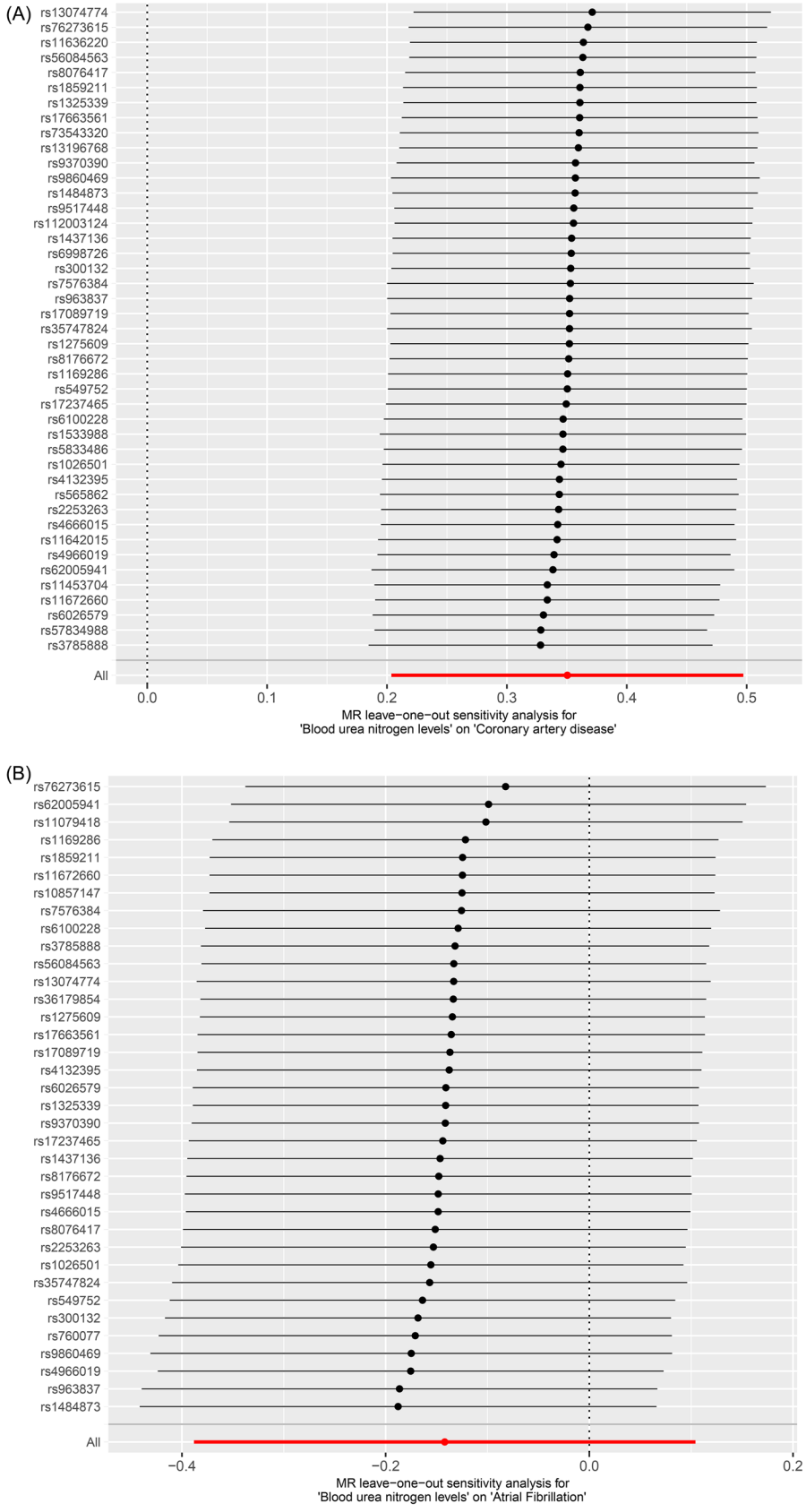

Figure 5. Leave one out analysis. The red lines are the analysis results of random effects IVW. (A) BUN levels and coronary artery disease; (B) BUN levels and atrial fibrillation; (C) BUN levels and arrhythmia; (D) BUN levels and congestive heart failure.

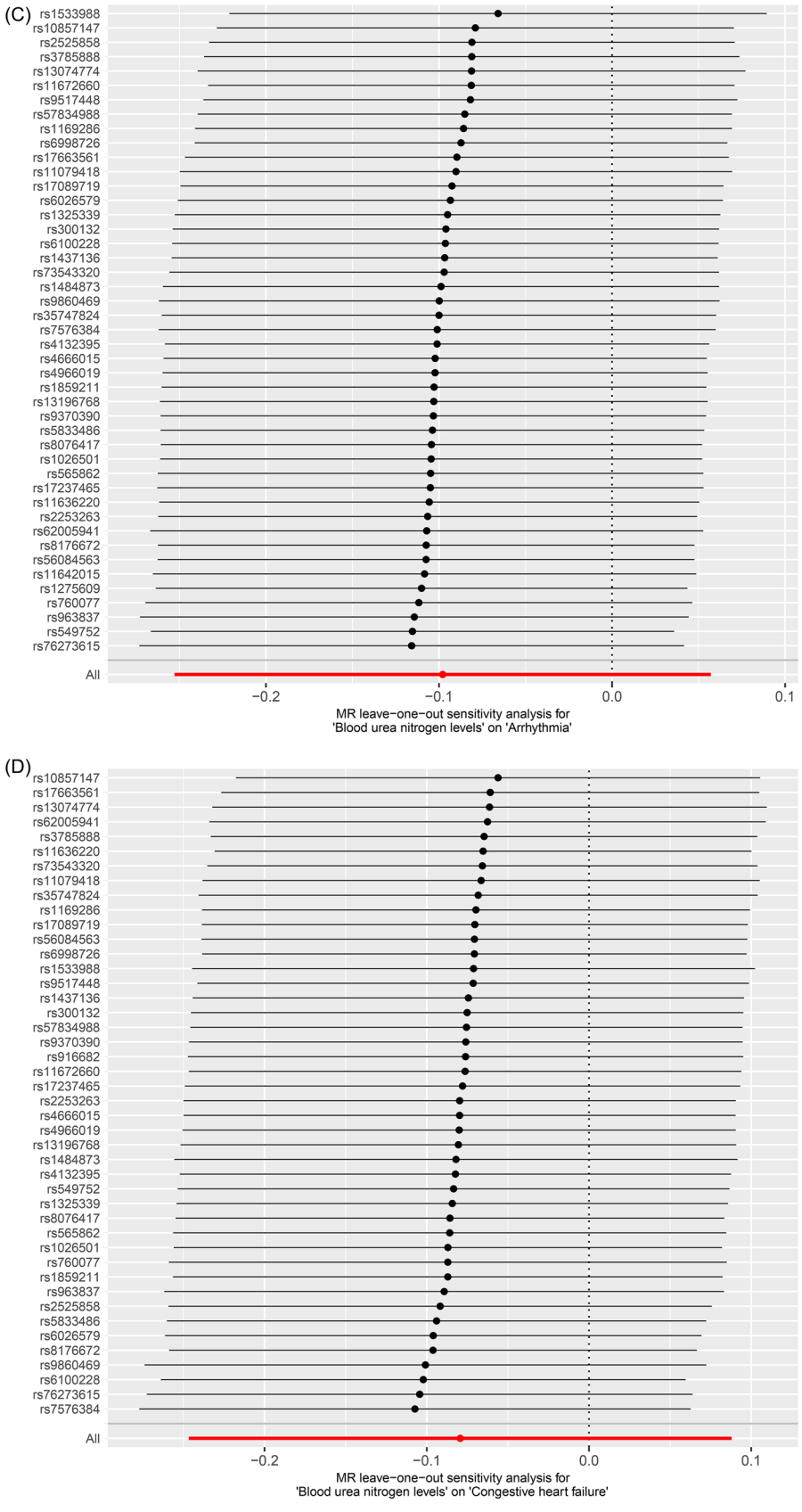

Figure 5. Continued.

glomeruli. It is the main component that maintains plasma osmotic pressure, and its concentration represents the balance between urea production and renal excretion. Therefore, BUN has been widely studied and has been found to be associated with a wide range of health problems. In this work, we confirmed a detrimental effect of BUN on CAD, which was in line with previous researches. CAD is one of the major CVDs threatening global population. The traditional risk factors of CAD include hypertension, diabetes mellitus, hyperlipidemia, obesity, smoking and psychosocial stress [28]. In an observational study, Hong et al. found an association between higher BUN level and an increased risk of CVD [10]. The possible explanation for the link between BUN and CAD might be the impaired renal function. As known, an elevated BUN level indicates renal dysfunction, which has been proved to be associated with CAD [29]. Jiang et al. found that a mild-to-severe decline in eGFR or an elevated level of BUN may be associated with an increased risk of incident CAD in middle-aged and elderly Chinese populations [30]. Kidney disease has been shown to induce endothelial dysfunction, which is recognized as one of the initial mechanisms leading to atherosclerosis [31]. In addition, BUN is also a biomarker for neurohormonal activation [6]. Reabsorption of BUN might be attributed to elevated vasopressin levels, which might consequently lead to atherosclerosis induced by oxidative stress acts on the vascular wall [32]. However, the current study found no associations of BUN with atrial fibrillation, arrhythmia, or congestive heart failure. As mentioned above, a 4-year cohort study, showed a high incidence of heart failure in older women with higher BUN levels, which is inconsistent with the present study [9]. This might be attributed to the specific population (older women) focused on in Lan et al.'s study. Besides, as known, observational study design is typically subject to residual confounding and reverse causality.

Randomized controlled trials (RCTs) are widely accepted in causal studies, but they cost considerably. There are currently few RCTs on the relationship between BUN and CVDs. Compared to traditional observational studies, MR design can simulate the process of an RCT design as genetic variants are randomly assigned. Thereby, the MR work could largely avoid reverse causation and confounding effects. Besides, as only East Asians were included, the work was free from population heterogeneity. Myocardial infarction (MI) risk differs among ethnic groups, although the extent to which genetic factors contribute remains unclear [33]. We anticipate that our research will provide a foundation for future studies investigating the relationship between BUN and CAD in diverse populations. In addition, by integrating multiple MR models and sensitivity analyses, the results observed in this MR study were relatively reliable.

However, our research has some limitations. Firstly, although various methods are used to analyze bio-functional pleiotropy, it is not possible to completely rule out potential confounders. Fortunately, multiple analytical methods yielded consistent results and provided no evidence of horizontal pleiotropy or heterogeneity, thereby confirming the reliability of the study's findings. Secondly, the incidence and mortality rates of CAD vary across different races. In this MR analysis, all participants were East Asians, and thus further research is needed to explain the potential causal relationship between BUN levels and CAD in other ethnic populations such as Europeans.

5. Conclusion

This study provides evidence that an increased level of BUN is a risk factor for coronary artery disease but not atrial fibrillation, arrhythmia, or congestive heart failure. The results would provide evidence for searching novel targets for CAD prevention. However, the possibility of a causal relationship in other subgroups of the population remains further investigation.

Author contributions

ZQH designed the research study, LJS performed the research and analyzed the data, ZYZ provided assistance and guidance in writing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

All data used in the current study are publicly available GWAS summary data.

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