

# Causal Association Between Birth Weight and Atrial Fibrillation: Evidence from a Two-Sample Mendelian Randomization Analysis

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## Research article

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# Abstract

## Background

Although several observational studies have shown an association between birth weight (BW) and atrial fibrillation (AF), controversy remains. In this study, we aimed to explore the role of elevated BW on the etiology of AF.

## Methods

A two-sample Mendelian randomization (MR) study was designed to infer the causality. The genetic data on the associations of single nucleotide polymorphisms (SNPs) with BW and AF were separately obtained from two large-scale genome-wide association study with up to 321,223 and 1,030,836 individuals respectively. SNPs were identified at a genome-wide significant level ( $p\text{-value} < 5 \times 10^{-8}$ ). The inverse variance-weighted (IVW) with fixed effects method was performed to obtain causal estimates as our primary analysis. MR-Egger regression was conducted to assess the pleiotropy and sensitivity analyses with various statistical methods were applied to evaluate the robustness of the results.

## Results

In total, 122 SNPs were identified as the genetic instrumental variables. MR analysis revealed a causal effect of elevated BW on AF (OR = 1.21, 95% CI = 1.13–1.29,  $p\text{-value} = 2.39 \times 10^{-8}$ ). The MR-Egger regression suggested no evidence of directional pleiotropy (intercept = 0.00,  $p\text{-value} = 0.62$ ). All the results in sensitivity analyses were consistent with the primary result, which confirmed the causal association between BW and AF.

## Conclusions

The findings from the two-sample MR study indicate a causal effect of elevated BW on AF. This suggests a convenient and effective method to ease the burden of AF by reducing the number of newborns with elevated BW.

## Introduction

Atrial fibrillation (AF) represents the most common sustained cardiac arrhythmia with significant morbidity and mortality, responsible for a substantial health care burden all over the world.[1–3] The global number of individuals with AF was estimated 33.5 million in 2010, and accumulated evidence have suggested an increasing prevalence and incidence of AF during the recent years.[3–5] Considerable effort has been made to manage this disease, whereas the benefit of eliminating the established AF

remains limited.[1, 2, 6] Further exploration of the AF pathophysiology and discovery of the new risk factors are warranted, since the efficient prevention is of great importance.[7, 8]

Birth weight (BW) represents a well-established risk factor for ischemic heart disease.[9–11] In addition, numerous studies have suggested that BW is also associated with several cardiovascular risk factors such as type 2 diabetes mellitus and hypertension.[12, 13] However, it remains inconclusive whether BW is associated with the risk of AF. To our knowledge, only four previous studies have explored the association between BW and AF, with discordant results.[14–17] Further investigation is warranted to reveal whether this association is causal.[18]

Mendelian randomization (MR) analysis has been increasingly used to infer the causation.[19, 20] MR exploits genetic variants, usually single-nucleotide polymorphisms (SNPs), as proxies for the exposure of interest.[19, 20] Based on Mendel's second law, these SNPs were randomly allocated at conception, which could be thought as a natural randomized–controlled trials.[21] MR analysis is less susceptible to potential unmeasured confounders and reverse causation.[19, 20] Two-sample MR is an extension of this methodology, which derives the genetic association data from two separate genome-wide association studies (GWASs).[22, 23] With the enlargement of the sample size, the statistical power is largely improved. In this study, we aim to systematically appraise the evidence of the causal association between BW and AF using the two-sample MR analysis.

## Methods

### Study design

A two-sample MR study was designed to investigate the causal association between BW and the risk of AF (Figure 1). This method was based on three key assumptions.[19] First, the genetic instrumental variables, i.e. SNPs, should be strongly associated with the BW. Second, the instrumental variables should be independent of confounders that may affect the association between the BW and the risk of AF. Third, the instrumental variables should be only associated with the risk of AF via BW.

### Data sources

#### Exposure: BW

The exposure in this study was genetically predicted BW, in standard deviations (SDs). The SNPs that proxied for BW were extracted from the hitherto largest genome-wide association study (GWAS) meta-analysis on BW using data from the Early Growth Genetics (EGG) Consortium and the UK biobank (n = 321,223).[24] This trans-ethnic (92.8% were European ancestry) meta-analysis consisted of three components: (i) 80,745 individuals of European ancestry from 35 studies within the EGG consortium, (ii) 12,948 individuals of diverse (non-European) ancestries from 9 studies within the EGG consortium, (iii) 227,530 individuals of all ancestries from the UK Biobank (Table S1). The data on BW were collected via

heterogeneous ways (i.e., measured at delivery, obtained from the birth records and medical registries, got from the parental interviews, and self-reported as adult).

## **Outcome: AF**

The outcome in this study was AF. Summary statistics data on associations of SNPs with AF were derived from a recently published GWAS ( $n = 1,030,836$ ).[25] This GWAS was the largest one on AF to date, which analyzed a total of 34,740,186 genotyped SNPs on up to 60,620 cases and 970,216 controls from 6 resources: The Nord-Trøndelag Health Study (HUNT), deCODE, the Michigan Genomics Initiative (MGI), DiscovEHR, UK Biobank, and the AFGen Consortium (Table S2). The majority (98.6%) of the individuals were European ancestry. AF was mainly diagnosed according to the International Classification of Diseases (ICD-9 and ICD-10).

## **Statistical analysis**

### **Selection and validation of instrumental variables (SNPs)**

To ensure a close relationship between the genetic instrumental variables and BW, SNPs were identified at a genome-wide significant level ( $p\text{-value} < 5 \times 10^{-8}$ ) from the corresponding GWAS summary dataset. To check for correlations between each SNPs, the pairwise-linkage disequilibrium (LD) was calculated using LD-Link based on European (<https://ldlink.nci.nih.gov/>).[26] When  $r^2 > 0.001$ , only the SNP with lower  $p$ -value was retained. In addition, the effects of SNPs on AF were obtained from the corresponding dataset. If the specified SNP was not available for AF, a highly correlated SNP ( $r^2 > 0.8$ ) was selected for proxy.[27] Any palindromic SNPs were removed from our analysis. Additionally, the known effects of SNPs on other traits were checked in the PhenoScanner (<http://www.phenoscanter.medschl.cam.ac.uk>).[28] SNPs associated with the confounders at the genome-wide significant level ( $p\text{-value} < 5 \times 10^{-8}$ ) were dropped. Finally, F statistic was calculated for each SNP in order to detect whether this SNP was valid ( $F > 10$ ) or not.

### **Primary MR analysis**

The two-sample MR method was employed to evaluate the causal association between BW and AF in this study. Specifically, the causal effect of each SNP was estimated using the Wald estimator, and the relevant standard error was calculated using the Delta method.[29] The inverse variance-weighted (IVW) with fixed effects method was performed to meta-analyze each Wald ratio as our primary analysis.[29] Results were presented as odds ratios (ORs) with 95% confidence intervals (CIs) of AF per SD increased BW. The association of each SNP with BW was further plotted against its effect on AF.

### **Pleiotropy assessment**

In addition to searching in the PhenoScanner database, MR-Egger regression was performed to evaluate the potential directional pleiotropy.[30] In MR-Egger regression, the intercept represented the estimated average value of the horizontal pleiotropy. When the  $p$ -value of intercept was large than 0.05, no

horizontal pleiotropy existed. The slope was interpreted as an unbiased estimate of the causal effect of BW on AF even if all the SNPs were invalid (i.e., the intercept significantly differed from zero). However, the slope estimating relied on an additional assumption known as the Instrument Strength Independent of Direct Effect (InSIDE). A violation of this assumption could also bias the estimate. Moreover, MR-Egger regression was statistically inefficient, which was expected to have considerably larger standard errors (SEs) than other analyses. As such, we mainly focused on whether the intercept test suggested evidence of potential horizontal pleiotropy. Subsequently, funnel plot was generated to visually inspect the pleiotropy, in which symmetry provided evidence against directional pleiotropy.[31]

## **Sensitivity analysis**

In the follow-up sensitivity analyses, the IVW with multiplicative random effects, penalized IVW, robust IVW, penalized robust IVW, maximum likelihood, simple median, weighted median and Mendelian Randomization Pleiotropy Residual Sum and Outlier (MR-PRESSO) methods were applied to test the robustness of our primary analysis. These methods were more robust for SNPs with potential heterogeneity and pleiotropy. In comparison with the fixed-effect IVW, the SE in random-effect IVW were supposed to be larger when there was heterogeneity across SNPs.[32] The penalized and robust methods could improve the robustness of estimates when heterogeneity and outliers existed.[33] The weighted median method was able to generate a consistent estimate of the causal effect if the weights of the valid SNPs exceeded 50%.[34] The MR-PRESSO method could detect and correct for outliers and then provided a robust estimate.[35] Subsequently, a leave-one-out analysis was conducted to determine whether the estimated causal effect was disproportionately affected by a single SNP.

## **Power calculation**

To investigate the statistical power, a power calculation was carried out using an online web-based tool named mRnd (<https://shiny.cnsgenomics.com/mRnd/>).[36] Specifically, the sample size, type-I error ( $\alpha$ ) rate, proportion of AF cases, OR of AF per SD of BW, and total phenotypic variance explained by all SNPs were inputted. In this study, the statistical power was required to be at least 80%.

An observed 2-sided p-value < 0.05 was considered as significant evidence for a causal association. All the analyses were implemented using the “MendelianRandomization” and “TwoSampleMR” R packages in R (version 3.6.2) software environment.[37, 38]

## **Ethics approval**

Our study only made use of the publicly available data, and hence, no additional ethics approval was required.

# **Results**

## **SNPs selection and validation**

In total, 229 SNPs were obtained from the GWAS dataset of BW, which achieved the genome-wide significance ( $p\text{-value} < 5 \times 10^{-8}$ ). After exclusion of the correlated SNPs, 145 SNPs were retained. Among these SNPs, 22 SNPs were associated with other traits that may affect our results, as shown in Table S3. Rs12623454 was palindromic that may cause ambiguity in the strand direction. After removing these 23 SNPs, the remaining 122 SNPs were identified as the genetic instrumental variables in our MR analysis. All these 122 SNPs were valid ( $F > 10$ ), and their characteristics and associations with BW and AF were shown in Table S4.

### **Primary MR analysis**

The primary result using fixed-effects IVW method was shown in Figure 2. The OR and 95% CI of AF per SD increased BW were 1.21 (1.13-1.29),  $p\text{-value} = 2.39 \times 10^{-8}$ . This result suggested that the genetically predicted BW was causally associated with the risk of AF. In addition, the visual inspection of the association of each SNP with BW and its effect on AF was shown in Figure S1.

### **Pleiotropy assessment and sensitivity analysis**

The result of the MR-Egger regression was shown in Table 1. The OR and 95% CI of the AF per SD increased BW were 1.31 (0.94-1.81),  $p\text{-value} = 0.11$ . This result was consistent with our primary result, although the 95% CI was much larger because of the statistical inefficiency as expected. The intercept test suggested no evidence of directional pleiotropy (estimate = 0.00,  $p\text{-value} = 0.62$ ). Additional evidence against directional pleiotropy was provided by the symmetric funnel plot, as shown in Figure 3.

The results of sensitivity analyses with various statistical methods were shown in Figure 4. All the results were consistent with our primary result, validating the robustness of our analyses. The leave-one-out analysis suggested that the overall estimate was unlikely driven by any single SNP, as shown in Figure 5.

### **Power calculation**

In the calculation, the sample size was set to be 1,030,836, the type-I error ( $\alpha$ ) rate was set to be 0.05, the proportion of AF was set to be 0.06, the OR of AF per SD of BW was set to be 1.21, the total phenotypic variance explained by the 122 SNPs was set 0.02, and finally the statistical power was obtained as 1.00, as shown in Table 2.

## **Discussion**

To our knowledge, this is the first MR study investigating the role of BW on AF. Our primary analysis demonstrated that genetically increased BW was significantly associated with the risk of AF. Consistent associations were observed in the sensitivity analyses with numerous statistical methods. Therefore, our study provided evidence to support the robust association between higher BW and an increased risk of AF in later life.

The association between BW and the risk of cardiovascular diseases was first described in 1989.[9] Since then, multiple studies have confirmed an established risk of low weight at birth on cardiovascular diseases in adulthood, such as coronary artery disease, myocardial infarction, type 2 diabetes mellitus and hypertension.[9–13] However, only four previous studies have assessed the potential association between BW and the risk of AF, with conflicting results.[14–17] The Women's Health Study of 27,982 women, including 735 AF cases during a median follow-up of 14.5 years, indicated that BW was significantly associated with the incident AF among women.[14] The Atherosclerosis Risk in Communities cohort of 10,132 individuals, identifying 882 AF cases during an average follow-up of 10.3 years, demonstrated that low BW was independently associated with increased risk of AF.[15] The prospective cohorts in Sweden of 29,551 men and 23,454 women, comprising 2,711 men and 1,491 women who developed AF during 12 years of follow-up, showed that low BW in men and high BW were associated with higher risk of AF.[16] The Helsinki Birth Cohort Study of 13,345 individuals, including 907 incident cases during 70.5 years of follow-up, suggested a significant U-shaped association between BW and AF.[17] Although several recognized confounding factors have been adjusted in these studies, the influence of unmeasured confounders was inevitable, which may account for the divergent results. MR analysis can avoid the potential unmeasured confounders thus making stronger causal inference.[19, 20] The present study provides evidence for the causal association between the elevated BW and the increased risk of AF.

BW variation is influenced by fetal genetics and maternal intrauterine environment.[24] It is impossible for observational studies to dissect whether the genetic effect or the external environment underpins a potential association with future AF risk. The association between the low BW and high AF risk observed in prior studies might be explained by adaptation of fetus to an adverse intrauterine environment and conferring permanent changes in metabolism leading to future diseases, a concept termed as “developmental origins of health and disease”.[39, 40] However, this association is spurious from the perspective of the genetics. The present study suggested that genetically predicted BW was causal associated with the increased risk of AF. Although the underlying mechanism remains unclear, two hypotheses can be proposed as follows. First of all, high adult height is put forward to explain the increased risk of AF associated with high BW. In the Women's Health Study and Swedish Study, adjustment for height substantially attenuated the association between high BW and the increased risk of AF.[14, 16] BW is considered as a robust predictor for adult height which has been confirmed as an independent risk factor for AF.[41–44] Besides, five possible shared biologic pathways (ERK5 signaling, Wnt/ $\beta$ -catenin signaling, androgen signaling, role of Oct4 in mammalian embryonic stem cell pluripotency, Growth hormone signaling) between adult height and AF have been identified in a prior study.[45] In addition, this association appears to be in part mediated via body mass as well. In the Women's Health Study, additional adjustment for body mass further attenuated the association between BW and AF risk.[14] Increased atrial size, involved in the pathophysiology of AF, has been recognized as a well-established risk factor for AF.[46] Given the potential association between body mass and left atrial size, it is plausible that the association of BW with AF may be mediated through body mass and left atrial

size subsequently.[47] Further investigations are warranted to explore the exact mechanism by which high BW is associated with high AF risk.

A major strength of this study is the design of MR analysis, which can avoid the potential unmeasured confounders and reverse causation in comparison to conventional observational studies.[19, 20] The use of MR analysis enables a causal inference for the association between BW and the risk of AF. Another important strength is that the genetic data were derived from the largest GWAS to date. Extremely large sample size ensures a good statistical power for MR analysis. An additional strength is that large number of SNPs were identified in this study, which is more conducive to reliable and precise results.

There are several limitations in our study that also require discussion. First, a potential threat to the reliability of the results is the violation of the requisite MR assumptions. Potential pleiotropy could not be completely ruled out, which may lead to biased estimates. However, no evidence of pleiotropic effect was observed in the pleiotropy assessment and sensitivity analyses with robust methods. Second, there was partial overlap between the individuals included in the GWAS datasets for BW and AF, which could bias the result if substantial. Although the precise degree of the overlap was difficult to quantified, the UK biobank, one of the three components of BW GWAS, was also part of the AF GWAS (12.9%). The real proportion was probably smaller, thus the risk of bias from sample overlap was likely to be low. Third, the associations between BW and the potential confounders were not explored in this study. Nevertheless, the known effects of SNPs on other traits had been checked in the PhenoScanner. Forth, most of the individuals in our study were of European ancestry, which may limit the generalizability of the results to other population. Fifth, we were unable to address the sexual disparities in association between BW and AF risk, because sex-specific genetic data were not available. Finally, we only revealed the causal association between BW and the risk of AF from a genetic perspective, without involving the maternal intrauterine environment.

## Conclusions

Our findings provide genetic evidence for causal association between high BW and the increased lifelong risk of AF. This suggests that reducing the number of newborns with elevated BW may be a feasible and effective prevention to ease the burden of AF.

## Abbreviations

AF Atrial fibrillation

BW Birth weight

MR Mendelian randomization

SNP Single-nucleotide polymorphism

GWAS Genome-wide association study

SD Standard deviation

EGG Early Growth Genetics

ICD International Classification of Diseases

LD Linkage disequilibrium

IVW Inverse variance-weighted

OR Odds ratio

CI Confidence interval

InSIDE Instrument Strength Independent of Direct Effect

SE Standard error

MR-PRESSO Mendelian Randomization Pleiotropy Residual Sum and Outlier

## **Declarations**

### **Ethics approval and consent to participate**

In this study, we only used summary results from previous GWASs that are publicly accessible. Ethics approval and consent to participate were available in the corresponding studies.

### **Consent for publication**

Not applicable.

### **Availability of data and materials**

Not applicable.

### **Competing interests**

The authors declare that they have no competing interests.

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### **Authors' contributions**

SC, GF and WZ conceived and designed the study. SC and FY performed statistical analysis. All authors statistical analysis. SC, FY and TX wrote the manuscript. YW and KZ revised the paper. All authors read and approved the final manuscript.

## Acknowledgements

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## Tables

**Table 1.** MR-Egger regression of the causal association between the birth weight and the atrial fibrillation.

MR-Egger	Estimate	SE	OR	LCI	UCI	p-value
slope	0.27	0.17	1.31	0.94	1.81	0.11
intercept	0.00	0.00	1.00	0.99	1.01	0.62

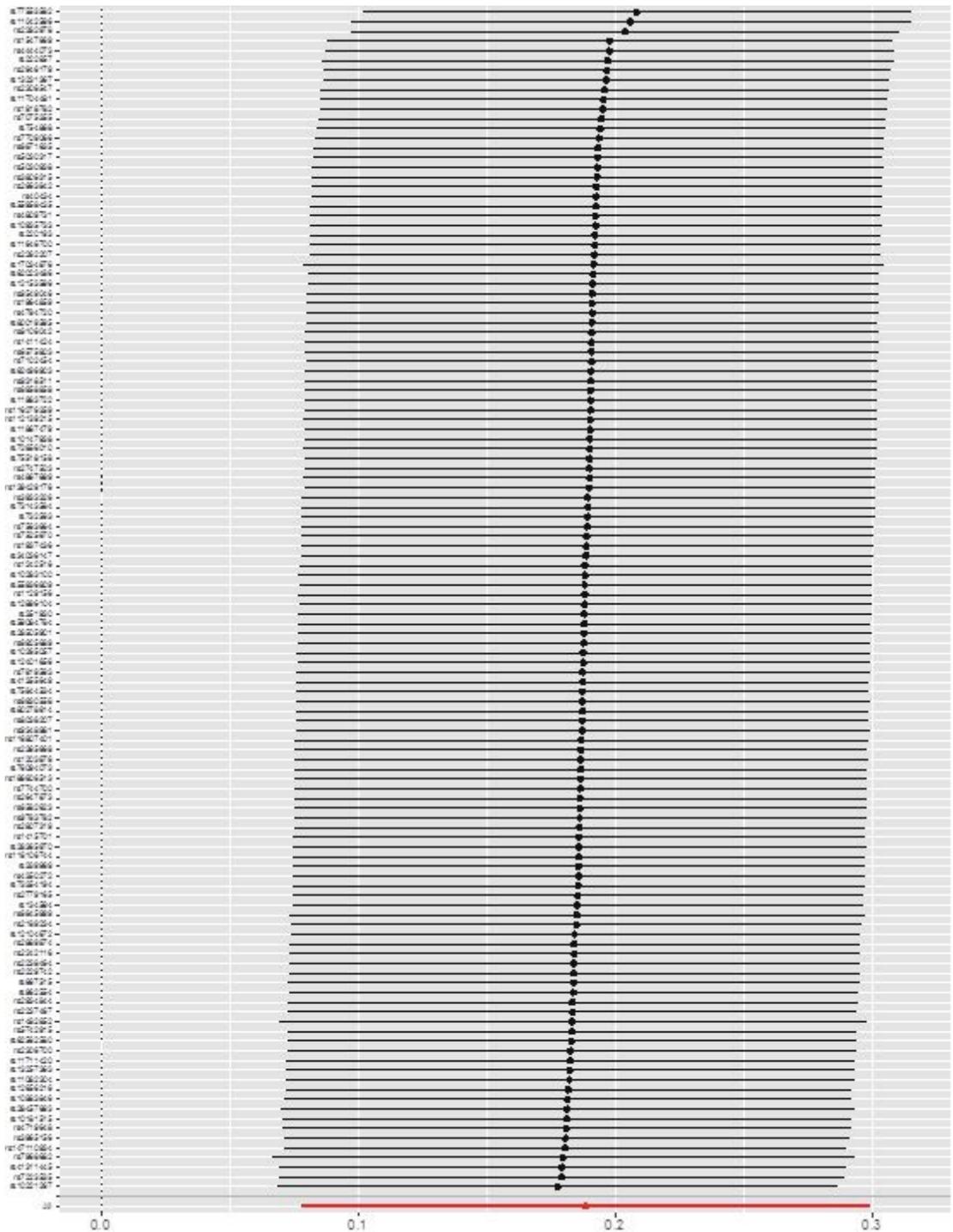
SE, standard error; OR, odd ratio; LCI, the lower confidence interval; UCI, the upper confidence interval.

**Table 2.** Power calculation for the analyses using the 122 SNPs.

Factors	Settings
Sample size	1,030,836
Type-I error rate	0.05
Proportion of AF cases	0.06
Odds ratio of AF per standard deviation of BW	1.21
Proportion of variance explained for the association between the 122 SNPs and BW	0.02
Power	1.00

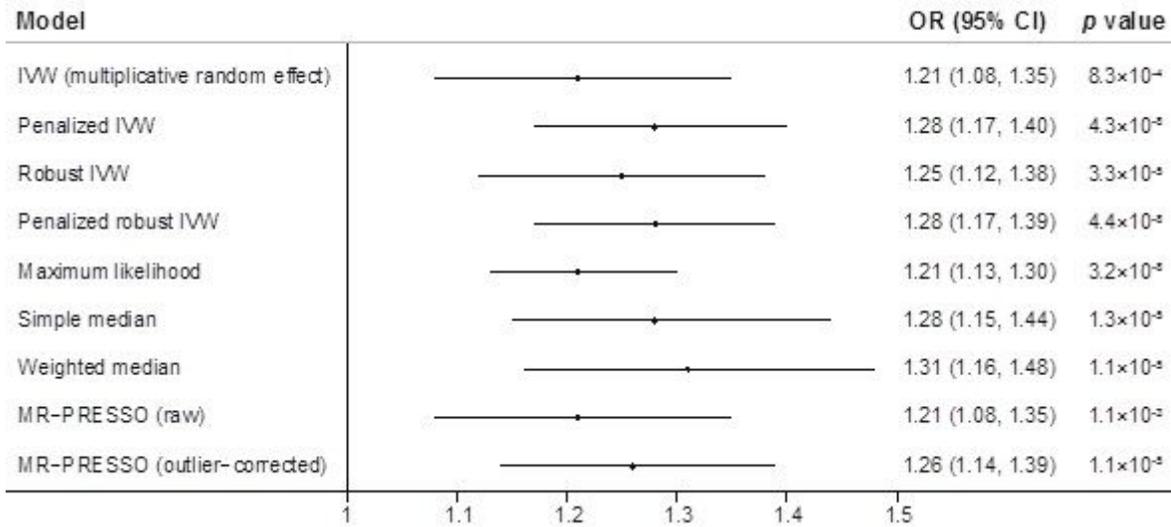
SNP, single nucleotide polymorphism; AF, atrial fibrillation; BW, birth weight.

## Figures



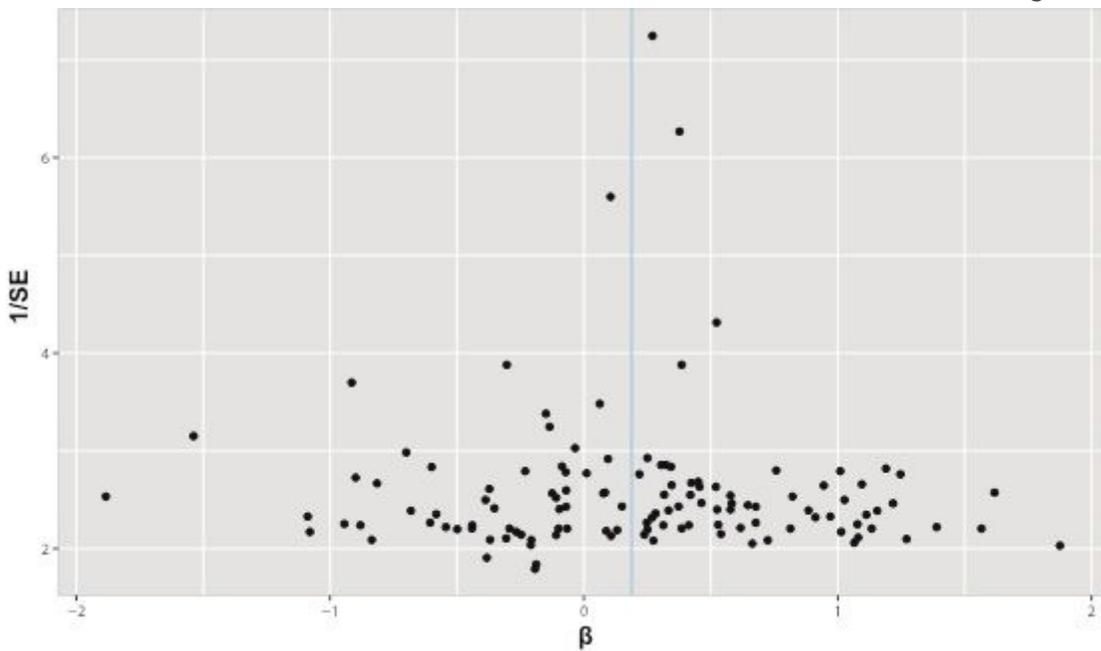
**Figure 1**

Leave-one-out analysis of the causal association between the birth weight and the atrial fibrillation. The black dots and bars indicate the estimates and 95% confidence interval when the specific SNP is removed. The red dot and line indicate the overall estimate and 95% confidence interval using the fixed-effects IVW method. SNP, single nucleotide polymorphism; IVW, inverse variance-weighted.



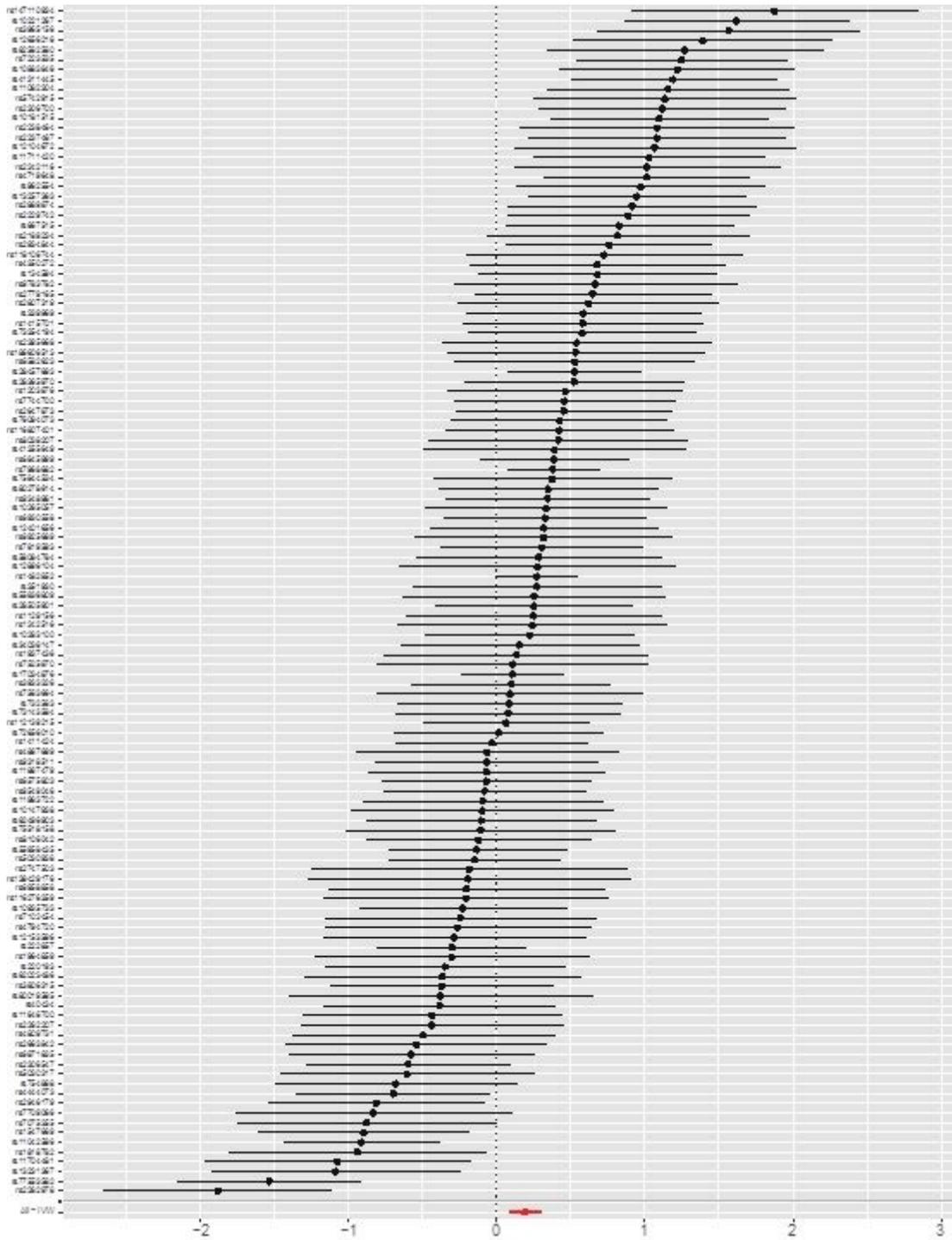
**Figure 2**

Association between the birth weight and the atrial fibrillation investigated with different statistical methods. OR, odds ratio; CI, confidence interval; IVW, inverse variance-weighted.



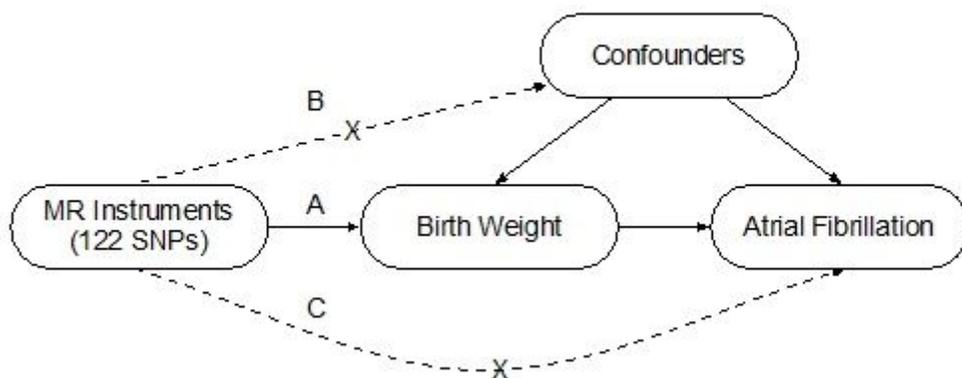
**Figure 3**

Funnel plot of the Mendelian randomization analysis. X axis presents the estimate of the causal effect and Y axis presents the relevant inverse standard error. The dots indicate each SNP, and the line indicates the overall estimate using fixed-effects IVW method. SNP, single nucleotide polymorphism; IVW, inverse variance-weighted.



**Figure 4**

Fixed-effects IVW analysis of the causal association between the birth weight and the atrial fibrillation. The black dots indicate the estimates of the causal effect using the relevant SNP, and the black bar indicate the relevant 95% confidence interval. The red dot and bar indicate the overall estimate and the 95% confidence interval using the fixed-effects IVW method. IVW, inverse variance-weighted; SNP, single nucleotide polymorphism.



**Figure 5**

Conceptual framework of the two-sample Mendelian randomization study design. This method is based on three core assumptions as follows: A. the SNPs should be associated with the birth weight; B. the SNPs should independent of the confounders; C. the SNPs should be associated with the atrial fibrillation only via the birth weight. SNP, single nucleotide polymorphism.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementary.docx](#)