Original Article

Exploring the impact of electrocardiographic parameters on the risk of common arrhythmias: a two-sample Mendelian randomization study

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Background: Observational studies have shown that heart rate (HR), heart rate variability (HRV), P-wave terminal force, P-wave duration, T-wave amplitude and PR interval are associated with risk factors for atrial fibrillation (AF) or bradycardia. Arrhythmias are associated with many causes of hospitalization. However, observational studies are susceptible to confounding factors that have not yet been identified. The objective of this study was to clarify the causal relationships by Mendelian randomization analysis.

Methods: We conducted a two-sample and multivariate Mendelian randomization (MVMR) analysis using genome-wide association study (GWAS) data from a European population to assess the total and direct causal effects of HR, three HRV traits, P-wave terminal force, P-wave duration, T-wave top amplitude in five-lead modes, and the PR interval on the risk of AF (N=191,205), bradycardia (N=463,010), and supraventricular tachycardia (SVT) (N=463,010).

Results: The results of the univariate MR analysis revealed the following significant causal effects: the higher the genetically predicted PR interval, the lower the risk of AF; the higher the HR and T-wave top amplitude (aVR leads and V3 + V4 + aVL leads), the lower the risk of bradycardia; and the higher HR and the lower PR interval, the higher the risk of SVT. The multivariate MR results indicated that the HRV_ standard deviation of the normal-to-normal (SDNN) interval had an independent causal effect on the risk of AF [odds ratio (OR): 0.515; 95% confidence interval (CI): 0.278–0.954; P=0.03], and the T-wave top amplitude in the aVR leads (OR: 0.998; 95% CI: 0.996–0.999; P<0.001) and the HRV_SDNN (OR: 0.988; 95% CI: 0.976–1.000; P=0.045) had independent causal effects on the risk of bradycardia.

Conclusions: The HRV_SDNN had an independent causal effect on AF, while the HRV_SDNN and T-wave top amplitude in the aVR leads had independent causal effects on bradycardia, which suggests that some of the electrocardiographic parameters have preventive effects on the incidence of AF and bradycardia.

Keywords: Mendelian randomization (MR); atrial fibrillation (AF); supraventricular tachycardia (SVT); bradycardia

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Introduction

Arrhythmia is a common reason for hospitalization. As life expectancy increases, the prevalence of arrhythmias continues to increase, and arrhythmias have become a leading cause of death (1,2). Atrial fibrillation (AF) and atrial flutter are not only the most common types of arrhythmia but are also risk factors for a variety of cardiovascular diseases (e.g., ischemic stroke and heart failure) (3). AF is associated with increasing morbidity and mortality, and thus represents a growing public health concern and economic burden (4-7). Bradycardia is a common arrhythmia or an abnormal heart rate (HR), for which a large number of pacemakers are implanted each year (8,9). Bradycardia is a concomitant symptom of certain diseases (e.g., severe acute respiratory syndrome coronavirus 2 infection, epilepsy, and multiple myeloma) (10-13) and may even lead to increased mortality in these patients (11,14). Another common type of arrhythmia is supraventricular tachycardia (SVT), which can be divided into several different subtypes according to the different mechanisms and can lead to obvious discomfort, pain, and a higher hospital admission rate (15). SVT is the most common form of tachycardia in infants (16), and the prevalence of SVT is also higher in older populations (it is more than five times more common in people aged ≥65 years than younger people) and in children. The true prevalence of SVT in children is unknown, but it is estimated that 1 in 250–1,000 children has SVT (17,18).

The electrocardiogram (ECG) describes the electrical activity of the heart at a macroscopic level and is the objective basis for the diagnosis of cardiac arrhythmias (19). Prediction for arrhythmias is crucial for early intervention and hence management of arrhythmias. A study has placed high hopes on ECG for arrhythmia prediction (20). Previous observational studies suggest that HR, heart rate variability (HRV), P-wave terminal force, P-wave duration, and the PR interval are all associated with an increased risk of AF (21-30). In addition, increased T-wave amplitude is associated with the risk of AF (31), and an increased PR interval is associated with the risk of atrial flutter (32). T-wave amplitude is associated with the risk of coronary heart disease and myocardial infarction, which may lead to bradycardia (33). However, observational studies are susceptible to confounding factors, such as age, gender, race (23-26), physical activity, and health status, which are risk factors for some HR abnormalities and have a large impact on ECG parameters. If a causal relationship between ECG parameters and arrhythmias can be clarified, it could help clinicians to refine the mechanism of arrhythmogenesis and predict or screen for the occurrence of arrhythmias using a cost-effective, early-identification method.

Mendelian randomization (MR) relies on the natural random assignment of genetic variants in the population during meiosis. These genetic variants are generally unaffected by confounding factors and reverse causality, thus enabling a more reliable assessment of the exposure-outcome causal associations (34). The present study adopted a two-sample MR method to assess the causal effect of different ECG parameters on several common arrhythmias using the latest genome-wide association study (GWAS) summary data. A multivariate Mendelian randomization (MVMR) analysis was also conducted to

Highlight box

Key findings

- Heart rate variability-standard deviation of the normal-to-normal (HRV_SDNN) and atrial fibrillation (AF) have an independent causal effect, the T-wave top amplitude in the aVR leads had independent causal effects on the risk of bradycardia.

What is known and what is new?

- Observational studies have been conducted to correlate changes in electrocardiogram (ECG) parameters with the occurrence of arrhythmias, but the results are inconsistent and susceptible to confounding factors.
- Newly reported evidence for an independent causal effect of HRV_SDNN and AF, as well as T-wave top amplitude in aVR leads and HRV_SDNN had independent causal effects on the risk of bradycardia.

What is the implication, and what should change now?

- This manuscript provides evidence of the causal relationship between some ECG parameters and arrhythmias, which will give a cost-effective early identification method for predicting or screening the occurrence of arrhythmias.
- A clear causal relationship would correlate the mechanism of arrhythmogenesis with the electrophysiological activity represented by ECG-related parameters, which would advance the understanding of arrhythmias.

assess the independent causal relationship between the ECG parameters and arrhythmias. We present this article in accordance with the STROBE-MR reporting checklist (35) (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-814/rc).

Methods

Study design

To explore the genetic association between the eight ECG-related parameters (exposure) and the risk of AF, bradycardia, and SVT, a two-sample MR analysis was conducted using the GWAS data. In the MR analysis, genetic variants were treated as instrumental variables (IVs) for exposure based on the three following assumptions: (I) relevance: genetic IVs are significantly associated with the eight ECG parameters; (II) independence: genetic IVs are not related to potential confounding factors that may affect the eight ECG parameters and AF, bradycardia, and SVT; (III) exclusion restriction: genetic IVs do not directly affect AF, bradycardia, and SVT, and only affect them through the 8 ECG-related parameters. The whole process is shown in *Figure 1*. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Data source

Publicly available GWAS databases, including the GRASP = HuGeAMP database, were searched to obtain eligible data sets of the eight ECG parameters and AF, bradycardia, and SVT.

Summary-level data on the ECG-related parameters

The summary-level ECG data were derived from several large-scale GWAS meta-analyses covering the eight ECG-related parameters based on European populations. The eight ECG parameters were the resting HR [max N=85,787 (European)] (36), three HRV traits {i.e., the root mean square of successive differences (RMSSD) [max N=26,785 (European)], the peak-valley respiratory sinus arrhythmia or high frequency power (pvRSA/HF) [max N=24,342 (European)], and the standard deviation of the normal-to-normal interval (SDNN) [max N=28,112 (European)]} (37), PR interval [N=271,570 (European)] (38), P-wave duration [N=37,678 (European) + 6,778 (African)], P-wave terminal force [N=33,955 (European) + 6,778 (African)] (39), and T-wave top amplitude [max N=37,977 (European)] in five-lead modes (septal: ECG lead V1 + V2; lateral: ECG lead I + aVL + V5 + V6; inferior: ECG lead II + III + aVF; anterior: ECG lead V3 + V4 + aVL; avr: ECG lead aVR) (40). For further details, see *Table 1*.

Summary-level data on HR abnormalities

Data related to AF and atrial flutter were obtained from the FinnGen consortium (R8, accessed on May 9, 2023, https://www.finngen.fi/en). The data set comprised 34,748 cases and 156,457 controls. The bradycardia and SVT data sets, comprising 1,254 cases and 461,756 controls for bradycardia and 1,306 cases and 461,704 controls for SVT, respectively, were both derived from the IEU GWAS database (https://gwas.mrcieu.ac.uk/) (41-43). All the GWAS summary data on outcomes were based on European populations (*Table 1*).

Statistics

Extraction of IVs

Single-nucleotide polymorphisms (SNPs) in exposure and outcome were searched in the GWAS database according to the above assumptions. SNPs that satisfied the GWAS significance ($P<5\times10^{-8}$) or threshold of $P<1\times10^{-5}$ (44) (when the number of SNPs used for the MR analysis was too few) in the exposure-GWAS were extracted as IVs to ensure that the genetic variants were significantly correlated with exposure. Only independent SNPs not in linkage disequilibrium (LD, $r^2<0.01$ within a 5,000-kb window) were retained. The remaining SNPs were then used to extract relevant information from the outcome-GWAS before coordinating the summary statistics so that the effect of the SNPs on the outcome and exposure was relative to the same allele, and the palindromic SNPs were excluded from the MR analysis [Supplementary file (Appendix 1) and Table S1].

Univariate MR analysis

The MR analysis was conducted following the above three assumptions. The inverse-variance weighted (IVW) (45) method was used as the primary method. To ensure that the three core assumptions were not breached, MR-Egger regression (46,47), weighted median (48,49), and a causal analysis using summary effect estimates (CAUSE) (50) were performed as the sensitivity analyses. We further used several visual plots, such as leave-one-out plots and funnel plots, to detect possible significant outliers. MR-Egger

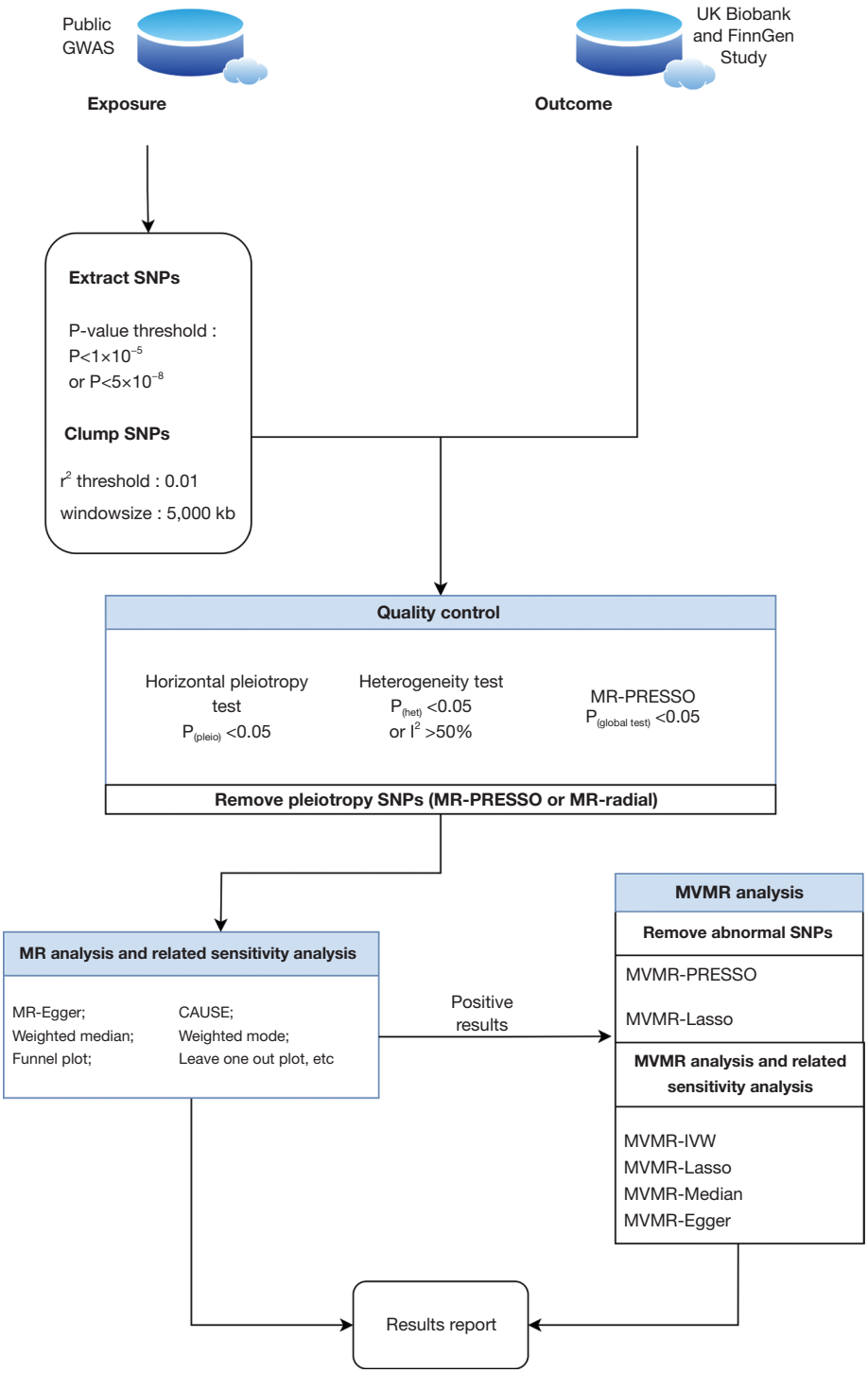

Figure 1 Flow diagram of the Mendelian randomization design. GWAS, genome-wide association study; SNP, single-nucleotide polymorphism; MR, Mendelian randomization; MVMR, multivariate mendelian randomization; het, heterogeneity; pleio, horizontal pleiotropy; CAUSE, causal analysis using summary effect estimates; MR-PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier; MR-Radial, IVW radial regression and egger radial regression; IVW, inverse-variance weighted.

Table 1 Description of the GWAS data sources used in the Mendelian randomization study

Exposure/outcome	Sample size	Ancestry	PMID/GWAS ID
HR	85,787	European	23583979
HRV_RMSSD	26,785	European	28613276
HRV_pvRSAHF	24,342	European	28613276
HRV_SDNN	28,112	European	28613276
PR interval	271,570	European	32439900
P-wave duration	37,678+6,778	European + African	28794112
P-wave terminal force	33,955+6,778	European + African	28794112
T-wave top amplitude	37,977	European	26962151
Atrial fibrillation and atrial flutter	34,748 cases and 156,457 controls	European	N/A
Bradycardia	1,254 cases and 461,756 controls	European	ukb-b-11664
Supraventricular tachycardia	1,306 cases and 461,704 controls	European	ukb-b-11748

GWAS, genome-wide association study; HR, heart rate (resting); HRV, heart rate variability; RMSSD, root mean square of successive differences; pvRSAHF, peak-valley respiratory sinus arrhythmia or high frequency power; SDNN, standard deviation of the normal-to-normal interval; N/A, not applicable.

follows the INstrument Strength Independent of Direct Effect (InSIDE) assumption (46,47), the weighted median approach assumes that valid IVs provide more than half of the weight (48), and the weighted mode assumes that multiple genetic variants are valid (49).

Heterogeneity was assessed by the Cochran Q heterogeneity test and I^2 statistics. A P value <0.05 or I^2 value >50% implied significant heterogeneity, and outlier SNPs were detected and excluded by the Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) test. If the MR-PRESSO test failed to detect outliers, then IVW radial regression and Egger radial regression were used to further detect and exclude outlier SNPs (51,52). Then, $25\%<I^2<50\%$ implied moderate heterogeneity, and the random-effects model was selected for analysis.

The presence of horizontal pleiotropy would violate the MR core assumptions, and the intercept test (P>0.05 indicates no pleiotropy) of MR-Egger regression was used to assess horizontal pleiotropy. An MR-PRESSO analysis was conducted to detect (the global test) and correct (the outlier test) the abnormal SNPs that might lead to horizontal pleiotropy and to evaluate significant differences in the causal estimate before and after outlier removal (distortion test) (51) [(available online: https://cdn.amegroups.cn/static/public/jtd-24-814-1.xlsx) for details of all the tool variables used for the MR analysis]. A CAUSE analysis was performed to account for correlated and uncorrelated horizontal pleiotropy, and a threshold of $P<1\times10^{-3}$ was used to ensure sufficient SNPs to assess the deleterious parameters. When estimating the correlations between the summary statistics due to sample overlap or population structure, all the variants were used if the total number of SNPs in the summary data set was less than 1,000,000 to avoid poor estimates of the confounding parameters, and the remaining steps were performed according to the default parameters in the CAUSE package (50).

MVMR analysis

Phenotypes with positive results in the univariate MR (P<0.05) analysis were used as exposures. An MVMR analysis was performed after the detection and removal of outlier SNPs by the MR-PRESSO analysis. The MVMR-IVW method was used as the primary multivariate method, and the associated sensitivity tests included the MVMR-Egger, MVMR-Lasso, and MVMR-median tests. MVMR-PRESSO and MVMR-Egger intercept tests were used to identify potential horizontal pleiotropy.

When performing the MVMR analysis with bradycardia as the endpoint, considering that T-wave top amplitude_avr and T-wave top amplitude_anterior are different leads of the same waveband that both essentially respond to ventricular repolarization, the exposures were divided into two groups for the MVMR analysis (HR, HRV_RMSSD,

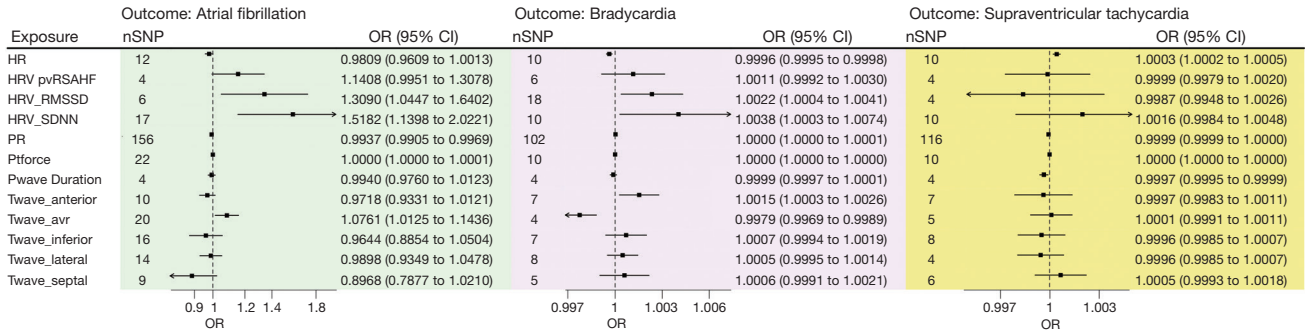

Figure 2 Forest plot of the univariate Mendelian randomization results. The causal effects of the ECG-related parameters on arrhythmia risk were expressed as the OR per unit. Error bars represent the 95% CIs of the estimates. nSNP, the number of single-nucleotide polymorphisms; HR, heart rate (resting); Twave, T-wave top amplitude; septal, ECG lead V1 + V2; lateral, ECG lead I + aVL + V5 + V6; inferior, ECG lead II + III + aVF; anterior, ECG lead V3 + V4 + aVL; avr, ECG lead aVR; Ptforce, P-wave terminal force; Pwave duration, P-wave duration; HRV, heart rate variability; RMSSD, root mean square of successive differences; pvRSAHF, peak-valley respiratory sinus arrhythmia or high frequency power; SDNN, standard deviation of the normal-to-normal interval; PR, PR interval; OR, odds ratio; CI, confidence interval.

HRV_SDNN, and T-wave top amplitude_avr or T-wave top amplitude_anterior). If the Cochran Q of the MVMR-IVW, the MVMR-Egger intercept test, and the MVMR-PRESSO global test all indicated the existence of horizontal pleiotropy or heterogeneity and the MVMR-PRESSO test still failed to detect significant outliers by increasing the number of simulation calculations, we supplemented the MVMR-Lasso method to identify and eliminate abnormal SNPs (53,54). MR-Lasso analysis is an analytical method that identifies some genetic variants as valid IVs and then evaluates causality by fitting the regularized regression model with a standard IVW method with only valid genetic variants (55).

The *F*-statistic for each SNP was calculated using the following formula: *F*-statistic = $beta^2/se^2$ (56). Considering the multiple tests, the significance threshold was set at P<0.00139 (α=0.05/36, 12 exposures and three outcomes) based on Bonferroni correction. Referring to previous articles (44), we considered the results to be strongly significant when P<0.00139 and the evidence to be suggestive when 0.00139<P<0.05. Bonferroni correction was not used in the MVMR analysis due to its mutually adjusted nature (57).

Software

All the analyses were performed with R software (version 4.1.1), and the MR analyses were performed using the "TwoSampleMR", "MendelianRandomization", "MRPRESSO", "RadialMR", and "CAUSE" packages.

Results

Univariate MR

The *F*-statistics for all the included SNPs were greater than 10, which avoided the influence of weak IVs in our study to a certain extent (available online: https://cdn.amegroups.cn/static/public/jtd-24-814-1.xlsx).

ECG-related parameters and AF

Evidence from the primary IVW MR method suggested that the genetically predicted PR interval was negatively associated with the development of AF [odds ratio (OR): 0.994; 95% confidence interval (CI): 0.991–0.997; $P=9.8\times10^{-5}$]. The genetically determined HRV_SDNN, HRV_RMSSD, and T-wave top amplitude_avr were positively associated with the development of AF (HRV_SDNN, OR: 1.518; 95% CI: 1.140–2.022; P=0.004; HRV_RMSSD, OR: 1.309; 95% CI: 1.067–1.605; P=0.01; T-wave top amplitude_avr, OR: 1.076, 95% CI: 1.012–1.144; P=0.02). The other genetically determined ECG-related parameters were not causally associated with the development of AF [*Figure 2* and Supplementary file (Appendix 1), Table S2].

ECG-related parameters and bradycardia

Evidence from the major IVW MR method suggested that the genetically determined T-wave top amplitude_avr, and HR were negatively associated with the occurrence of bradycardia (T-wave top amplitude_avr, OR: 0.998; 95% CI: 0.997–0.999; P<0.001; HR, OR: 1.000; 95% CI: 0.999–1.000; P<0.001). The evidence suggested that the HRV_RMSSD, HRV_SDNN, and T-wave top amplitude_anterior were positively associated with the occurrence of bradycardia (HRV_RMSSD, OR: 1.002; 95% CI: 1.000–1.004; P=0.02; HRV_SDNN, OR: 1.004; 95% CI 1.000–1.007; P=0.03; T-wave top amplitude_anterior, OR: 1.001; 95% CI: 1.000–1.003; P=0.02), whereas the other genetically determined ECG-related parameters were not causally associated with the occurrence of bradycardia [*Figure 2* and Supplementary file (Appendix 1), Table S2].

ECG-related parameters and SVT

Evidence from the primary IVW MR approach suggested a positive correlation between the genetically determined HR and the occurrence of SVT (OR, 1.000; 95% CI: 1.000–1.001; P<0.001). The evidence suggested that the PR interval and P-wave duration were negatively associated with the occurrence of SVT (PR interval, OR: 1.000; 95% CI: 1.000–1.000; P=0.001; P-wave duration, OR: 1.000; 95% CI: 1.000–1.000; P=0.007), whereas the other genetically determined ECG-related parameters were not causally related to the occurrence of bradycardia [*Figure 2* and Supplementary file (Appendix 1), Table S2].

Sensitivity analyses

The results of some sensitivity analyses suggested possible heterogeneity [Supplementary file (Appendix 1), Table S2]; however, there was no evidence of horizontal pleiotropy and heterogeneity (Egger-intercept test and heterogeneity test, P>0.05) [Supplementary file (Appendix 1), Tables S3,S4]. In addition, the MR-PRESSO method and the leave-one-out plot did not detect abnormal SNPs, and the funnel plot was roughly symmetrical [Supplementary file (Appendix 2)].

The higher values of Eta and Q suggested that the results were more influenced by the multiplicity of the correlation levels (50,58). The CAUSE analysis results showed that the causal model did not hold in estimating the causal associations described above (all P>0.05) [Supplementary file (Appendix 1), Table S5].

MVMR

All exposures with positive results (P<0.05) in the univariate MR were selected as exposures for the MVMR analysis.

ECG-related parameters and AF

After adjusting the T-wave top amplitude_avr, PR interval, and HRV_RMSSD, we found that the HRV_SDNN had an independent causal effect on the occurrence of AF (HRV_SDNN, OR: 0.515; 95% CI: 0.278–0.954; P=0.03). In addition, no outliers were detected by the MVMR-PRESSO test, and no heterogeneity and pleiotropy were detected by the MR-Egger intercept test and heterogeneity test (both P>0.05) [*Figure 2* and Supplementary file (Appendix 1), Table S6].

ECG-related parameters and bradycardia

After adjusting the HR and HRV_RMSSD and eliminating the outliers (rs11578508 and rs6127471), we found that the T-wave top amplitude_avr and HRV_SDNN had independent causal effects on the occurrence of bradycardia (T-wave top amplitude_avr, OR: 0.998; 95% CI: 0.996–0.999; P<0.001; HRV_SDNN, OR: 0.988; 95% CI: 0.976–1.000; P=0.045), while the HR and HRV_RMSSD had no independent causal effects on the occurrence of bradycardia. After adjusting for the T-wave top amplitude_anterior and HR and eliminating the outliers (rs7633988 and rs6127471), we found that the HRV_SDNN and HRV_RMSSD were independently causally related to the occurrence of bradycardia (HRV_RMSSD, OR: 1.008; 95% CI: 1.000–1.016; P=0.04; HRV_SDNN, OR: 0.988; 95% CI: 0.977–1.000; P=0.04). All the other sensitivity analysis results were generally consistent with those found using the MVMR-IVW method. In addition, no outliers were detected by the MVMR-PRESSO test, and no heterogeneity or pleiotropy was detected by the MR-Egger intercept test and heterogeneity test (both P>0.05) [*Figure 3* and Supplementary file (Appendix 1), Table S6].

ECG-related parameters and SVT

Of the 116 SNPs significantly associated with the PR interval in the univariate analysis, 39 SNPs were associated with the HR only, 12 SNPs were associated with the P-wave duration only, and 19 SNPs were associated with both the HR and P-wave duration. Considering the overlap of some

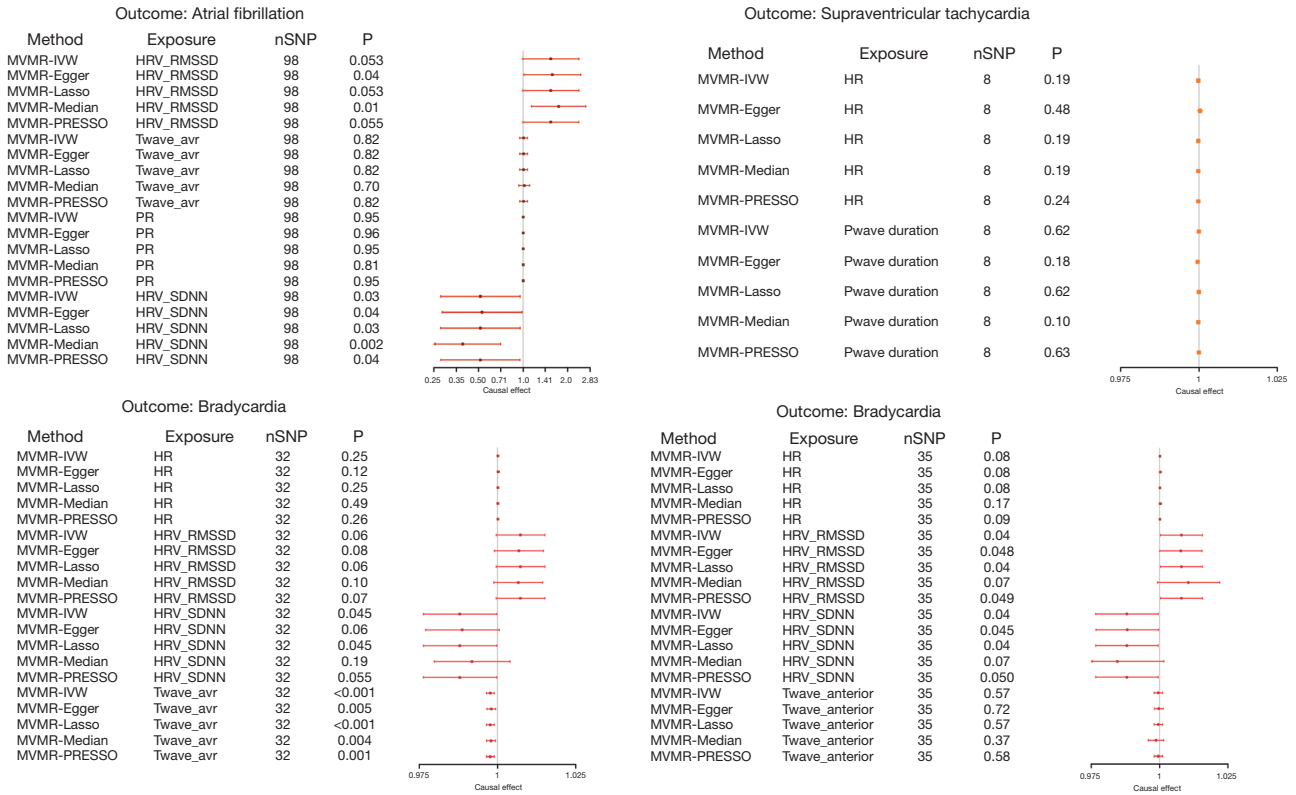

Figure 3 Forest plot of the multivariable Mendelian randomization results. The causal effects of the ECG-related parameters on arrhythmia risk were expressed as the OR per unit. Error bars represent the 95% CIs of the estimates. MVMR, multivariate mendelian randomization; IVW, inverse-variance weighted; HR, heart rate (resting); HRV, heart rate variability; RMSSD, root mean square of successive differences; PR, PR interval; SDNN, standard deviation of the normal-to-normal interval; Twave, T-wave amplitude; avr, ECG lead aVR; anterior, ECG lead V3 + V4 + aVL; Pwave duration, P-wave duration; nSNP, the number of single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.

SNPs caused by the inclusion of the P-wave duration in the PR interval, an MVMR analysis was performed with the HR and P-wave duration as exposures (59).

The results suggested that there was no independent causal relationship between the HR or P-wave duration and the occurrence of SVT. The results of the sensitivity analyses were similar to those found using the IVW method. No heterogeneity or horizontal pleiotropy were detected by the heterogeneity and MR-Egger intercept tests, and no outliers were detected by the MR-PRESSO analysis (all P>0.05) [*Figure 3* and Supplementary file (Appendix 1), Table S6].

Discussion

Using a univariate MR analysis, we not only drew conclusions consistent with those drawn by previous studies on the causal relationship between the HRV_SDNN, PR interval, and HRV_RMSSD and the occurrence of AF, as well as the resting HR, PR interval, and P-wave duration and the occurrence of SVT (26,60,61), we also identified novel causal relationships between the T-wave top amplitude (aVR leads) and the occurrence of AF, as well as between the resting HR, HRV_SDNN, HRV_RMSSD, and T-wave top amplitude (aVR leads and V3 + V4 + aVL leads) and the occurrence of bradycardia.

Statistics

Unlike previous studies (26,60,61), the present study employed a more rigorous MR-Radial approach to minimize potential horizontal pleiotropy. However, this may have resulted in the loss of a portion of potentially valid SNPs. Furthermore, taking into account the interactions

between the different ECG parameters, MVMR analyses were conducted to explore the independent effects of ECG parameters on heart rate abnormalities. Notably, the MVMR analysis suggested that there was a causal relationship between the HRV_SDNN and AF, as well as the T-wave top amplitude in the aVR leads and HRV_SDNN and the occurrence of bradycardia remained.

The results of the CAUSE analysis were found to be inconsistent with the aforementioned results obtained via IVW and other sensitivity methods. However, given the relatively relaxed threshold (1×10^{-3}) for extracting IVs and the strictness of removing variants with ambiguous alleles (G/C or A/T), we postulated that the CAUSE analysis might remove SNPs that are strongly correlated with exposure and used in other MR analyses, thereby resulting in the loss of some information, particularly when the number of SNPs used in other MR analyses is low. CAUSE was employed to circumvent false alarms caused by correlated horizontal pleiotropy. The results of the MR-Egger intercept test, MR-PRESSO, and other methods for detecting uncorrelated horizontal pleiotropy did not reach statistical significance. Additionally, the effect size of CAUSE for detecting correlated horizontal pleiotropy was relatively small. Therefore, the disparate results observed between CAUSE and IVW do not indicate that the positive IVW result is a false alarm due to correlated horizontal pleiotropy.

ECG-related parameters and AF

Nevertheless, in contrast to previous study (60), no causal relationships were identified between alterations in HR and the occurrence of AF. This may be because we did not stratify the resting HR in the present study. We might not have found a causal relationship between the total resting HR and the occurrence of AF due to the U-shaped association between the resting HR and the AF risk ratio that has been reported in previous study (60).

The effect of the HRV_SDNN on the occurrence of AF changed, and the significance of the causal relationships between the T-wave top amplitude (aVR leads), HRV_RMSSD, and PR interval and the occurrence of AF, as well as those between the resting HR and P-wave duration and the occurrence of SVT, was not observed in the multivariate analysis results. This result was expected given the strong correlation between the resting HR, HR variability index, and ECG parameters; therefore, the effect of the HRV_SDNN on the occurrence of AF changed after adjusting for other parameters, while the independent causal effect of some parameters on AF or SVT was no longer significant.

ECG-related parameters and bradycardia

As more electrical activity is transmitted by parasympathetic nerves than by sympathetic nerves, the resting HR in humans is mainly determined by the parasympathetic sector (62). Further, the changes in RMSSD also represent parasympathetic activity (63). However, the multivariate analysis results suggested that RMSSD and the resting HR had no independent effect on the occurrence of bradycardia. Even so, the positive results of the univariate MR analysis of RMSSD and the resting HR, and the lower P value of RMSSD in the two multivariate analyses suggested that the acetylcholine (ACh) released from the vagus nerve may play an important role in the occurrence of bradycardia.

The ACh released from the vagus nerve can stimulate Gαi/o-coupled muscarinic M2 receptors and affect membrane excitability via the Gβγ-mediated direct activation of G protein-coupled inwardly rectifying potassium (GIRK) channels (62). The decrease in HRV_RMSSD implies a decrease in the phase change of cardiac vagal activity, which suggests a diminished activation of the GIRK channels. In addition, rs180238 and rs4262 (partial SNPs used for the MVMR analysis) were found to be significantly associated with a guanine nucleotide binding protein (G protein, gamma 11) (*GNG11*) in the expression quantitative trait loci of the HRV SNPs (37), which encodes the Gα βγ heterotrimer of the gamma 11 subunit and is expressed at high levels in the heart (64,65). Reduced gamma-11 availability may reduce Gβγ component-induced GIRK activation. Therefore, the exponential decrease in the HRV_RMSSD may imply an attenuation in the activation affecting GIRK channels. Meanwhile, studies have shown that excessive vagal stimulation is dependent on increased GIRK currents in mice and directly leads to atrioventricular block (which often occurs with bradycardia) (66,67).

The SDNN represents sympathetic and parasympathetic activity, but it is not clear whether changes in HRV are related to sympathetic or vagal nerves (63). Research has shown that knocking out the gene for a key factor (RGS4) in the cardiac vagal pathway may result in unchanged resting HR but bradycardia in mice after the administration of M2 receptor-receptor agonists (68). The independent causal relationship between the SDNN and bradycardia after adjustment for RMSSD and HR may imply that sympathetic nerves play an important role in genetically

mediated bradycardia. Sympathetic nerves in the fight-or-flight response can increase the HR by secreting catecholamines that stimulate β-adrenergic receptors in cardiomyocytes (69), but norepinephrine may have less of an effect on the resting HR and does not reduce the release of ACh in the human heart (70). However, in addition to norepinephrine, sympathetic nerves also release different levels of co-transmitters (e.g., adenosine triphosphate, neuropeptide-Y, and galanin) depending on the level of stimulation. Among these, galanin has been shown to reduce vagally mediated bradycardia (71). Thus, lower sympathetic activity may imply a reduction in co-transmitters, leading to the weakened inhibition of bradycardia.

In the univariate analysis, the T-wave top amplitude (aVR lead) was causally associated with the occurrence of AF and bradycardia. A decrease in the T-wave top amplitude may indicate an abnormal ventricular repolarization process, possibly related to myocardial pathology and autonomic disorders. Bradycardia and T-wave depression caused by alterations in the autonomic nervous system have been observed in athletes (72-74). The aVR lead is the only lead in the body ECG that does not face the "typical" associated wall of the left ventricle (75). A decrease in the T-wave top amplitude detected by the aVR lead may indicate a lesion of the right ventricular myocardium or a disruption of the sympathetic-parasympathetic balance on the right side of the heart, which may play a role in the pathogenesis of AF (76). The different results between the T-wave top amplitude_avr and T-wave top amplitude_anterior in the multivariate analysis of bradycardia suggest that the change in the top amplitude of the T-wave under the aVR leads is more informative.

Limitations

This study had several limitations. First, due to the overlap of SNPs in the GWAS, we did not analyze whether there was an independent causal relationship between the PR interval and the occurrence of SVT, which would require a larger sample of GWAS data for a correlation analysis. Second, referring to previous MR studies and clinical trials (26,60,61,77-81), this study also unified AF with atrial flutter as an outcome. Although atrial flutter is less common and may occur over time in the same individual, caution is needed in interpreting these results (82,83). Third, a U-shaped relationship between some ECG-related parameters and HR abnormalities has been observed in some observational studies; thus, further stratification studies on ECG-related parameters need to be conducted. Fourth, P-wave duration and P-wave terminal force were included in the GWAS for ethnic groups other than Europeans, which could affect the robustness of the MR results. As the relevant GWAS research is mainly conducted among participants of European descent, further research is needed to assess the universality of our results among other ethnic groups. Fifth, despite the relatively low power values observed in our study, this does not affect our significant results [Supplementary file (Appendix 1), Table S7]. Sixth, as with the other two samples of Mendelian randomization, our study is limited to an analysis of causality and does not provide specific cutoff values. Further analysis would require larger studies and individual-level data. Sixth, the sample for the PR interval GWAS was partly from the UK Biobank, and thus might overlap with the SVT and bradycardia samples. Although the exact number of overlapping samples could not be determined, we calculated the sample overlap rate (60,543/463,010=0.13) according to the maximum overlap and used a stronger IV (*F*-statistic: 29.9–1,224.3) to avoid large bias or type I error rates (84). Nevertheless, the results of both sets of MR analyses should be interpreted with caution.

Conclusions

The present study provides new evidence of independent causal relationships between the HRV_SDNN and occurrence of AF, as well as the aVR lead T-wave top amplitude, and HRV_SDNN and the occurrence of bradycardia. Given the limitations of this study, the results should be interpreted with caution in the clinical context; however, the results of this study may still provide some reference for the prediction and prevention of arrhythmias in the future.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-814/coif). The authors have no conflicts of interest to declare.

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