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ORIGINAL ARTICLE

Examining the Causal Relationship between Circulating Metabolic Biomarkers and Arrhythmia Via a Mendelian Randomization Study

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Abstract

Introduction: Arrhythmias, characterized by abnormal heart rhythms, are a significant public health concern. The relationship between circulating metabolic biomarkers and arrhythmia development is actively investigated. Mendelian randomization (MR) offers insight into causal links between metabolic biomarkers and disease outcomes.

Methods: In this two-sample MR study, we used data from the NHGRI-EBI GWAS Catalog and UK Biobank to explore causal relationships between metabolic biomarkers and arrhythmia risk. Rigorous criteria selected genetic instrumental variables and MR methods like inverse variance weighting were applied.

Results: Our analysis identified three metabolic biomarkers associated with increased arrhythmia risk: creatinine, tyrosine, and the phospholipids to total lipids ratio in very large HDL. These findings suggest specific metabolic disturbances may contribute to arrhythmia development.

Conclusion: This MR study reveals insights into the links between metabolic biomarkers and arrhythmia risk. These associations suggest metabolic factors play a role in arrhythmia pathogenesis, offering opportunities for targeted interventions and personalized treatments. Further research is needed to understand mechanisms and clinical implications.

Keywords: Circulating metabolic biomarkers, arrhythmia, mendelian randomization.

Introduction

Arrhythmias, characterized by abnormal heart rhythms, are a significant public health concern associated with adverse cardiovascular outcomes. The intricate interplay between circulating metabolic biomarkers and arrhythmia development has garnered increasing research interest in elucidating the underlying mechanisms and identifying potential therapeutic targets [1]. Circulating metabolic biomarkers, the small molecules involved in various metabolic pathways, play crucial roles in cellular function and signaling processes [2]. However, the causal relationship between specific blood circulating

metabolic biomarkers and arrhythmia remains a topic of ongoing investigation. The previous studies were observational in nature and had limited sample sizes. One major issue is the difficulty in establishing the causality direction. It is uncertain whether arrhythmia triggers changes in plasma circulating metabolic biomarkers levels or if the variations in plasma circulating metabolic biomarkers concentrations are responsible for causing arrhythmia [3]. Mendelian randomization (MR) offers a valuable approach to assess causal relationships between circulating metabolic biomarkers and disease outcomes by leveraging genetic variants as instrumental variables. By utilizing genetic variants that influence circulating metabolic biomarkers levels independently of confounding factors, MR studies can provide insights into the potential impact of circulating metabolic biomarkers on arrhythmia risk. Understanding these causal relationships is essential for identifying novel biomarkers, elucidating disease mechanisms, and informing targeted interventions for arrhythmia prevention and management [4].

In this study, we aim to investigate the causal relationship between blood circulating metabolic biomarkers and arrhythmia through a comprehensive Mendelian randomization analysis. By examining a diverse array of circulating metabolic biomarkers and employing robust sensitivity analyses, we seek to identify circulating metabolic biomarkers that may influence arrhythmia risk and shed light on the underlying mechanisms driving this association. This research has the potential to advance our understanding of the metabolic basis of arrhythmias and pave the way for personalized therapeutic strategies based on metabolite profiles.

Methodology and Materials

Study Design

In this investigation, we applied a two-sample Mendelian randomization approach using aggregate data to examine the relationships between various plasma circulating metabolic biomarkers and the susceptibility to arrhythmia. The plan was predicated on three fundamental principles: (1) genetic instruments accurately anticipate the exposure ($P<5\times10^{-8}$); (2) genetic instruments are independent of potential confounders, and (3) genetic instruments influence the outcomes solely via risk factors. **Figure 1** provides an overview of our study design.

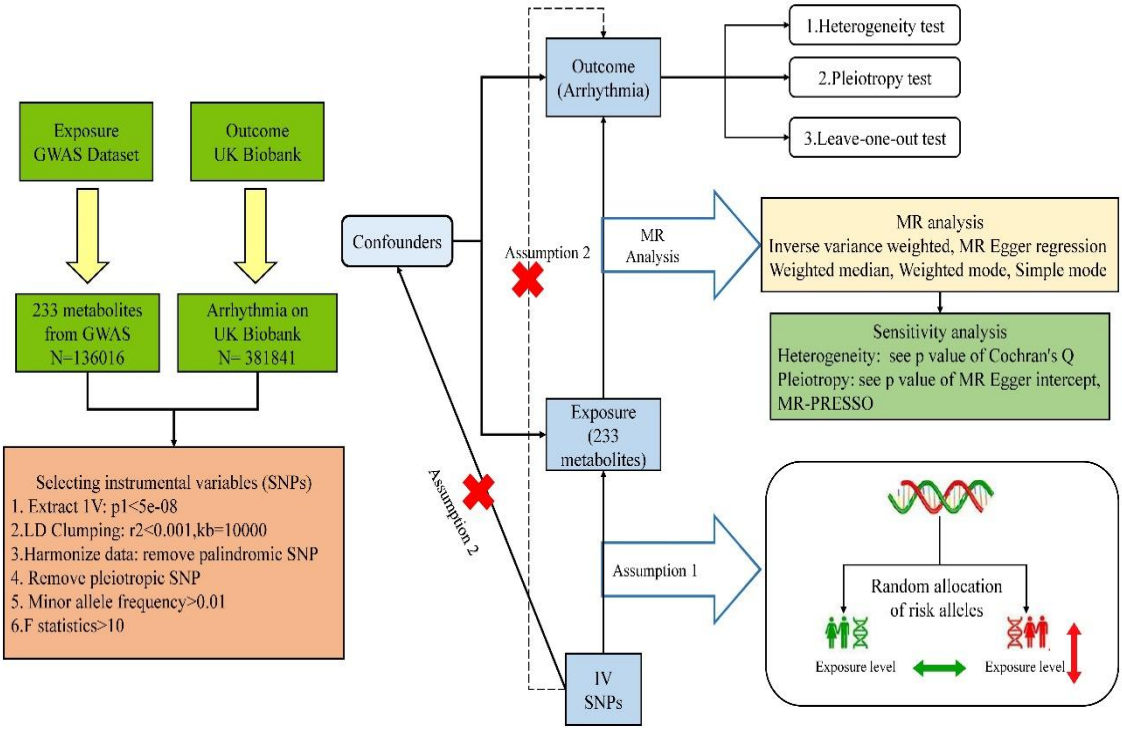


Figure 1: The flowchart of study designs

Data Sources

In our study, we leveraged GWAS data obtained from publicly available databases, specifically utilizing the NHGRI-EBI GWAS catalogue (https://www.ebi.ac.uk/gwas) (accession number: GCST90301941–GCST90302173) to download 233 circulating metabolic biomarkers [5]. To focus on arrhythmia-related associations, we employed study-specific keywords to search the (https://pheweb.org/UKB-SAIGE/). For the estimation of approximately 22 million SNPs genotyped using high-density arrays, we utilized a reference panel sourced from Sardinian sequences [6]. Correlations were evaluated while accounting for relevant covariates. Our study benefitted from the UK Biobank and GWAS database, a valuable resource that integrates genetic information from participants with detailed health records. The extensive and diverse data available in this database offers valuable insights into the genetic underpinnings of various diseases, with the potential to drive the development of novel diagnostic approaches, treatment strategies, and preventive interventions. Utilizing the ID of each arrhythmia type, we accessed data from the UK Biobank database, comprising 381841 European individuals (922 case patients and 380919 control participants).

Genetic Instrument Selection

In our research, we established rigorous criteria for the selection of genetic instrumental variables (IVs) related to SNPs and circulating metabolic biomarkers traits. Due to the substantial volume of SNPs meeting genome-wide thresholds ($p < 5 \times 10\text{-}8$), we implemented even more rigorous standards ($p < 5 \times 10\text{-}9$) for the identification of instrumental variables (IVs) [7]. Instrumental variables (IVs) were categorized based on the linkage disequilibrium (LD) reference dataset obtained from the 1000 Genomes Project, using a cutoff of $R2 < 0.001$ within a 1,000-kilobase (kb) distance. This precise methodology enabled us to pinpoint the most pertinent IVs for our analysis.

Due to the constrained size of GWAS datasets for circulating metabolic biomarkers, we utilized a p-value threshold of $5 \times 10\text{-}8$ and a somewhat relaxed clustering threshold ($R2 < 0.1$ within a 500 kb distance) [8]. This approach enabled us to include a suitable quantity of instrumental variables (IVs) while maintaining statistical strength. To ensure the effectiveness of our genetic instruments, we specifically selected IVs with F-statistics greater than 10, thus pinpointing promising instruments for producing reliable and consistent results in our studies.

In our analysis, the instrumental variables (IVs) were derived from the summary data concerning arrhythmia outcomes. To uphold the reliability of our study, we excluded SNPs exhibiting potential pleiotropic effects ($p < 10\text{-}5$) on arrhythmia types [9]. Consistency in effect size estimations was ensured by harmonizing the SNPs across both exposure and outcome datasets, facilitating coherent comparisons and accurate conclusions based on the same genetic variants. Additionally, Genetic variants with effect allele frequencies (EAFs) higher than 0.42 or those that were incompatible with harmonization were omitted from our analysis [7]. This careful approach to SNP selection and harmonization ensured the integrity and consistency of our Mendelian randomization analysis.

Statistical Analyses

The examination was performed through R v3.5.3 program (http://www.Rproject.org). A range of methodologies, a variety of methods, such as inverse variance weighting (IVW), weighted median, and mode, were employed to investigate the potential cause-and-effect connection among 1400 types of metabolites and the occurrence of arrhythmia, employing the MR v0.4.3 tool. Heterogeneity among the chosen instrumental variables (IVs) was evaluated through Cochran's Q test and the correlated significance level (**Table 1**).

Table:1 Heterogeneity of circulating metabolic biomarkers and arrhythmia

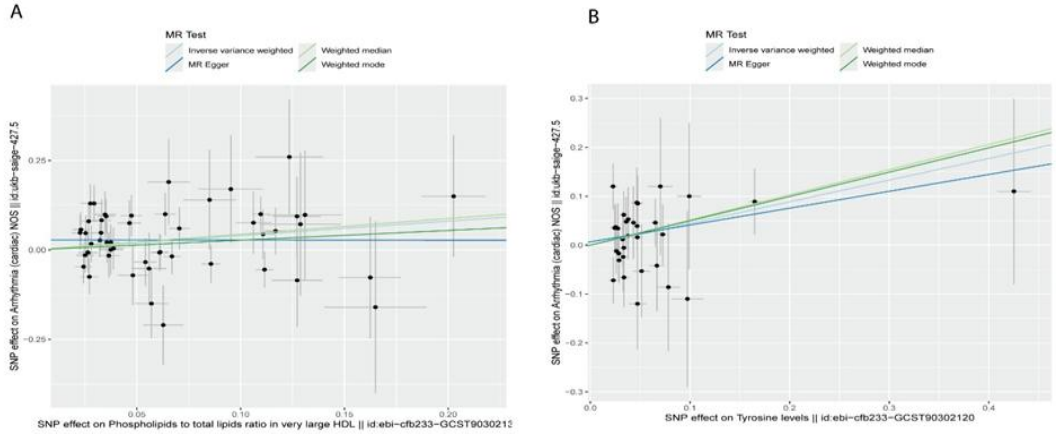
exposure	method	Q	Q_df	Q_pval
Phospholipids to total lipids ratio in very large HDL	MR Egger	54.821775	49	0.2633481
Phospholipids to total lipids ratio in very large HDL	Inverse variance weighted	57.756204	50	0.2104953
Tyrosine levels	MR Egger	22.581828	30	0.8320530
Tyrosine levels	Inverse variance weighted	22.729937	31	0.8587649
Creatinine levels	MR Egger	64.725863	67	0.5560362
Creatinine levels	Inverse variance weighted	65.341411	68	0.5689174

If the null hypothesis was declined, the irregular influences IVW approach was preferred over the constant factors IVW technique. The MR-Egger technique was used to tackle horizontal pleiotropy, and the MR-PRESSO approach was utilized to uncover and remove potential horizontal pleiotropic outliers that could influence the consequences (**Table 2**).

Table 2: Pleiotropy of circulating metabolic biomarkers and arrhythmia

exposure	egger_intercept	se	pval
Phospholipids to total lipids ratio in very large HDL	0.027990232	0.0172831	0.1117569
Tyrosine levels	0.006694128	0.0173941	0.7030643
Creatinine levels	-0.015423235	0.0196582	0.4354720

To validate the robustness of the findings, scatter plots **(Figure 3)**, funnel plots **(Figure 4)**, and leave-one-out **(Figure 5)** analyses were conducted. These evaluations confirmed that the results were unaffected by outliers, indicating a robust and consistent association [10].



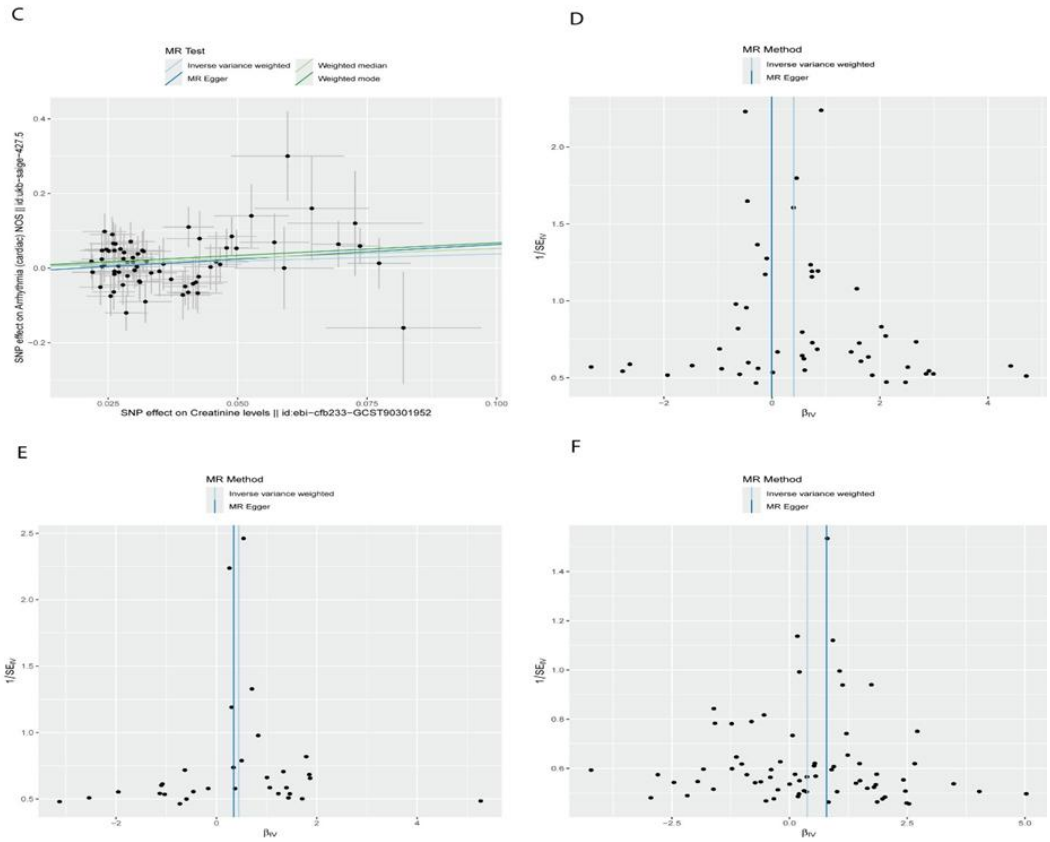


Figure 3, 4: The scatter plot and the funnel plot demonstrating of circulating metabolic biomarkers and arrhythmia.

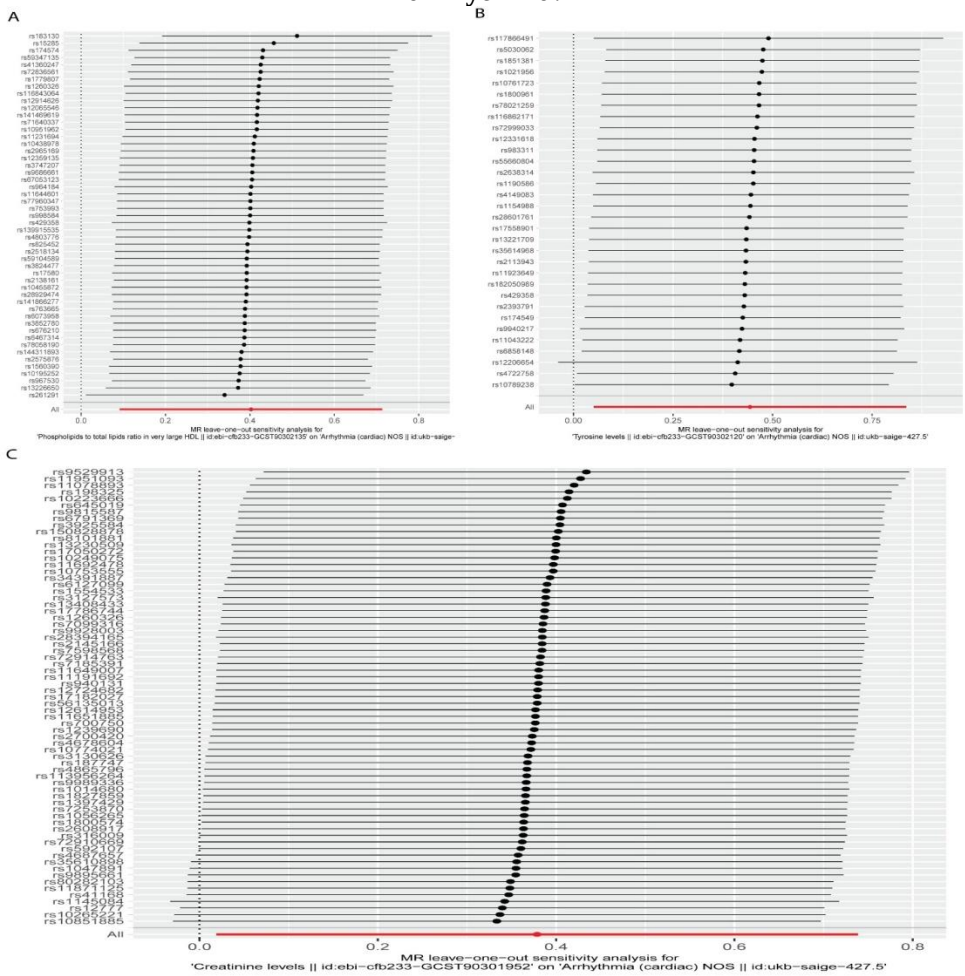


Figure 5: Leave-one-out showed causal relation between of circulating metabolic biomarkers and arrhythmia.

Results

In our investigation, we explored 3 circulating metabolic biomarkers phenotypes potentially connected to the development of arrhythmia disease. Narrowing our focus to three key circulating metabolic biomarkers, we presented our findings in **Figure 2**.

Exposure	Method	No.of SNP	OR(95% CI)	P
Tyrosine levels	Inverse variance weighted	32	1.558 (1.052 to 2.307)	0.027
Tyrosine levels	MR Egger	32	1.411 (0.746 to 2.672)	0.298
Tyrosine levels	Weighted median	32	1.673 (0.965 to 2.899)	0.067
Tyrosine levels	Weighted mode	32	1.645 (0.952 to 2.840)	0.084
Creatinine levels	Inverse variance weighted	69	1.460 (1.019 to 2.093)	0.039
Creatinine levels	MR Egger	69	2.197 (0.745 to 6.476)	0.158
Creatinine levels	Weighted median	69	1.691 (0.984 to 2.905)	0.057
Creatinine levels	Weighted mode	69	1.968 (0.820 to 4.723)	0.134
Phospholipids to total lipids ratio in very large HDL	Inverse variance weighted	51	1.496 (1.096 to 2.042)	0.011
Phospholipids to total lipids ratio in very large HDL	MR Egger	51	0.995 (0.557 to 1.778)	0.988
Phospholipids to total lipids ratio in very large HDL	Weighted median	51	1.551 (1.003 to 2.400)	0.049
Phospholipids to total lipids ratio in very large HDL	Weighted mode	51	1.313 (0.746 to 2.313)	0.350

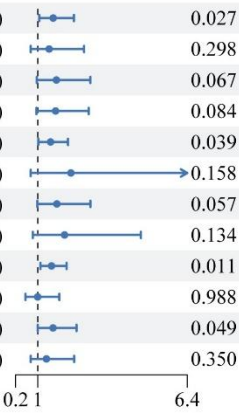


Figure 2: the causal relationship between circulating metabolic biomarkers and arrhythmia.

Utilizing Mendelian randomization (MR) analysis, we unveiled significant causal links between specific circulating metabolic biomarkers and the susceptibility to arrhythmia. Notably, heightened levels of Creatinine levels (The odds ratio for this data stands at 1.4604, with a 95% confidence interval of 1.0190-2.0930, and a significance level of $p < 0.0391$), Tyrosine levels (The odds ratio for this data equals 1.5579, with a 95% confidence interval of 1.0523-2.3066, and a significance level of $p < 0.0267$), and the Phospholipids to total lipids ratio in very large HDL (The odds ratio for this data signifies 1.4957, with a 95% confidence interval of 1.0956-2.0417, and a significance level of $p < 0.0112$) were pinpointed as factors linked to an increased probability of developing arrhythmia.

Discussion

Current strategies for preventing and treating arrhythmia by addressing risk factors are in need of further refinement. Additionally, there is a lack of study on the impact of readily available initial indicators for therapy approaches for arrhythmia. It is essential to align adjustable risk factors along with promising biomarkers and establish the causal links among them and the disorder for early arrhythmia control. In this investigation, we executed a comprehensive Mendelian randomization (MR) investigation to clarify the link between serum circulating metabolic biomarkers and arrhythmia, employing various sensitivity analyses. Our findings identified 13 blood circulating metabolic biomarkers strongly associated with arrhythmia, with three circulating metabolic biomarkers - tyrosine levels, creatinine levels, and the phospholipids to total lipids ratio in very large HDL - suggested to elevate the risk of arrhythmia. This research enriches our comprehension of the mechanisms behind arrhythmia and presents a fresh method for forecasting and averting this cardiac condition.

Arrhythmia is a health issue defined by an abnormal heart rhythm. In a healthy heart, the electrical signals that regulate the heartbeat coordinate the contraction of the heart's chambers to pump blood effectively throughout the body. However, in individuals with arrhythmia, these electrical signals are disrupted, causing the heart to beat too quickly (tachycardia), too slowly (bradycardia), or irregularly [11]. Metabolism can play a significant role in the development of arrhythmias through various mechanisms involving the heart's electrical activity and function [3]. Dyslipidemia, or abnormal lipid metabolism, can result in the accumulation of fats in heart tissue, leading to structural changes that can disrupt the heart's electrical conduction system and increase the risk of arrhythmias [12, 13]. Metabolic Disorders Conditions like diabetes, thyroid disorders, and metabolic syndrome can impact the heart's electrical activity and increase the risk of arrhythmias. For example, in diabetes,

high blood sugar levels can damage the nerves that control the heart's rhythm, leading to arrhythmias [14, 15].

Tyrosine is an amino acid that plays a crucial role in the production of several important neurotransmitters in the brain, such as dopamine, norepinephrine, and epinephrine. These neurotransmitters are involved in regulating mood, stress response, and cognitive function. Additionally, Tyrosine serves as a building block for thyroid hormones, crucial for controlling metabolism and energy generation in the body. [16]. Amino acids act as the basic building blocks of proteins and play a role as precursors for neurotransmitters, with some neurotransmitters being produced either directly or indirectly from particular amino acids [17]. Adjusting the consumption of these amino acids could potentially influence the activity of their corresponding neurotransmitters. Within the blood-brain barrier, various amino acids vie for entry into the brain. Consequently, the effect of a particular amino acid supplement on brain function may be more foreseeable than that of a supplement comprising a blend of diverse amino acids [18]. Monitoring tyrosine levels can provide valuable insights into the functioning of the brain and overall health. Low tyrosine levels may be associated with symptoms such as fatigue, depression, and cognitive impairment, while high tyrosine levels could indicate certain health conditions or dietary imbalances [19]. It is important to maintain adequate levels of tyrosine through a balanced diet that includes protein-rich foods like meat, dairy products, nuts, and seeds. Individual tyrosine requirements vary, so it is advisable to seek guidance on monitoring and optimizing tyrosine levels. Other study mentioned that p-cresol, derived from tyrosine, is one of the key gut microbiota-derived metabolites associated with incident major adverse cardiovascular events and poorer survival risks [20]. Our study also demonstrates that tyrosine levels are associated with a risk factor effect on arrhythmias. These results emphasize the potential importance of tyrosine and its metabolites in influencing cardiovascular health outcomes, underscoring the need for additional research in this area to explore potential therapeutic interventions.

Creatinine is a waste product that is produced when creatine, a molecule that plays a key role in energy production in muscles, breaks down. It is generated at a relatively constant rate in the body and is filtered out of the blood by the kidneys [21]. Creatinine levels in the blood are used as a marker to assess kidney function. The kidneys work to remove waste products, including creatinine, from the blood and excrete them in the urine. Elevated levels of creatinine in the blood can indicate impaired kidney function or other health issues [22, 23]. Monitoring creatinine levels is an important part of evaluating kidney health and overall body function. Based on the findings of the study, it can be inferred that elevated creatinine levels above 1.3 mg/dL are linked to QTc prolongation in patients admitted to the intensive care unit, suggesting that increasing creatinine levels may be a risk factor for QTc prolongation [24]. The study revealed an association between the difference in estimated glomerular filtration rates (eGFR) based on creatinine levels and the development of atrial fibrillation (AF). Individuals with a negative eGFR difference (suggesting elevated creatinine levels) exhibited an increased risk of AF, whereas those with a positive difference showed a decreased risk. These results indicate that increased creatinine levels, as indicated by the eGFR difference, could be considered a risk factor for atrial fibrillation [25]. Furthermore, our research also indicates that creatinine levels are associated with a risk factor for arrhythmia. These findings highlight the significance of monitoring creatinine levels in evaluating the risk of QTc prolongation and arrhythmias.

The phospholipids to total lipids ratio in very large HDL refer to the proportion of phospholipids, which are a type of lipid molecule that contains a phosphate group, relative to the total amount of lipids present in the very large high-density lipoprotein (HDL) particles. This ratio provides insight into the composition and structure of these specific HDL particles, which are known for their role in transporting cholesterol and other lipids in the bloodstream. Variations in the phospholipids to total lipids ratio in very large HDL may have implications for cardiovascular health and disease risk, making it a potentially important biomarker for studying lipid metabolism and associated health outcomes [26]. The function of the phospholipids to total lipids ratio in very large HDL is to serve as a measure of the relative proportion of phospholipids within

these specific high-density lipoprotein (HDL) particles compared to the total amount of lipids present. This ratio can provide valuable information about the structural and functional properties of very large HDL particles, since phospholipids are essential for preserving the lipid membrane's integrity and facilitating the transport of lipids, including cholesterol, throughout the body [27]. By analyzing the phospholipids to total lipids ratio in very large HDL, researchers can gain insights into the composition of these HDL particles and their potential impact on lipid metabolism, cardiovascular health, and disease risk. Changes in this ratio may indicate alterations in the lipid transport and metabolism pathways, which could have implications for cardiovascular diseases such as atherosclerosis and arrhythmia. Studying this ratio can help uncover potential biomarkers or therapeutic targets for improving lipid metabolism and reducing the risk of cardiovascular complications [28]. One study has indicated that the phospholipids to total lipids ratio in very large HDL is linked to protective effects against Intervertebral disc degeneration (IVDD) [29]. However, our Mendelian randomized study uncovered a significant relationship between the phospholipids to total lipids ratio in very large HDL and the risk factor for arrhythmia. This implies that alterations in this specific circulating metabolic biomarkers may impact the development or modulation of arrhythmia risk. Delving deeper into the foundational mechanisms of this association could provide valuable insights into potential therapeutic targets for preventing and managing arrhythmia. Given the discrepancy in these findings, additional research is essential to confirm and elaborate on these results.

Limitations

Our research has certain limitations that warrant acknowledgment. Firstly, despite conducting multiple sensitivity analyses, we were unable to comprehensively evaluate horizontal pleiotropy. Secondly, the lack of individual-level information hindered the possibility of conducting stratified observational analyses within this cohort, which could have offered additional insights. Thirdly, our study exclusively utilized a European database, which could potentially restrict the generalizability of the results to other ethnicities. Additionally, we applied a less rigorous criterion to evaluate the outcomes, potentially leading to the inclusion of false-positive results in this analysis. Despite these limitations, this Mendelian randomization-based approach enabled us to thoroughly explore the potential association between arrhythmia risks and altered metabolite profiles.

Conclusions

Based on the robust findings from our Mendelian randomization study, we have successfully established a significant causal link between circulating metabolic biomarkers and arrhythmia. These results serve as a cornerstone in unraveling the intricate metabolic mechanisms that underlie arrhythmia development. Importantly, our research opens up promising avenues for tailored interventions and personalized treatment strategies aimed at mitigating arrhythmia risk. By elucidating the specific impact of circulating metabolic biomarkers on arrhythmia susceptibility, our study enriches the broader landscape of cardiovascular health knowledge. Furthermore, the implications of our findings extend to the realm of precision medicine, offering potential advancements in the management and treatment of arrhythmia.

Author Contribution: **Panhaleap Meas**, **Pengkhun Nov**, acquisition of data, analyzing,

interpretation of data, and drafting the article; **Vicheth Virak** designing, revising, and guiding the study. The authors read and approved.

Data Availability All the data for this article can be found on GWAS database.

Declaration of conflict of interest: None.

Ethics approval: Not applicable

Consent for publication All the authors of the article agreed to be published

in the journal.

Competing interests, the authors declare no competing interests.

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