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ORIGINAL RESEARCH

The Role of Circulating Fatty Acids in Mediating the Effect of Insomnia on Heart Failure: A Two-Step, Two-Sample Mendelian Randomization Study

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Purpose: Previous studies support the causal effect of insomnia on heart failure. Fatty acid metabolism plays key roles in the occurrence and development of heart failure. It is unclear whether fatty acids play roles in the causal association between insomnia and heart failure. This study aims to investigate the mediating role of fatty acids in the association between insomnia and heart failure.

Methods: We performed two-step, two-sample Mendelian randomization analysis by applying SNPs as genetic instruments for exposures, mediators and outcomes. Summary data obtained from genome-wide association studies for insomnia, proposed fatty acid mediators and heart failure were used in this study. The overall effect of insomnia on heart failure includes direct and indirect effects.

Results: Genetically predicted insomnia has a significant causal effect on circulating total fatty acids, saturated fatty acids, monounsaturated fatty acids and omega-3 fatty acids. In addition, different circulating fatty acids have no causal effect on insomnia incidence. A significant positive correlation between genetic predicted insomnia and heart failure (OR = 1.10, 95% CI: 1.06–1.14, $P<0.001$) was observed. Finally, we found that circulating fatty acids play a mediating role in the causal association between insomnia and heart failure. Total fatty acids, saturated fatty acids and monounsaturated fatty acids explained 3% (95% CI: 0%-7.5%), 3% (95% CI: −1.1%-7.5%), 4% (95% CI: 0%- 9.7%) of the overall effect of insomnia on heart failure, respectively.

Conclusion: These results support circulating fatty acids as potential mediators in the causal association between insomnia and heart failure.

Keywords: Mendelian randomization, insomnia, heart failure, circulating fatty acids

Introduction

Heart failure refers to ventricular dysfunction caused by changes in the structure and function of the heart, and is one of the main causes of death in elderly patients.[1] Insomnia is the most common sleep disorder, characterized by difficulty falling or remaining asleep, difficulty waking up in the morning, or feeling that sleep was nonrestorative.[2] Observational studies have shown harmful effects of insomnia on the heart.[3–5] Insomnia can significantly increase the incidence of heart failure.[3]

The concentration of free fatty acids is an adjustable risk factor for metabolic diseases.[6,7] Studies have shown a correlation between disordered fatty acid metabolism and the risk of heart failure.[8,9] Moreover, clinical observational studies have shown that insomnia can lead to disturbances in fatty acid metabolism.[10–13] Therefore, the mediating role of fatty acids in insomnia and heart failure deserves attention.

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Mendelian randomization (MR) is an acknowledged method using genetic variation as an instrumental variable to examine the causal relationship between risk factors and outcomes, Under certain assumptions, the estimated values of the exposure outcome relationship generated by MR are unlikely to be biased due to unobserved confounding factors.[14] Previous MR studies support the potential causal effect of insomnia on heart failure.[15,16] In this study, we investigated the mediating role of fatty acids in the association between insomnia and heart failure using MR analysis (Figure 1).

Methods

Study Design

In this study, all the data were acquired from currently published genome-wide association studies (GWASs). Ethical approval was obtained from the Ethics Committee of The First Affiliated Hospital of Xinxiang Medical University. The flow chart for the study design overview is shown in Figure 2. We used two-sample MR methods with GWAS summary level data. Two-step, two-sample MR was used to assess whether an intermediate trait has a mediating effect between exposure and outcome. First, we tested the effects of insomnia on heart failure and then the effects of potential mediation using two-step MR. In step one, we tested the causal effects of insomnia on potential mediators, and in step two, we tested the causal effects of potential mediators on heart failure.

Data Sources

Genetic Instrumental Variables for Insomnia

The definition of insomnia in this study is consistent with the previous study.[17] Among the most recent GWASs on insomnia, genetic investigations were performed by UK Biobank (UKB) and 23and Me, Inc. (23andMe). We identified 209 single nucleotide polymorphisms(SNPs) (linkage disequilibrium (LD) blocks <5000kb apart), which were obtained from a primary meta-analysis of 1331010 individuals of European descent, that independently contributed to insomnia at

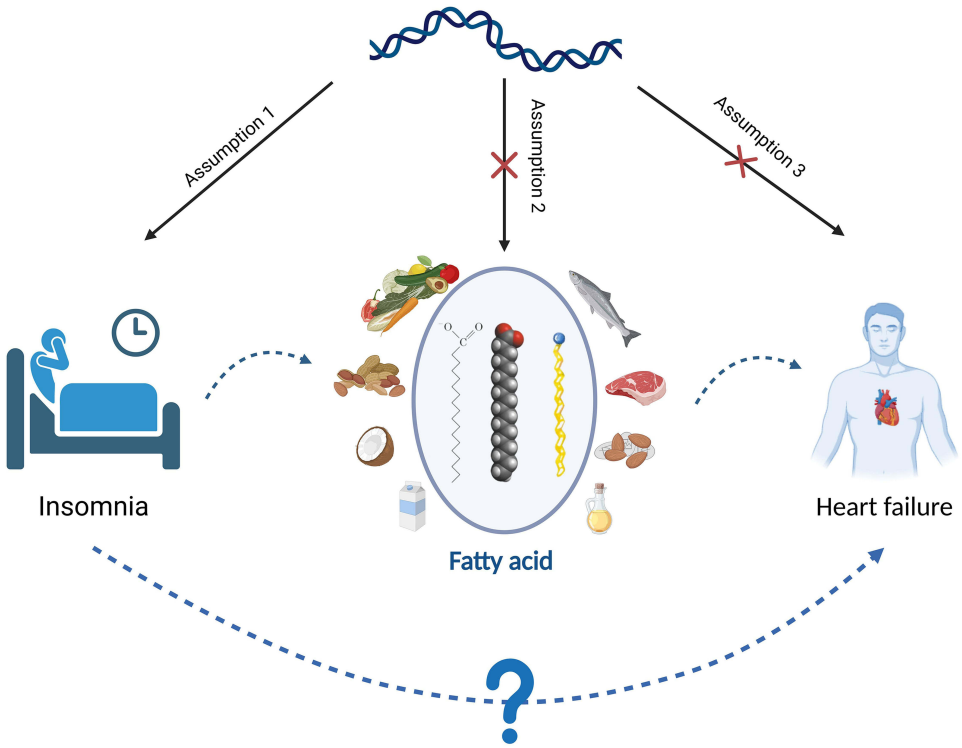

Figure 1 MR hypothesis of two sample MR study. We have selected SNPs associated with Insomnia and used different types of fatty acids as a mediator to investigate the causal inference of Insomnia on Heart failure. Assumption 1 (relevance assumption): genetic variants used in an MR study need to be robustly related to the exposure of interest; Assumption 2 (Independence assumption): genetic variants are not associated with any confounding factors that affect the exposure-outcome association; Assumption 3 (exclusion restriction): there are no effects of the genetic variants on the outcome unless via the effect of genetic variants on the exposure. Created in BioRender. Yu, B. (2025) https://BioRender.com/m57d424.

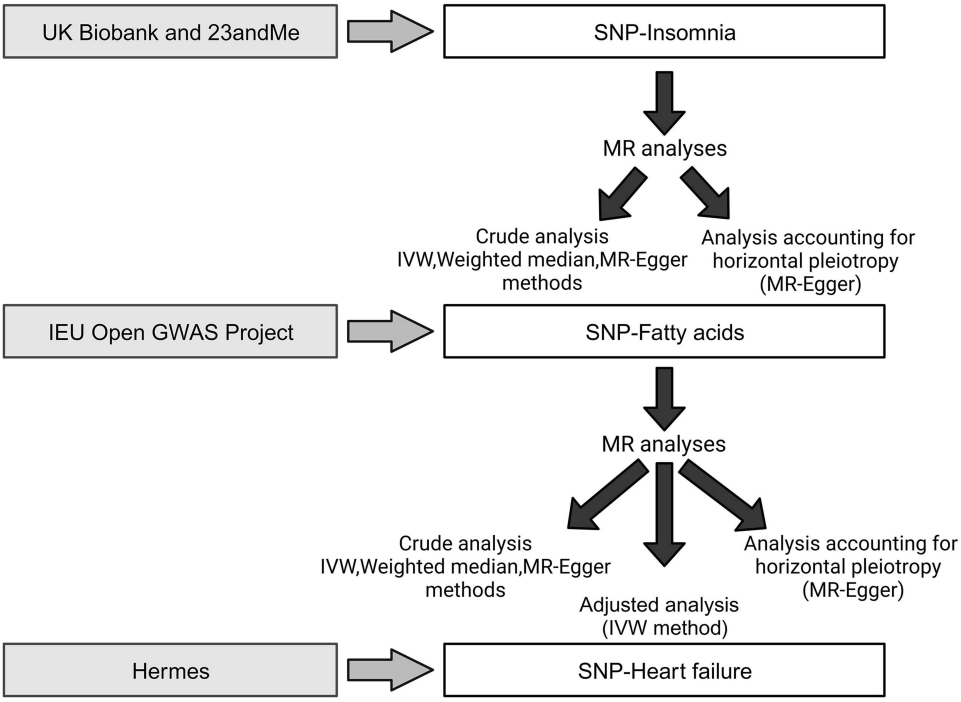

Figure 2 Analysis diagram. Summary data for SNP phenotypes were extracted from GWAS consortia datasets (UK Biobank, 23andMe, IEU Open GWAS Project, Hermes). Insomnia and mediators on Heart failure were derived using the IVW method.

the genome-wide level ($P < 5*10^{-8}$). These variants were defined as independent of each other on the basis of low correlation ($R^2< 0.1$) and were located at 202 genomic risk loci. We confirmed the presence of two (chr2:66,785,180 and chr5:135,393,752) out of six previously reported loci for insomnia.[17] The value of F-statistics for all instrumental variables was 42.67.

Mediation Analysis

SNPs associated with the phenotypes were extracted from publicly available GWAS consortia. Data on different types of fatty acids (including total fatty acids, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, omega-6 polyunsaturated fatty acids, omega-3 polyunsaturated fatty acids and the ratio of omega-6/omega-3) associated with the outcome were obtained from the IEU open GWAS project (https://gwas.mrcieu.ac.uk), which includes samples from 115006 individuals of European ancestry.[18]

Study Outcome

Data on Heart failure were obtained from the Heart Failure Molecular Epidemiology for Therapeutic Targets (HERMES) GWAS. As a GWAS meta-analysis, this study includes 47,309 heart failure cases and 930,014 controls of European ancestry across 26 studies from the HERMES Consortium.[19] The HERMES consortium is an international collaboration that aims to generate insights into the causal pathways leading to heart failure to inform new therapeutic approaches (Supplement Table 1).

Statistical Analysis

We tested for potential bidirectional causal effects among insomnia, potential mediators and heart failure using the inverse-variance weighting (IVW) approach described below.

To guard against horizontal pleiotropy, we used three different analytical approaches for both step one (effect of insomnia on heart failure and potential mediators) and step two (effect of potential mediators on heart failure) of the two-step MR mediation approach.[20]

We conducted several sensitivity analyses, including IVW, weighted median, and MR-Egger regression methods, to assess the robustness of the MR data. We assessed the heterogeneity of individual genetic variants using the modified Cochran's Q statistic. To avoid causal estimates that were mainly driven by a single SNP, we conducted a leave-one-out analysis. All the statistical analyses were conducted using R (version 4.0; the R Foundation for Statistical Computing, Vienna, Austria) software.[21,22]

Results

Bidirectional MR Analysis Between Insomnia and Circulating Fatty Acids

First, we analyzed the effects of insomnia on different circulating fatty acids. As shown in Figure 3 and Supplement Table 2. The IVW analysis showed that genetically predicted insomnia as the exposure had a significant and positive causal association with circulating total fatty acids, saturated fatty acids, monounsaturated fatty acids and the omega-6/omega-3 ratio and a significant and negative causal association with omega-3 fatty acids (P <0.05).

Exposure	Outcome	Method	OR(95% CI)	*P*-value
Insomnia	Saturated fatty acids			
		IVW	1.04 (1.02 to 1.06)	<0.001
		Weighted median	1.04 (1.01 to 1.06)	0.002
		MR Egger	1.05 (0.96 to 1.15)	0.298
	Monounsaturated fatty acids			
		IVW	1.06 (1.03 to 1.08)	<0.001
		Weighted median	1.04 (1.02 to 1.07)	<0.001
		MR Egger	1.06 (0.97 to 1.17)	0.198
	Polyunsaturated fatty acids			
		IVW	0.99 (0.97 to 1.02)	0.679
		Weighted median	0.99 (0.97 to 1.01)	0.223
		MR Egger	1.01 (0.91 to 1.12)	0.833
	Omega−6 fatty acids			
		IVW	0.99 (0.97 to 1.03)	0.980
		Weighted median	0.99 (0.97 to 1.02)	0.563
		MR Egger	1.00 (0.90 to 1.11)	0.954
	Omega−3 fatty acids			
		IVW	0.98 (0.96 to 0.99)	0.034
		Weighted median	0.99 (0.97 to 1.01)	0.294
		MR Egger	1.02 (0.95 to 1.10)	0.587
	Omega−6 /Omega−3			
		IVW	1.02 (1.00 to 1.04)	0.011
		Weighted median	1.01 (0.99 to 1.04)	0.253
		MR Egger	0.98 (0.92 to 1.05)	0.572
	Total fatty acids			
		IVW	1.03 (1.01 to 1.06)	0.007
		Weighted median	1.02 (0.99 to 1.04)	0.066
		MR Egger	1.04 (0.95 to 1.15)	0.383

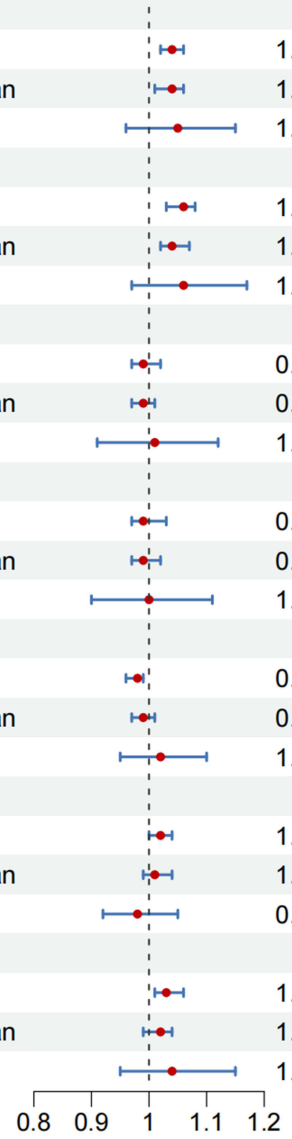

Figure 3 2SMR estimates of the causality between Insomnia exposure and circulating fatty acids.
Abbreviations: omega-6 /omega-3, the ratio of omega-6 fatty acids /omega-3 ratio fatty acids; IVW, inverse-variance weighting; MR-Egger, MR-Egger regression.

Then, we investigated the effects of different circulating fatty acids on insomnia. There were no significant causal associations between different circulating fatty acids and insomnia (P>0.05) (Figure 4).

Effect of Insomnia on Heart Failure

This study revealed a significant positive correlation between the genetically predicted insomnia and the risk of heart failure (OR = 1.10, 95% CI: 1.06–1.14, P<0.001). The more severe the insomnia is, the greater the risk of heart failure. The weighted median method and MR–Egger regression method yielded similar results as the IVW method (Table 1 and Supplement Table 3).

Effect of Fatty Acids on Heart Failure

We investigated the causal association between genetically predicted fatty acids and heart failure. We found a positive causal relationship between circulating total fatty acids, monounsaturated fatty acids, and omega-3 fatty acids and the risk of heart failure but a negative causal association with omega-6/omega-3 fatty acids (Table 2 and Supplement Table 4).

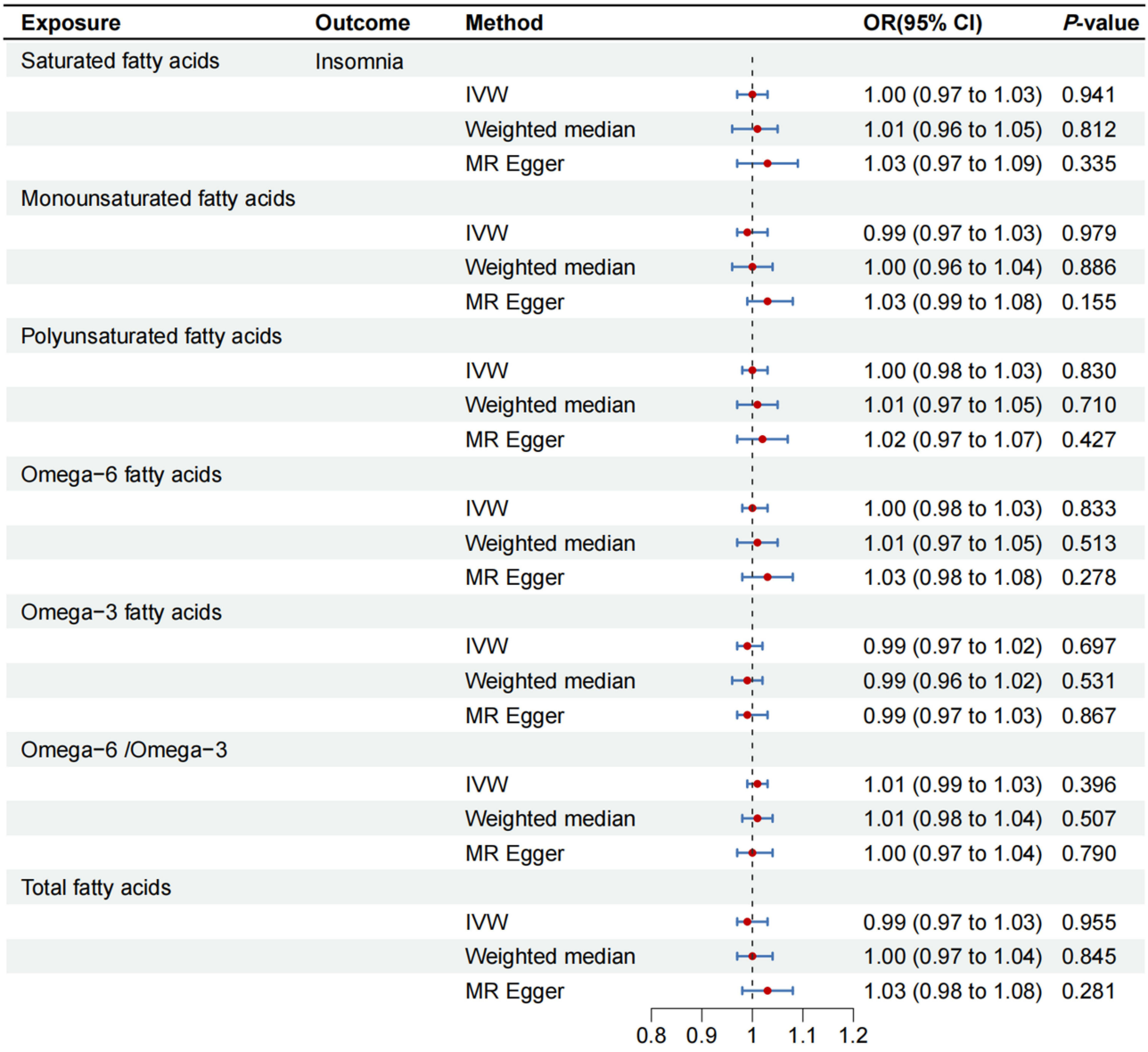

Figure 4 2SMR estimates of the causality between circulating fatty acids exposure and Insomnia.
Abbreviations: omega-6 /omega-3, the ratio of omega-6 fatty acids /omega-3 ratio fatty acids; IVW, inverse-variance weighting; MR-Egger, MR-Egger regression.

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Table 1 2SMR Estimates of the Causality Between Insomnia Exposure and Heart Failure

Exposure	Outcome	*IVW*		*Weighted Median*		*MR-Egger*	
		OR(95% CI)	***P-value***	**OR(95% CI)**	***P-value***	**OR(95% CI)**	***P-value***
Insomnia	Heart failure	1.04(1.02–1.06)	0.0004	1.04(1.01–1.06)	0.0017	1.05(0.96–1.15)	0.2985

Table 2 2SMR Estimates of the Causality Between Different Types of Fatty Acids and Heart Failure

Mediators	Outcome	IVW		Weighted Median		MR-Egger	
		OR(95% CI)	***P-value***	**OR(95% CI)**	***P-value***	**OR(95% CI)**	***P-value***
Saturated fatty acids	Heart failure	1.07(0.98–1.17)	0.1333	1.11(1.02–1.20)	0.0148	0.97(0.82–1.15)	0.7122
Monounsaturated fatty acids		1.08(1.00–1.16)	0.0382	1.11(1.04–1.19)	0.0020	0.97(0.86–1.09)	0.5926
Polyunsaturated fatty acids		1.07(0.98–1.17)	0.1160	1.12(1.04–1.20)	0.0030	1.08(0.92–1.27)	0.3664
Omega-6 fatty acids		1.06(0.97–1.16)	0.2259	1.11(1.03–1.20)	0.0071	1.06(0.88–1.27)	0.5377
Omega-3 fatty acids		1.07(1.01–1.14)	0.0256	1.07(1.02–1.12)	0.0081	1.07(0.98–1.17)	0.1294
Omega-6/omega-3		0.93(0.89–0.97)	0.0019	0.94(0.90–0.99)	0.0086	0.94(0.88–1.01)	0.0807
Total fatty acids		1.09(1.01–1.18)	0.0335	1.11(1.04–1.20)	0.0040	0.98(0.85–1.12)	0.7323

Table 3 Different Types of Fatty Acids Mediate the Causal Effect of Insomnia Exposure on Heart Failure

Mediators	Total Effect	Direct Effect A	DirectEffect B	Indirect Effect	Mediated Proportion(%)(95% CI)
	β	β	β		
Saturated fatty acid	0.093	0.040	0.069	0.003	3(−1.1–7.5)
Monounsaturated fatty acid	0.093	0.054	0.074	0.002	4(0–9.7)
Total fatty acids	0.093	0.033	0.084	0.003	3(0–7.5)

Mediating Effects of Circulating Fatty Acids on Insomnia–Heart Failure Effects

We explored the role of circulating fatty acids as mediators in the causal association between insomnia and heart failure and demonstrated the proportion of each mediator explaining the impact of insomnia on heart failure. This study revealed that circulating fatty acids potentially mediate the causal association between insomnia and heart failure. Total fatty acids, saturated fatty acids and monounsaturated fatty acids explained 3% (95% CI: 0%-7.5%), 3% (95% CI: −1.1%-7.5%), 4% (95% CI: 0%- 9.7%) of the overall effect of insomnia on heart failure, respectively (Table 3). The results of sensitivity analyses were shown in Supplement Figures 1–3, Supplement Tables 5 and 6.

Discussion

This is the first study to explore the extent to which circulating fatty acids mediate the causal relationship between insomnia and heart failure using statistical methods to explain horizontal pleiotropy. Consistent with the findings of previous studies, we found that genetically predicted insomnia is associated with a greater risk of heart failure. We also found that the severity of genetically predicted insomnia was significantly positively correlated with the levels of circulating total fatty acids, saturated fatty acids, and monounsaturated fatty acids and with the omega-6/omega-3 ratio and negatively correlated with the omega-3 fatty acid level. Furthermore, this study revealed that total fatty acids, saturated fatty acids, and monounsaturated fatty acids potentially play a mediating role in the causal association between insomnia and heart failure.

Most previous observational studies have shown that insomnia is associated with an increased risk of heart failure in both Western and Eastern populations, and this MR study also supports this result.[15,16] Sleep plays an important role in cardiovascular diseases, including heart failure. One study performed by our research group suggested that genetically predicted short sleep duration is a potential causal risk factor for various cardiovascular diseases, including hypertension, chronic ischemic heart

disease, coronary artery disease and myocardial infarction, among404044UKB participants.[23] In addition, an MR study conducted by Yuan et al, which included 397959 self-reported insomnia patients and933057control participants, revealed a potential causal association between genetically predicted insomnia and an increased risk of various cardiovascular diseases, including heart failure, coronary artery disease, and atrial fibrillation.

A meta-analysis of 20 studies, including 12 clinical trials and 8 longitudinal studies, revealed that omega-3 fatty acid supplementation can significantly improve the sleep quality of patients and alleviate insomnia. Moreover, a meta-analysis conducted by Murphy et al identified 12 cohorts and showed that the concentration of circulating n-3 polyunsaturated fatty acids, as a biomarker, is negatively correlated with sleep duration.[24] The preset MR analysis revealed no significant correlation between the genetically predicted levels of circulating unsaturated fatty acids and the degree of insomnia in patients. These differences are speculated to be due to the presence of confounding factors in observational studies, as well as heterogeneity in different studies. In addition, this study revealed a positive association between circulating omega-3 fatty acids and the risk of heart failure, which is consistent with the findings of previous research.[25,26] Previous observational studies have shown the relationship between omega-3 fatty acids and the risk of heart failure to be controversial.[27] A meta-analysis showed that omega-3 fatty acids are negatively associated with the risk of heart failure and can reduce the inflammatory level in heart failure patients, which is the opposite trend to the results from this MR analysis.[28] The reason for this difference is currently unclear, but it is speculated that this difference is related to pleiotropic genetic instruments. Our study also revealed a positive association between the level of monounsaturated fatty acids and the risk of heart failure. This finding is consistent with previous study findings.[29] In this study, there was no significant causal association, but a trend toward a positive association between saturated fatty acids and the risk of heart failure was observed (OR =1.07, 95% CI: (0.98–1.17), P=0.133).

Finally, we investigated the mediating role of fatty acids in the causal association between insomnia and heart failure. As shown in Table 2, total fatty acids, saturated fatty acids, and especially monounsaturated fatty acids play a potential mediating role. The role of saturated fatty acids in cardiovascular disease is relatively clear. In general, the level of saturated fatty acids is positively associated with the risk of cardiovascular disease.[30] The present study showed a similar trend. However, the role of monounsaturated fatty acids in heart health is controversial. A considerable number of previous studies have shown that monounsaturated fatty acids have a certain cardioprotective effect: monounsaturated fatty acids can improve lipid metabolism, alleviate inflammatory responses, and reduce endothelial cell damage. In addition, monounsaturated fatty acids can also inhibit platelet aggregation and exhibit antithrombotic effects.[31,32] However, some recent studies have shown opposite results regarding the role of monounsaturated fatty acids in heart health. Bock et al reported that higher levels of circulating palmitoleic acid and oleic acid in monounsaturated fatty acids are associated with cardiovascular metabolic risk factors in heart failure patients with preserved ejection fraction.[33] Monounsaturated fatty acids can induce proinflammatory pathways, endoplasmic reticulum stress, and insulin resistance, which may contribute to the progression of heart failure pathophysiology.[34] In this study, MR analysis was used to demonstrate a positive association between monounsaturated fatty acid levels and the risk of heart failure. The mechanism underlying the effect of monounsaturated fatty acids on heart failure is currently unclear and requires further exploration.

Compared to single-sample MR, two-sample MR is less likely to produce false-positive results because it does not require obtaining gene exposure associations (ratio denominator) and gene outcome associations (ratio numerator) from the same participant sample. In addition, the main advantage of two-sample MR is the improvement in statistical efficiency, especially in detecting binary disease outcomes (ie, coronary heart disease or type 2 diabetes), because of the use of summary data from GWASs.[22,35] Finally, we included only participants of European ancestry in the exposure and outcome datasets, thus minimizing population stratification bias. However, this population restriction may limit the generalizability of our findings to other populations. This study is very extensive and utilizes genetic variation to avoid key limitations mediated by traditional multivariate regression methods. Horizontal pleiotropy is one of the main limitations of MR studies. However, to explore the potential impact of pleiotropy, we used different MR methods (IVW, median-based estimator, and MR–Egger) with different assumptions, and we evaluated the consistency of each estimator.

This study has several limitations. First, the number of SNPs used as instrumental variables used in this study was relatively small, and there was some heterogeneity in the results, which may have affected the detection effect. Second, the available data we used was aggregated statistical data and lacked more detailed data at the individual outcome level, which may inevitably lead to bias in our results. Third, while this study used large-scale published GWAS data, the definition of insomnia should be further refined and clarified in future. Finally, the data in this study were all taken from individuals of

European ancestry, and there was a lack of analysis of other ethnic groups, which led to racial limitations in this study. Whether the conclusions of this article can be extended to other populations still requires further relevant studies for verification.

Conclusions

In summary, this study showed that genetically predicted insomnia has a causal effect on the risk of heart failure. We also found that the severity of genetically predicted insomnia was significantly positively correlated with the levels of circulating total fatty acids, saturated fatty acids, and monounsaturated fatty acids and negatively correlated with the level of omega-3 fatty acids. Total fatty acids, saturated fatty acids, and monounsaturated fatty acids play a potential mediating role in heart failure caused by insomnia. The role of fatty acids in heart failure caused by insomnia warrants further exploration in the future.

Acknowledgments

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declared no potential conflicts of interest in this work.

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