

Original Article

Causal inference between physical activity and chronic diseases: Insights from a two-sample Mendelian randomization study

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ABSTRACT

Chronic diseases are major causes of global death and disability, significantly impacting individual health and imposing economic burdens. This study aims to investigate the causal relationship between physical activity (PA) and the development of chronic diseases. Using a Mendelian randomization (MR) approach, we incorporated average PA and its subtypes (more than 450 000 participants) as exposure measures and eight chronic diseases as outcome measures. Data were obtained from the European Genome-Wide Association Study (GWAS). The primary causal analysis technique employed was the inverse variance weighting (IVW) method, with MR-Egger, weighted median, weighted mode, and simple mode used to validate the results. Sensitivity analyses were performed to assess heterogeneity and pleiotropy. The IVW approach results show that vigorous physical activity (VPA) is associated with a modest reduction in the risk of major coronary heart disease ($OR = 0.95$, 95% CI : $0.91-0.99$, $p = 0.01$). The causal directions of the other four MR methods are consistent with this result and validated by sensitivity analysis. No substantial associations were found between other levels of PA and chronic disease. Our findings underscore the importance of VPA in preventive cardiology and suggest its potential role in public health initiatives. Further research should explore the impact of PA on different demographic groups and the dose-response relationship of VPA on heart health.

1. Introduction

Chronic diseases, which are distinguished by their extended duration and gradual advancement, are the primary contributors to mortality and impairment on a worldwide scale.^{1,2} According to the World Health Organization, chronic diseases account for 71% of all deaths globally, with cardiovascular diseases being the leading cause. In particular, ischemic heart disease and stroke contribute to over 15 million deaths annually.^{3,4} Furthermore, the Global Burden of Disease Study reports that non-communicable diseases, including chronic respiratory diseases and diabetes, contribute significantly to the global burden of disease, causing immense economic and social impact.^{5,6} Their pervasive impact not only strains individual health but also imposes extensive economic burdens on societies. The rising prevalence of such diseases underscores an urgent need for effective management strategies to mitigate their long-term

effects on patients' lives and healthcare systems.^{2,7}

Physical activity (PA) is increasingly recognized as a cornerstone of chronic disease prevention and management.^{8,9} Regular engagement in PA ranging from light-intensity exercises to vigorous physical exertions has been linked to numerous health benefits, including improved cardiovascular function,^{10–12} enhanced respiratory capacity,¹³ and better overall health outcomes.¹⁴ For instance, a meta-analysis by Li and Siegrist demonstrated that higher levels of PA are linked to a significantly lower risk of coronary heart disease, while Arem et al. found that leisure-time PA was associated with a reduced risk of 13 different types of cancer.^{15,16}

However, observational studies generally cannot establish cause and effect. To address this limitation, more robust methodological approaches are necessary. Mendelian randomization (MR) offers a powerful tool to infer causality by leveraging genetic variants as instrumental variables for PA.^{17,18} This method minimizes the influence of

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Abbreviations	
APA	Average physical activity
IVs	Instrumental variables
IVW	Inverse variance weighting
IVW-FE	Fixed-effect IVW
IVW-RE	Random-effect IVW
LPA	Light physical activity
MR	Mendelian randomization
MVPA	Moderate to vigorous physical activity
PA	Physical activity
SNPs	Single nucleotide polymorphisms
VPA	Vigorous physical activity
GWAS	Genome-Wide Association Study
OR	Odds ratio
CI	Confidence interval
min	minutes

confounding factors and reverse causation, providing more reliable evidence on the causal effects of PA on chronic disease outcomes. Several studies have applied MR to explore the relationship between physical activity and various health outcomes. For instance, Zhou et al. used MR to investigate the causal effect of physical activity on cardiovascular disease and found a significant protective effect.¹⁹ Similarly, Doherty et al. applied MR to assess the impact of physical activity on obesity and metabolic traits, demonstrating a beneficial causal effect of increased physical activity levels.²⁰

While these studies have advanced our understanding of the causal role of physical activity in various health outcomes, there remains a need for more comprehensive evidence to support public health recommendations. In this study, we focus on leverage the MR approach to elucidate the causal effects of different levels of PA on chronic diseases. By elucidating these relationships, our study seeks to provide a clearer understanding of the role of physical activity in chronic disease prevention and to inform public health strategies and recommendations.

2. Methods

2.1. Study design

This study employed a two-sample MR design to examine the causal relationship between PA and chronic diseases. The eight chronic diseases included in our study are as follows: major coronary heart disease, atherosclerotic heart disease, chronic ischemic heart disease, chronic bronchitis, chronic gastritis, osteoarthritis, rheumatoid arthritis, chronic fatigue syndrome. The MR study utilized data from genome-wide association studies (GWAS) of these diseases to determine the causal effects of different levels of physical activity. In order to ensure the accuracy and reliability of our results, we utilized instrumental variables (IVs) adhering to three foundational principles: a robust association with the exposure, absence of confounder association, and an effect on the outcome that stems solely from the exposure, excluding any horizontal pleiotropic effects.²¹ Only IVs conforming to these standards were included in our MR analysis. Additionally, as this research reanalysis data from prior studies, it did not necessitate further ethical approval.

2.2. Data sources

GWAS data for average physical activity (APA), moderate to vigorous physical activity (MVPA), and vigorous physical activity (VPA) in this MR study from research of habitual physical activity in approximately 377 000 UK Biobank participants.²² Self-reported levels of PA during work were measured using a touchscreen questionnaire, similar to the

International Physical Activity Questionnaire. For MPA, participants were asked: “In a typical week, on how many days did you do 10 minutes (min) or more of moderate physical activities like carrying light loads or cycling at a normal pace? (Do not include walking)”. For VPA, participants were asked: “In a typical week, how many days did you do 10 min or more of vigorous physical activity? (These are activities that make you sweat or breathe hard, such as fast cycling, aerobics, or heavy lifting)”. MVPA was calculated by summing the total minutes per week of MPA (multiplied by four) and the total minutes per week of VPA (multiplied by eight), corresponding to their metabolic equivalents. For APA, participants wore an Axivity AX3 wrist-worn accelerometer for up to seven days, and the average value was recorded.

GWAS data on light physical activity (LPA) from a research data of 27 accelerometry-based physical activity measures in over 88 000 people from the UK Biobank.²³ Participants also wore a wrist-worn accelerometer for up to 7 days to measure the duration of LPA. LPA was defined as the time when the acceleration was between ≥ 30 mg and < 100 mg.

GWAS data for eight chronic diseases were sourced from the UK Biobank, a large-scale, population-based prospective study designed to explore the genetic and non-genetic determinants of diseases prevalent in middle-aged and elderly populations.²⁴ More information can be found in Table 1.

2.3. Ethical approval

All European GWAS countries incorporated in this secondary analysis received ethical approval from their respective institutions for data collection the collection of informed consent and no further ethical approval was required.

2.4. Genetic instrumental variables selection

Single nucleotide polymorphisms (SNPs) associated with PA at genome-wide significance ($p < 5 \times 10^{-8}$) were selected as IVs.²⁵ To ensure the independence of IVs, we applied a linkage disequilibrium correlation coefficient threshold of $r^2 < 0.001$ and implemented a clumping window size larger than 10 000 kb. We also accounted for potential confounding factors such as body mass index and alcohol intake, which could influence exposure or outcome.^{26–28} Consequently, we performed a thorough search using PhenoScanner²⁹ to exclude SNPs associated with these factors ($p < 5 \times 10^{-8}$) from our selection of IVs. Additionally, palindromic, incompatible, and SNPs that were directly associated with outcomes were excluded from consideration as IVs during the harmonization of exposure and outcome statistics. Such as those that are palindromic (where the alleles are A/T or G/C) with intermediate allele frequencies (close to 0.5), were identified. These SNPs pose a challenge because their effect direction cannot be confidently determined. Furthermore, any SNPs for which we discovered corresponding exposure data but lacking corresponding outcome data were also eliminated from the pool of IVs, to ensure that each SNP had a corresponding effect size and standard error in the outcome data. In order to mitigate potential bias introduced by weak instrumental variables, we evaluated the strength of the IVs by calculating the *F*-statistic using formula $F \text{ exposure} = \beta^2 \text{ exposure} / SE^2 \text{ exposure}$.³⁰ We removed IVs with *F*-statistics < 10 to mitigate the risk of weak instrument bias.³¹

2.5. Statistical analyses

We applied the primary analytical tool, known as the inverse-variance weighted (IVW) method, for our analysis involving statistical research.³² The selection between the fixed-effect IVW (IVW-FE) model and the random-effect IVW (IVW-RE) model is contingent upon the results obtained by Cochran’s *Q* heterogeneity test. If heterogeneity is detected ($p < 0.05$), we opt for the IVW-RE, which offers a more cautious estimation. Conversely, if there is no heterogeneity, we employ the IVW-FE instead.³³ IVW methods, which adhere to meta-analytic principles, are commonly

Table 1
Details of exposure and outcome GWAS datasets.

Dataset type	GWAS ID	Author	Population	Sample size	PMID
Exposure					
Average physical activity	ebi-a-GCST006099	Klimentidis YC	European	91 084	29899525
Light physical activity	ebi-a-GCST90061421	Qi G	European	88 411	35043453
Moderate to vigorous physical activity	ebi-a-GCST006097	Klimentidis YC	European	377 234	29899525
Vigorous physical activity	ebi-a-GCST006098	Klimentidis YC	European	98 060 cases and 162 995 controls	29899525
Outcome					
Major coronary heart disease	ukb-d-I9_CHD	Neale lab	European	10 157 cases and 351 037 controls	NA
Atherosclerotic heart disease	ukb-b-1668	Ben Elsworth	European	12 171cases and 450 839 controls	NA
Chronic ischaemic heart disease	ukb-a-534	Neale lab	European	8 755cases and 328 444 controls	NA
Chronic bronchitis	ukb-b-16207	Ben Elsworth	European	7 844cases and 454 169 controls	NA
Chronic gastritis	ukb-d-K11_CHRONGASTR	Neale lab	European	1 790cases and 359 404 controls	NA
Osteoarthritis	ukb-b-14486	Ben Elsworth	European	38 472cases and 424 461 controls	NA
Rheumatoid arthritis	ukb-a-105	Neale lab	European	3 730cases and 333 429 controls	NA
Chronic fatigue syndrome	ukb-b-8961	Ben Elsworth	European	2 076cases and 460 857 controls	NA

employed in conducting causal analyses for MR studies.^{34–36}

We used MR-Egger, weighted median, weighted mode, and simple mode as four additional MR methods to improve the directionality and dependability of our results. The MR-Egger regression framework pre-supposes that over 50% of IVs encounter horizontal pleiotropy.³⁷ Conversely, the weighted median method is based on the premise that less than 50% of instrumental variables exhibit horizontal pleiotropy.³⁸ Causal associations were deemed valid only for exposure-outcome pairs that exhibited consistent effects across all MR methods and yielded significant outcomes in the IVW analysis.

Moreover, we used the Steiger Test to detect whether there is reverse causation in the results of the study.³⁹ To ascertain horizontal pleiotropy, MR-Egger regression was implemented.^{37,40} Furthermore, we utilized the MR-PRESSO test, which is a crucial part of the MR-PRESSO framework, to determine if the MR estimations were stable after removing probable pleiotropic outliers.⁴⁰ Subsequently, we conducted a leave-one-out analysis to assess the impact of individual SNPs on the MR estimate, specifically examining if any one SNP had a substantial influence or bias.⁴¹ Each SNP is systematically omitted from the IVs in this analysis, and the causal effect is recalculated without that particular SNP. If the MR estimate undergoes substantial alteration with the removal of a specific SNP, it indicates that this SNP may exert an impact on the overall outcome. On the other hand, if the MR estimates consistently remain the same during all rounds, it suggests that the results are not influenced by any one SNP, indicating the absence of bias.

p less than 0.05 is the predetermined level of significance for statistical analysis. The study showed the causative linkages using odds ratios (OR) together with their matching 95% confidence intervals (95% CI). The analyses were conducted using the "TwoSampleMR" packages (version 0.5.6)⁴² and "MRPRESSO" packages (version 1.0)⁴³ in R software (version 4.2.3). We used the "harmonise_data" function from the "TwoSampleMR" package in R to systematically harmonize the data.

Table 2
Sensitivity analysis results of vigorous physical activity on chronic diseases.

Outcome	Steiger Test		Heterogeneity		Pleiotropy			
	Correct causal direction	p	IVW		MR-Egger regression	MR-PRESSO		
			Q	p_Q		$p_{\text{Global Test}}$	Outliers	$p_{\text{Distortion Test}}$
Major coronary heart disease	TRUE	8.38E-28	6.21	0.29	0.61	0.31	NA	NA
Atherosclerotic heart disease	TRUE	2.50E-22	8.79	0.07	0.20	0.10	NA	NA
Chronic ischaemic heart disease	TRUE	1.22E-21	5.59	0.35	0.83	0.39	NA	NA
Chronic bronchitis	TRUE	2.37E-26	6.60	0.25	0.09	0.30	NA	NA
Chronic gastritis	TRUE	5.62E-19	9.34	0.10	0.68	0.14	NA	NA
Osteoarthritis	TRUE	4.50E-21	10.53	0.06	0.11	0.10	NA	NA
Rheumatoid arthritis	TRUE	2.37E-21	5.09	0.41	0.96	0.40	NA	NA
Chronic fatigue syndrome	TRUE	1.07E-27	3.56	0.47	0.62	0.05	NA	NA

IVW, inverse-variance weighted.

3. Results

3.1. SNP

Within the GWAS datasets encompassing various levels of PA, a total of 3–18 SNPs were chosen as IVs. [Supplementary File 1: Table S1](#) details the characteristics of the chosen SNPs, with F -statistics ranging between 29.98 and 55.26, indicating a reduced risk of weak instrument bias. [Supplementary File 1: Table S2](#) lists the confounding factors that were excluded.

3.2. Results of MR analyses

No heterogeneity was detected in the study of VPA ($p_{\text{heterogeneity}} > 0.05$; [Table 2](#)). Consequently, the IVW-FE model was employed as the primary MR method for this analysis. For other levels of physical activity, the heterogeneity can be reviewed in [Supplementary File 1: Tables S3–S5](#). The IVW model was implemented based on these results.

The MR analysis showed that there was a significant association between genetically predicted VPA and a decreased risk of major coronary heart disease (IVW-FE: $OR = 0.95$, 95% CI : 0.91–0.99, $p = 0.01$; [Figs. 1 and 2 A](#)). This effect direction was consistent across four supplementary MR analysis methods. Nevertheless, the studies did not reveal any substantial causal connections between different levels of PA and chronic diseases ([Supplementary File 1: Tables S6–S8](#)).

3.3. Sensitivity analysis results

For the analysis of VPA on chronic diseases, the Steiger test did not reveal any evidence of reverse causation, and all causal directions remained consistent ($p < 0.05$; [Table 2](#)). In the MR-Egger regression and MR-PRESSO analysis, no evidence of pleiotropy or outliers was found

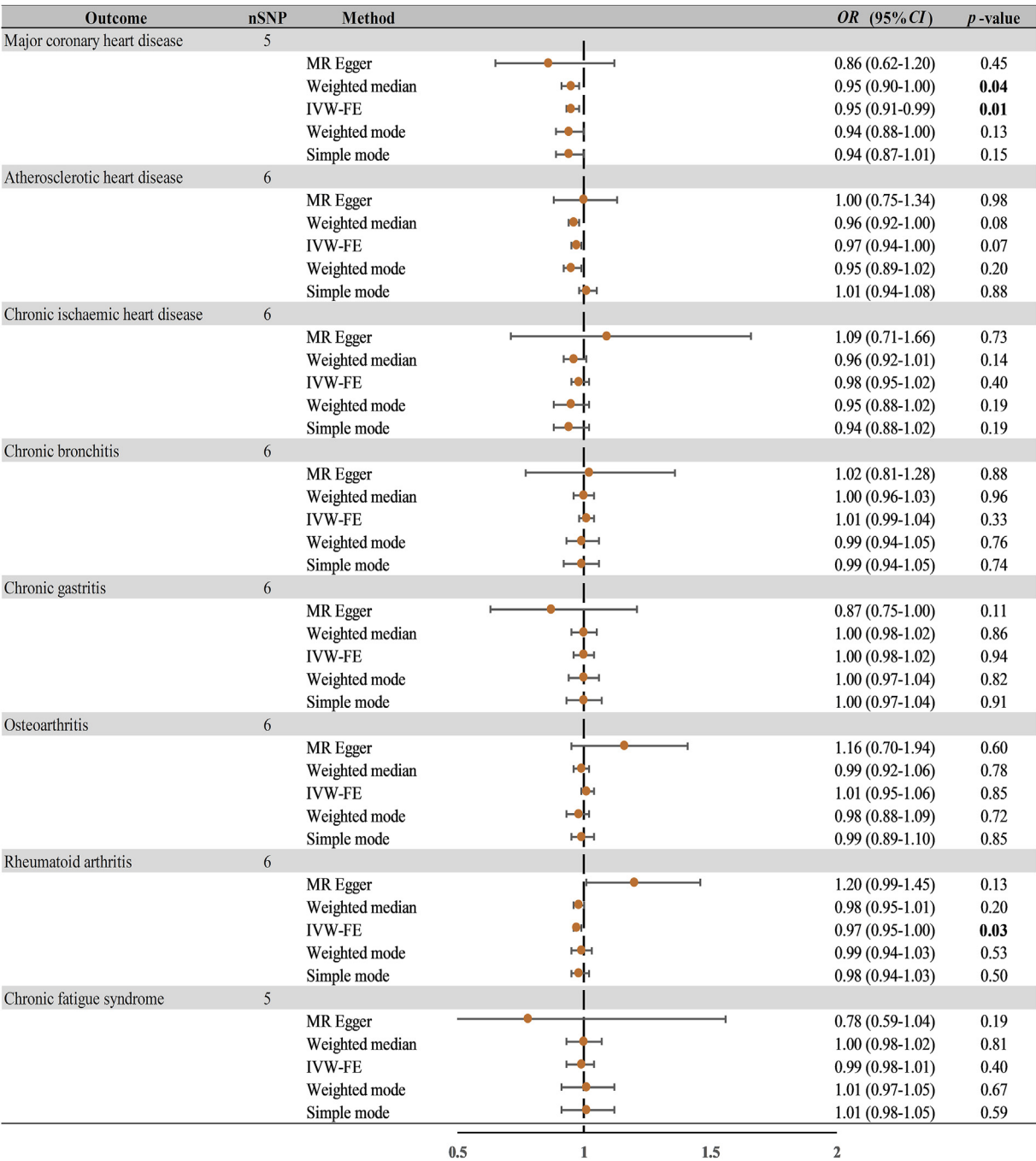


Fig. 1. Associations between genetically predicted vigorous physical activity (VPA) and chronic diseases. The figure shows the odds ratios (OR) and 95% confidence intervals (CI) for the association between VPA (measured in minutes per week) and various chronic diseases. SNP, single nucleotide polymorphism. IVW, inverse variance weighting.

(Both tests $p > 0.05$; [Table 2](#)). Furthermore, the strength and reliability of the MR findings were confirmed by a leave-one-out sensitivity analysis, which demonstrated that the exclusion of any one SNP did not have a significant impact on the results ([Fig. 2B–Supplementary file 2: Figs. S1–S7](#)).

For the analysis of other levels of PA on chronic diseases, the Steiger test did not reveal any evidence of reverse causation, and all causal directions remained consistent ($p < 0.05$; [Supplementary file 1: Tables S3–S5](#)). Additionally, MR-PRESSO detected one outlier (rs9293503) in the analysis for APA on chronic fatigue syndrome and two outliers (rs2114286 and rs2942127) in the analysis for MVPA on atherosclerotic heart disease. These outliers were excluded from the

analysis, but the association remained significant ($p_{APA} = 0.150$; $p_{MVPA} = 0.997$; [Supplementary file 1: Tables S3 and S5](#)). Furthermore, no instances of pleiotropy or outliers were identified in the subsequent MR-Egger regression and MR-PRESSO analyses ($p > 0.05$ for both tests; [Supplementary file 1: Tables S3–S5](#)). Finally, the strength and reliability of the MR findings were confirmed by a leave-one-out sensitivity analysis. This analysis shown that the exclusion of any one SNP did not have a substantial impact on the results ([Supplementary file 2: Figs. S8–S31](#)).

4. Discussion

Our MR analysis, after accounting for confounders such as alcohol

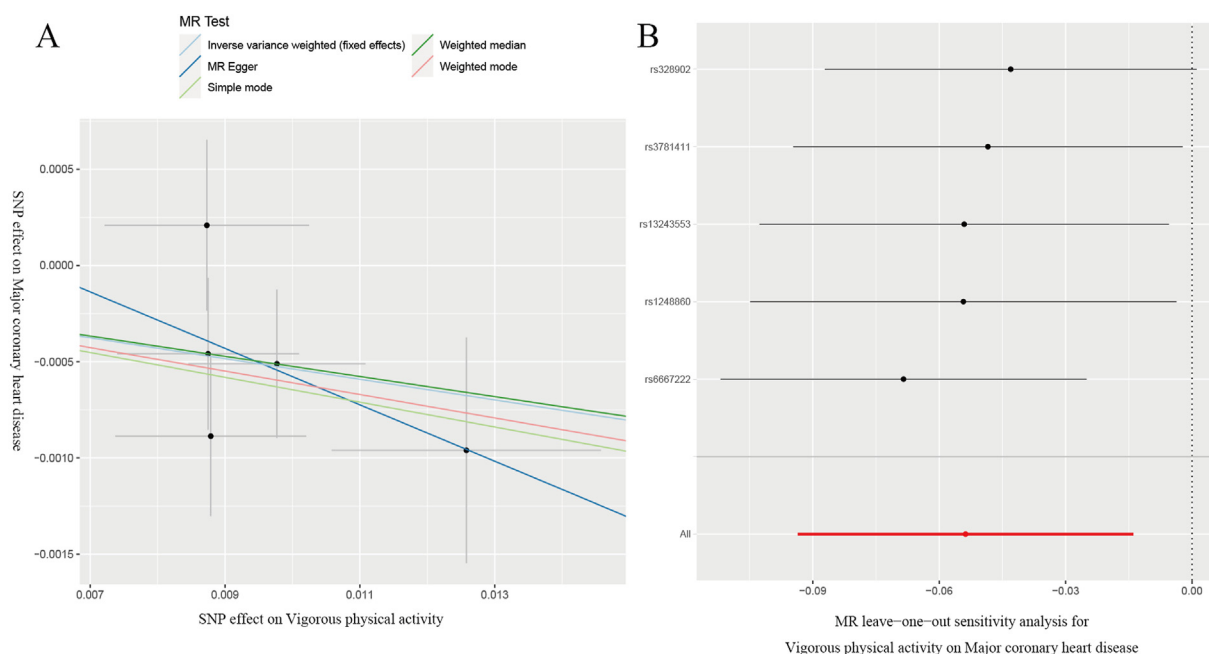


Fig. 2. The analysis of the impact of vigorous physical activity (VPA) on chronic diseases. (A) Scatter plot of genetic associations, showing the relationship between VPA (measured in minutes per week) and chronic disease risk. (B) Leave-one-out sensitivity analysis, illustrating the robustness of the causal estimates when each single nucleotide polymorphism (SNP) is excluded in turn. IVW, inverse variance weighting. MR, Mendelian randomization.

intake and body mass index, has identified a significant causal relationship between VPA and a reduced risk of major coronary heart disease. This finding emphasizes the practical significance of VPA in the realm of preventative cardiology, potentially guiding public health initiatives aimed at reducing the incidence of major coronary heart disease through physical activity recommendations. To provide a comprehensive discussion of these findings, we compared our results with several related studies.

Firstly, a systematic review and meta-analysis explored dose-response associations between accelerometry-measured physical activity, sedentary time, and all-cause mortality.⁴⁴ The study found that higher levels of physical activity significantly reduced all-cause mortality, with a dose-response relationship observed. Our findings align with this study, indicating that VPA offers significant health benefits, particularly in reducing the risk of coronary heart disease. Secondly, another study assessed the associations of accelerometry-assessed and self-reported physical activity and sedentary behavior with all-cause and cardiovascular mortality.⁴⁵ The results showed that higher levels of physical activity, whether measured by accelerometry or self-reported, were associated with lower all-cause and cardiovascular mortality. Our findings further support this view, highlighting the critical role of VPA in reducing cardiovascular disease risk. Additionally, a study on the associations of sedentary behavior with cardiovascular disease mortality and cancer mortality, and the moderating effect of physical activity levels, indicated that higher levels of physical activity can mitigate the adverse effects of sedentary behavior on cardiovascular disease and cancer mortality.⁴⁶ Our study concurs with these findings, suggesting that increasing VPA levels not only helps reduce coronary heart disease risk but also offsets the negative health impacts of sedentary behavior. Finally, a dose-response meta-analysis investigated non-occupational physical activity and its association with cardiovascular disease, cancer, and mortality outcomes.⁷ The study found that higher levels of non-occupational physical activity were significantly associated with reduced cardiovascular disease and all-cause mortality, with a clear dose-response relationship. Our results corroborate these findings, emphasizing the protective effects of VPA, particularly in preventing major coronary heart disease.

While our findings concur with previous research emphasizing the cardio-protective nature of VPA,^{47–49} our MR study distinguishes itself by validating these associations through genetic instruments that suggest causality, not just correlation. Expanding on the mechanisms, VPA may confer cardiac benefits through the following paths. Firstly, VPA enhances cardiovascular efficiency,⁵⁰ strengthening the heart muscle and improving blood circulation. It also positively influences lipid metabolism,^{51,52} reducing harmful cholesterol levels which are a significant contributor to coronary artery disease.^{53,54} Moreover, VPA has been shown to lower blood pressure,^{55,56} a key risk factor for major coronary heart disease. At the same time, VPA promotes anti-inflammatory responses within the body,⁵⁷ further protecting against the development of atherosclerotic plaques.⁵⁸ Recent systematic reviews have highlighted the potential of various compounds and physical activities in reducing oxidative stress and inflammation. Citrus Limon has been identified for its potential to mitigate oxidative stress and inflammation following physical activity.⁵⁹ N-3 polyunsaturated fatty acids combined with physical exercise have been noted to alleviate pain intensity in women suffering from primary dysmenorrhea.⁶⁰ Additionally, VPA improves glucose control, which is particularly beneficial in reducing the risk of coronary disease in individuals with diabetes or prediabetic conditions.^{61,62} These diverse mechanisms collectively contribute to the cardio-protective effects of VPA.

The robustness of our study is due to the use of MR, which allows for a more refined causality inference, circumventing the typical confounders and issues of reverse causation inherent in observational research. Furthermore, our approach through MR analysis not only establishes this connection with a high degree of confidence but also does so in a cost-effective manner, reducing the financial burden typically associated with large-scale randomized controlled trials. Despite these advantages, our study still has certain limitations. The SNPs used in our study explain only a small fraction of the genetic variance in physical activity levels, indicating that many other genetic factors may contribute to this trait. The modest effect sizes of the SNPs suggest that the observed changes in physical activity levels are relatively small, which may limit the clinical significance of our findings. Given the polygenic nature of physical activity, future studies should consider incorporating additional genetic

variants and other factors to better understand the genetic architecture of this trait. Furthermore, the conclusions of our study may be affected by population stratification, where genetic associations are confounded by population differences. It is also essential to consider that while our findings are indicative, they are contingent upon the specific genetic context of the population studied and may not be directly generalizable to all groups. Hence, there is a clear necessity for subsequent research to validate these findings across varied populations (e.g., age, sex, ethnicity) and investigate the dose-response relationship of VPA on heart health more deeply. Future studies should also aim to consolidate the biologically plausible pathways through which VPA exerts its protective effects on the cardiovascular system, thus strengthening the evidence base for the role of VPA in the prevention of major coronary heart disease.

5. Conclusions

In conclusion, our study elucidates the significant role of VPA in reducing the risk of major coronary heart disease. By leveraging MR, we have provided evidence that suggests a causal relationship, highlighting the potential of VPA as a key factor in cardiovascular disease prevention. Our findings serve as a valuable reference for public health strategies, emphasizing the importance of incorporating VPA into lifestyle recommendations to combat major coronary heart disease and improve population health outcomes.

Ethical approval statement

All European GWAS countries incorporated in this secondary analysis received ethical approval from their respective institutions for data collection the collection of informed consent and no further ethical approval was required.

Data availability statement

The data employed in this study is freely accessible and can be downloaded from the UK Biobank at <http://www.nealelab.is/uk-biobank> and the NHGRI-EBI GWAS database at <https://www.ebi.ac.uk/gwas/>.

CRedit authorship contribution statement

Peng Qiu: Writing – original draft, Software, Methodology, Conceptualization. **Junyu Wu:** Writing – original draft, Data curation. **Min Li:** Validation, Formal analysis. **Zhiguang Zhao:** Supervision. **Qirong Wang:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.smhs.2024.09.002>.

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