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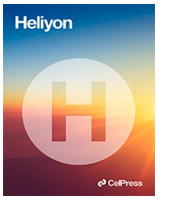

Vitamin D levels and five cardiovascular diseases: A Mendelian randomization study

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ABSTRACT

Cardiovascular disease is the leading cause of death worldwide, whilst vitamin D levels have been found to be associated with cardiovascular disease. To investigate the causal relationship between vitamin D levels and five cardiovascular diseases, a genome-wide association study (GWAS) was carried out using data on vitamin D levels (sample size = 79366), angina pectoris (18168 cases and 187840 controls), coronary heart disease (21012 cases and 197780 controls), lacunar stroke (6030 cases and 248929 controls), heart attack (10693 cases and 451187 controls), and hypertension (55917 cases and 162837 controls), with a Mendelian randomization (MR) analysis being subsequently performed. Six single nucleotide polymorphisms were used as instrumental variables (IVs). In addition, sensitivity analysis was performed to verify the reliability of the MR results here. The results showed a causal relationship between vitamin D levels and angina pectoris (OR = 0.51, 95 % CI: 0.28–0.93, P = 0.03), coronary heart disease (OR = 0.53, 95 % CI: 0.34–0.81, P = 0.004), and lacunar stroke (OR = 0.41, 95 % CI: 0.20–0.86, P = 0.02), but no causal relationship with heart attacks (OR = 1.00, 95 % CI: 0.99–1.01, P = 0.76) or hypertension (OR = 0.99, 95 % CI: 0.73–1.34, P = 0.94). Additionally, our IVs data showed no heterogeneity or pleiotropy, whilst the results of the MR analysis were reliable. This study contributes to the prevention and treatment of these five cardiovascular diseases.

1. Introduction

Cardiovascular disease accounted for one-third of all deaths worldwide in 2019 and is a major contributor to morbidity and mortality [1]. Women typically die from cardiovascular disease in higher numbers than men, accounting for 49 % and 40 % of deaths in women and men, respectively [2,3]. However, studying cardiovascular disease presents a significant challenge for scientists and clinicians. Although animal models have been used to help in elucidating the pathogenesis of cardiovascular disease, the development of this field has slowed due to genetic variation and interspecies differences [4].

Angina pectoris is a type of chest pain that occurs when the heart muscle does not receive enough oxygen-rich blood. It is often triggered by physical activity or emotional stress [5]. Heart attack, also known as myocardial infarction, refers to the damage or injury to the heart muscle caused by reduced or interrupted blood flow in the coronary arteries. This can cause permanent damage to the heart muscle and can be life-threatening [6–8]. The characteristic feature of coronary heart disease is the gradual narrowing or blockage of the coronary arteries due to the accumulation of lipid deposits and other substances on the inner lining of the artery, which

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affects the blood supply to the heart. This disease is often accompanied by symptoms such as chest pain, tightness, palpitations, shortness of breath, and others [9,10]. Lacunar stroke is an important subtype of stroke, accounting for a quarter of all ischemic strokes. Its underlying cause may differ from other stroke subtypes, as it is typically a manifestation of small vessel disease rather than due to large vessel atheroma or cardioembolism [11]. Factors that lead to an increase in blood volume or a decrease in the ability of blood vessels to dilate can cause hypertension [12].

Vitamin D undergoes two hydroxylation steps to produce its active form and is an essential fat-soluble vitamin. During the first step, 25-hydroxyvitamin D is produced, and vitamin D levels can be determined by measuring the 25-hydroxy group [13]. Vitamin deficiency is a common concern worldwide [14], whilst much concern surrounding vitamin D deficiency has been focused on its association with the risk of non-skeletal diseases, particularly various cardiovascular diseases [15]. Observational studies have shown that vitamin D levels are associated with a variety of complex human characteristics and diseases [16]. Additionally, it has been reported that low plasma vitamin D levels in European populations may increase the risk of cardiovascular disease [17–19].

Mendelian randomization (MR) is an emerging analytical method that can explore the causal relationship between exposure and outcome using genetic variants such as instrumental variables (IVs) [20]. Causal relationships between vitamin D and cardiovascular diseases have previously been investigated using the MR method. Yang et al. found no genetic evidence for a significant association between serum vitamin D levels and the risk of atrial fibrillation [21], whilst Jiang et al. found that increased serum 25(OH)D levels were associated with a reduced risk of low back pain in a European population [22]. Furthermore, Hu et al. found no causal relationship between vitamin D and dental caries or periodontitis [23].

In this study, we used MR analysis to analyze the causal relationship between vitamin D levels and five cardiovascular diseases: angina pectoris, coronary heart disease, lacunar stroke, heart attacks, and hypertension.

2. Materials and methods

2.1. Study overview

We performed an MR analysis using vitamin D levels as the exposure and five cardiovascular diseases (lacunar stroke, angina pectoris, hypertension, major coronary heart disease event, and heart attack) as the outcome to investigate the causal relationship between vitamin D levels and these five cardiovascular diseases.

2.2. Data source

We collected genome-wide association study (GWAS) summary datasets from the GWAS catalog database (https://www.ebi.ac.uk/gwas/) on vitamin D levels [24] (sample size = 79366 Number of SNPs = 2,538,249) and lacunar stroke (6030 cases and 248929 controls Number of SNPs = 6,909,434). Data for angina pectoris (18168 cases and 187840 controls Number of SNPs = 16,380,426), hypertension (55917 cases and 162837 controls Number of SNPs = 16,380,466), and major coronary heart disease events (21012 cases and 197780 controls Number of SNPs = 16,380,466) were obtained from the FinnGen database (https://www.finngen.fi/en) [25,26]. In addition, we supplemented a United Kingdom Biobank (http://www.nealelab.is/uk-biobank) study on heart attack (10693 cases and 451187 controls Number of SNPs = 9,851,867). The GWAS data used were all obtained from a European cohort. In the GWAS data on cardiovascular disease for this species, the cases represent the morbidity of the disease.

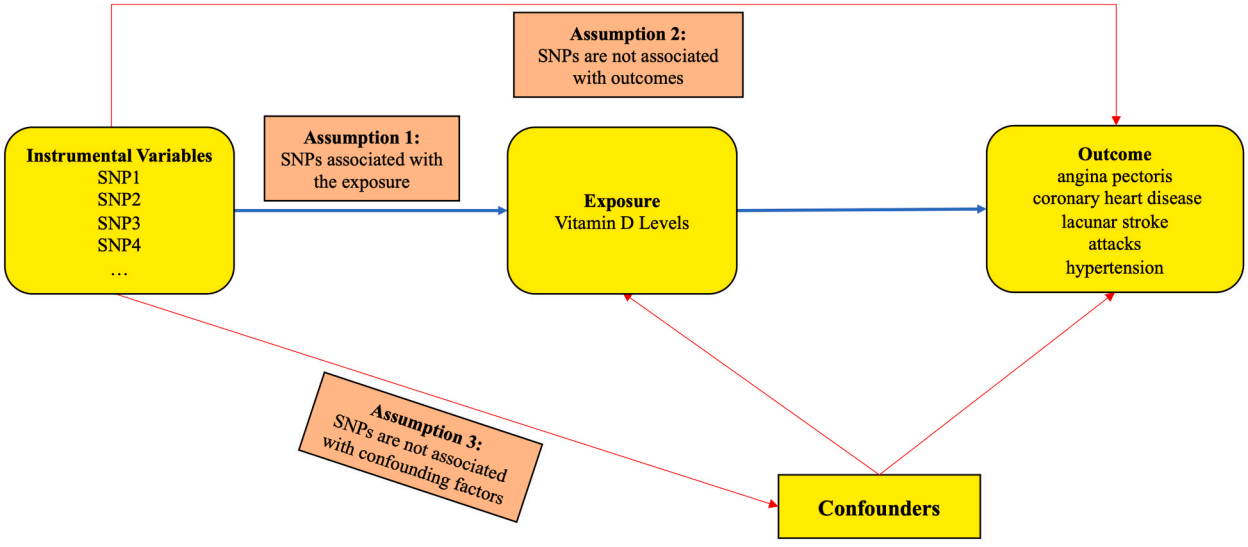

Fig. 1. MR analysis flow chart.

2.3. Genetic variants selection criteria

MR analysis must satisfy three assumptions: 1. Single nucleotide polymorphisms (SNPs) strongly correlate with exposure factors; 2. SNPs cannot be directly correlated with outcomes; 3. SNPs cannot be correlated with any possible confounding factors [27,28]. To satisfy these assumptions, we performed the following screening of SNPs. SNPs with a minor allele frequency (MAF) < 1 % were removed to reduce the risk of false positives. In addition, to avoid linkage disequilibrium (LD), we deleted SNPs that had a physical distance below 10,000 kb and $R^2 < 0.001$. The IVs were selected from SNPs that satisfied the genome-wide association threshold ($P <$ 5E−08) in the exposure data, and, we removed SNPs associated with the outcome to avoid reverse causation. To mitigate the risk of weak instrumental bias, we used the F-statistic (F = beta2/se2) to evaluate the strength of the instrumental variable. A value of $F > 10$ was considered as an indicator of a sufficiently strong correlation between the instrumental variable and exposure. This approach ensured that the results of the Mendelian randomization analysis were not influenced by weak instrumental bias [29] (Fig. 1).

2.4. Statistical analysis

We used two-sample Mendelian randomization (MR) analysis to estimate the causal effect of vitamin D levels on five previously listed cardiovascular diseases using genome-wide association study (GWAS) data [30]. We extracted single nucleotide polymorphisms (SNPs) in the instrumental variables (IVs) from the GWAS results. The MR analysis was conducted using the R package "TwoSampleMR" (https://github.com/MRCIEU/TwoSampleMR), which implements several MR methods. In this study, we used three commonly used MR methods, including the inverse variance weighted (IVW), MR-Egger, and weighted median methods, to assess the causal relationship between vitamin D levels and the five cardiovascular diseases mentioned above. The IVW method combines the estimates of each SNP using inverse-variance weighting to estimate the causal effect. IVW is a method used in MR to perform meta-analysis of the effects of multiple SNPs on multiple loci. The prerequisite for the application of IVW is that all SNPs are valid instrumental variables and independent of each other. MR-Egger does not impose a regression line to pass through the origin and allows for directional pleiotropy in the instrumental variables. The presence of pleiotropy is indicated when the regression intercept is non-zero and the P-value for the intercept is less than 0.05. Weighted median calculates the median of the distribution function of individual SNP effect sizes weighted by their strengths. WM provides robust estimates when at least 50 % of the information comes from valid instrumental variables [28,31].

2.5. Sensitivity analysis

To review the reliability of the MR analysis results, we performed a test for heterogeneity and pleiotropy. The lower the heterogeneity, the more reliable the MR results. Cochran's Q test was used to analyze heterogeneity, whilst pleiotropy was detected using MR-Egger intercept analysis, and funnel plots were used to determine whether the SNPs were distributed on both sides of the IVW line.

3. Results

3.1. Association of vitamin D levels with five cardiovascular diseases

To evaluate the association of vitamin D levels with cardiovascular diseases, we used six SNPs as instrumental variables (IVs), as shown in Tables 1 and 2. Two SNPs (rs2298850 and rs8018720) with intermediate allele frequencies were removed from the analysis because they were palindromic, which could lead to inaccurate results. The F-statistic values of the remaining IVs ranged from 56 to 272, indicating that the IVs were strong and provided sufficient statistical power to detect a causal effect of vitamin D levels on the cardiovascular diseases analyzed. Detailed information on the SNPs used as IVs in the analysis is presented in Table 3, including the SNP ID, effect allele, reference allele, SNP position, Chr, Beta, Se and P. We also assessed the correlation between the IVs and the outcome group and found that none of the SNPs were significantly correlated with the cardiovascular diseases analyzed, suggesting that the assumptions were not violated.

IVW analysis showed a causal relationship between vitamin D levels and angina pectoris (Odd ratio, OR = 0.51, 95 % confidence interval, CI: 0.28–0.93, P = 0.03), coronary heart disease (OR = 0.53, 95 % CI: 0.34–0.81, P = 0.004), and lacunar stroke (OR = 0.41, 95 % CI: 0.20–0.86, P = 0.02). However, no causal relationship was found between vitamin D levels and heart attacks (OR = 1.00, CI: 0.99–1.01, P = 0.76) or hypertension (OR = 0.99, CI: 0.73–1.34, P = 0.94) (Fig. 2).

Table 1
Characteristics of eight genetic variants as instrumental variables (IVs).

SNP	Chr	Pos	Effect allele	Other allele	beta	SE	P	F
rs17775309	4	73017958	G	T	0.0173	0.0021	2.45e−16	67.8662
rs12785878	11	71167449	T	G	0.0363	0.0022	3.81e−62	272.2500
rs2060793	11	14915310	G	A	−0.0296	0.0021	2.98e−45	198.6757
rs2597193	11	14505962	A	G	0.0187	0.0022	6.26e−17	72.2500
rs4762258	12	96359257	G	A	0.0158	0.0021	1.66e−13	56.6077
rs17216707	20	52732362	C	T	−0.0263	0.0027	8.14e−23	94.8820

Table 2
The P value of MR Egger, Weighted median and IVW analysis.

Methods	Angina pectoris	Coronary heart disease	Lacunar stroke	Heart attack	Hypertension
MR Egger	0.662	0.352	0.192	0.154	0.538
Weighted median	0.025	0.028	0.015	0.403	0.482
Inverse variance weighted	0.028	0.004	0.018	0.758	0.945

Table 3
P value of SNPs in vitamin D levels and five cardiovascular diseases.

SNPs	Vitamin D levels	Angina pectoris	Coronary heart disease	Lacunar stroke	Heart attack	Hypertension
rs17775309	2.445e−16	1.592e−01	8.324e−01	2.388e−01	1.200e−01	3.642e−01
rs12785878	3.812e−62	8.052e−02	1.082e−01	6.058e−02	5.200e−01	5.720e−01
rs2060793	2.982e−45	1.368e−01	1.337e−01	2.738e−01	1.500e−01	6.736e−01
rs2597193	6.263e−17	3.635e−02	4.016e−01	2.066e−01	2.200e−01	8.748e−01
rs4762258	1.664e−13	3.103e−02	2.267e−01	1.828e−01	8.400e−01	7.312e−01
rs17216707	8.141e−23	4.670e−01	7.305e−02	3.340e−01	9.900e−01	4.513e−01

3.2. Sensitivity analysis

Our sensitivity analyses showed that the IVs used in our study did not exhibit heterogeneity ($P > 0.05$) or pleiotropy ($P > 0.05$), as presented in Table 4 and Fig. 3 (A-E). This suggests that the causal effect of vitamin D levels on the cardiovascular diseases analyzed was not confounded by other factors. Furthermore, we assessed the potential publication bias in our MR analysis using a funnel plot, which showed that the results of our analysis were not affected by publication bias (Supplementary Material). These results support the robustness of our findings and suggest that the causal association between vitamin D levels and the analyzed cardiovascular diseases is likely to be valid.

In summary, our sensitivity analyses showed that our MR analysis was robust and not affected by heterogeneity, pleiotropy, or publication bias. These findings provide further support to our main results, indicating a causal association between vitamin D levels and a reduced risk of angina pectoris, coronary heart disease, and lacunar stroke, but not with heart attacks or hypertension.

4. Discussion

We analyzed the causal relationship between vitamin D levels and five cardiovascular diseases using MR methods. As a result, we found that vitamin D levels were negatively associated with angina pectoris, coronary heart disease, and lacunar stroke, but not with a heart attack or hypertension. This may imply that vitamin D supplementation could reduce the risk of three cardiovascular diseases (angina pectoris, coronary heart disease, and lacunar stroke) but may not show any effect on heart attacks or hypertension. Our findings could provide new insights into the treatment and prevention of angina pectoris, coronary heart disease, and lacunar strokes.

However, there are some limitations to our study that should be considered. First, our study only included individuals of European ancestry, which may limit the generalizability of our findings to other ethnic populations. Second, we used summary statistics from GWAS, which may introduce measurement errors and bias in our analysis. Third, our study only investigated the causal relationship between vitamin D levels and five cardiovascular diseases, and additional research is needed to explore the potential effects of vitamin D on other cardiovascular outcomes.

MR analysis must satisfy three major assumptions. When we selected instrumental variables, we used a threshold ($P < 5E\text{-}08$) to screen for SNPs in the GWAS data for vitamin D levels; therefore, the selected SNPs were all strongly associated with vitamin D levels.

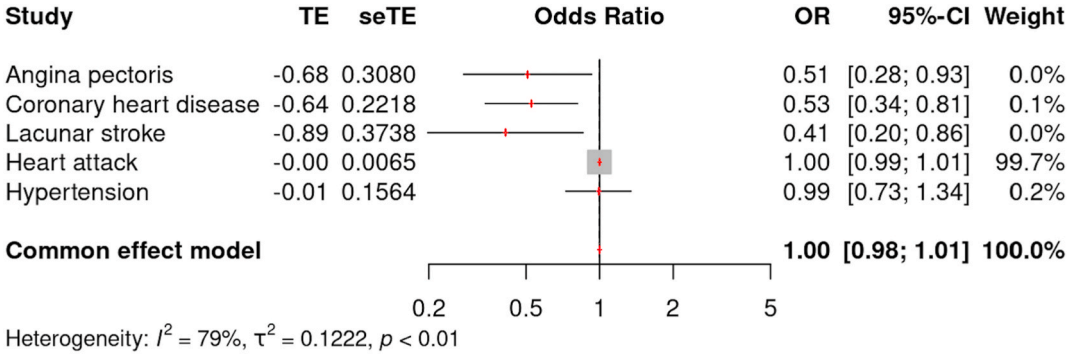

Fig. 2. MR analysis between vitamin D levels and five cardiovascular diseases. TE represents beta. seTE represents standard error of treatment effect.

Table 4
The P value of sensitivity analysis.

Methods	Angina pectoris	Coronary heart disease	Lacunar stroke	Heart attack	Hypertension
MR-Egger	0.904	0.859	0.422	0.159	0.532
Heterogeneity	0.130	0.870	0.447	0.269	0.845

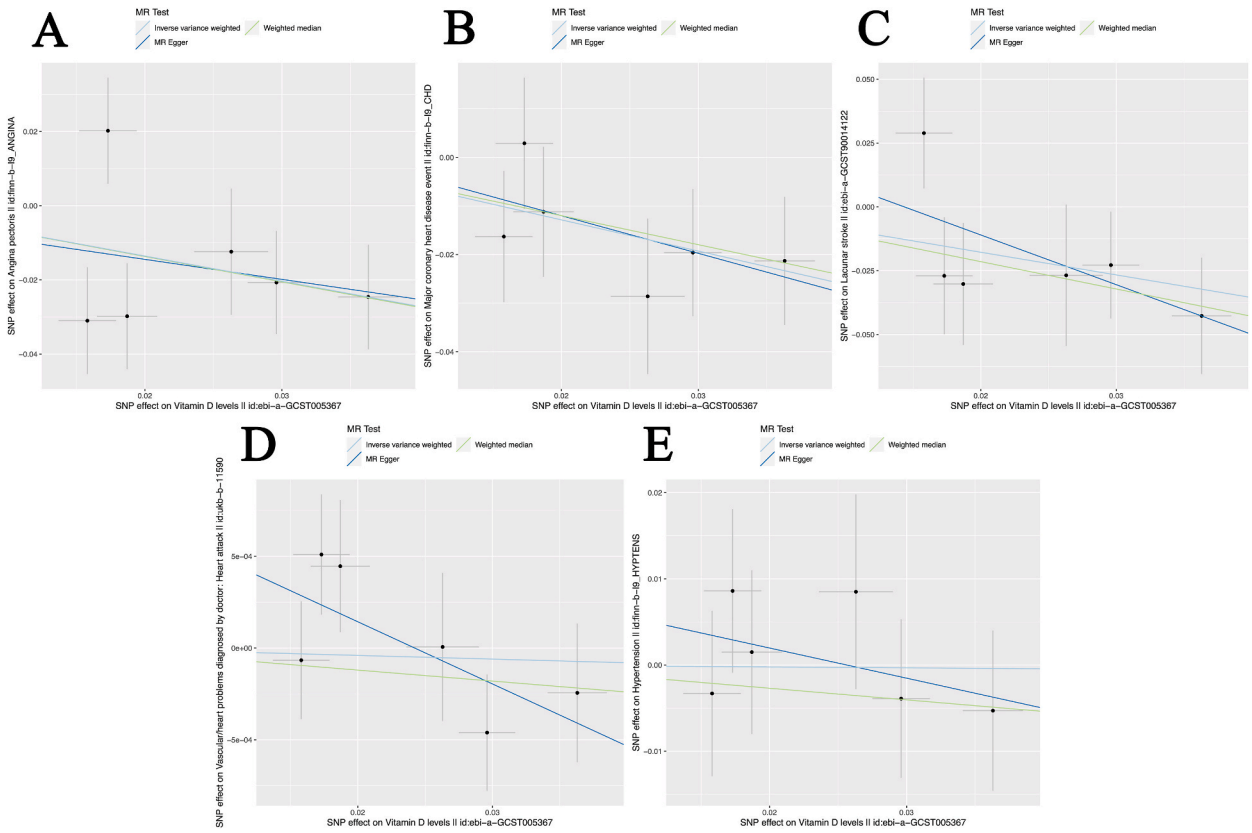

Fig. 3. MR test of vitamin D levels with five cardiovascular diseases. A: Angina pectoris. B: Coronary heart disease. C: Lacunar stroke. D: Heart attack. E: Hypertension.

This satisfied the first assumption. None of the SNPs were correlated with the outcome group, which satisfied the second assumption. MR analysis eliminates the need to consider confounders and reverse causality [32]. Therefore, our data can be analyzed using MR. Finally, the absence of heterogeneity and pleiotropy in our IVs data suggested that the results of our MR analysis were reliable.

In previous studies [33], observational analyses have found an association between vitamin D levels and coronary heart disease and stroke, which is consistent with our study's findings. Another study found [34] that vitamin D deficiency can increase the risk of cardiovascular disease and that correcting low vitamin D status in the population may reduce the burden of CVD. However, our study results suggest that vitamin D levels only have an impact on some cardiovascular diseases. some studies have shown that vitamin D supplementation is helpful for patients with angina pectoris and that patients with angina have higher rates of vitamin D deficiency than healthy controls [35,36]. Our analysis using MR methods found there is causal relationship between vitamin D levels and angina pectoris, with higher levels of vitamin D being associated with a lower risk of angina pectoris. Low vitamin D levels may be a risk factor for developing coronary heart disease [37] and we arrived at the same conclusion here. Our results showed a causal relationship between vitamin D levels and the development of coronary heart disease, with elevated vitamin D levels reducing the risk of developing coronary heart disease. Some previous studies have shown that vitamin D levels were associated with stroke [38]. Although we did not find any previous research on the relationship between vitamin D levels and lacunar stroke, our results found a causal relationship between vitamin D levels and lacunar stroke, with elevated vitamin D levels reducing the risk of lacunar stroke. Additionally, we did not find any record of an association between vitamin D levels and heart attacks. Herein, there was no causal relationship between vitamin D level and heart attacks. Wu et al. found that lower vitamin D levels may increase the risk of developing hypertension [39], however, our study did not find a causal relationship between vitamin D levels and hypertension. Further research is still required to establish a causal relationship between vitamin D levels and hypertension.

5. Conclusion

In conclusion, we analyzed the causal relationship between vitamin D levels and five cardiovascular diseases (angina pectoris, coronary heart disease, lacunar stroke, heart attack, and hypertension) using the MR method. The results of this showed a causal relationship between vitamin D levels and angina pectoris, coronary heart disease, and lacunar stroke, although no causal relationship was found with heart attacks or hypertension. Our results provide new insights for the prevention and treatment of these five cardiovascular diseases, which may have important clinical implications.

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Data Availability statement

Data ids:
Vitamin D levels: ebi-a-GCST005367.
GWAS catalog: Download Links: https://gwas.mrcieu.ac.uk/files/ebi-a-GCST005367/ebi-a-GCST005367.vcf.gz.
Angina pectoris: finn-b-I9_ANGINA.
Finngen: Download Links: https://r5.finngen.fi/pheno/I9_ANGINA.
Coronary heart disease: finn-b-I9_CHD.
Finngen: Download Links: http://r5.finngen.fi/pheno/I9_CHD.
Lacunar stroke: ebi-a-GCST90014122.
GWAS catalog: Download Links: https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90014122/
Heart attack: ukb-b-11590.
UK Biobank: Download Links: http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90014001-GCST90015000/GCST90014122.
Hypertension: finn-b-I9_HYPTENS.
Finngen: Download Links: http://r5.finngen.fi/pheno/I9_HYPTENS.
All the research-related data can be found in publicly available repositories.

Ethics statement

Additional ethical approval is not required for this study, as we used summarized statistics only.

CRediT authorship contribution statement

Zhishuai Zhang: Conceptualization, Data curation, Formal analysis, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Shizheng Qiu:** Data curation, Formal analysis, Methodology, Software. **Zhaoqing Wang:** Conceptualization, Data curation. **Yang Hu:** Conceptualization, Data curation, Funding acquisition, Resources.

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.heliyon.2023.e23674.

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