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Emergency Medicine: Open Access

Research Article

A Mendelian Randomization Study Investigated the Association between Socioeconomic Status and the Risk of Myocardial Infarction

Qiang Luo[1], Meijia Liu[2], Xueqing Sun[1], Longbo Li[1], Guan Wang[1], Yongfeng Shi[1*], Bin Liu[1]

[1]Department of Cardiology, The Second Hospital of Jilin University, Changchun, China; [2]Department of Ultrasound, The Second Hospital of Jilin University, Changchun, China

ABSTRACT

Background: The causal relationship between socioeconomic factors and the risk of cardiovascular disease is not well understood. We applied a two sample Mendelian Randomization (MR) to find the causal link between Socioeconomic Status (SES) and the risk of Myocardial Infarction (MI) using data from large scale Genome-Wide Association Studies (GWAS) of socioeconomic status and myocardial infarction.

Method: Using a two sample MR design, the genetic tools for the exposure SES and the outcome MI were gathered from different GWAS data sources. We first identified the causal effect of the socioeconomic determinants on SES and then investigated the causal relationship between SES and MI. Inverse variance weighted method, weighted median method, MR-Egger regression, MR Pleiotropy RESidual Sum and Outlier test were used for MR analyses.

Results: Age of full time education has a reverse causal relationship with MI (OR=0.57, 95% CI=0.38-0.87, p=0.0096). There is a potential causal association between self-reported household income and the risk of MI (OR=0.41, 95% CI=0.32-0.52, $p=8.82 \times 10^{-14}$). Furthermore, heavy physical work is significantly associated with an increased risk of MI (OR=1.79, 95 percent CI=1.02-3.13, p=0.042).

Conclusion: Our MR analysis supports the hypothesis that low SES levels could increase MI incidence.

Keywords: Mendelian randomization; Socioeconomic status; Myocardial infarction; Association

INTRODUCTION

Cardiovascular Diseases (CVD) continue to be the leading cause of chronic disease related mortality worldwide, despite breakthroughs over the past century. Traditional CVD risk factors include hypertension, dyslipidemia, diabetes, a family history of early Coronary Heart Disease (CHD) and smoking. The relationship between socioeconomic factors and the risk of CVD is not well understood. Cardiovascular disease and socioeconomic variables are severe and ongoing public health concerns in developed nations [1].

Socioeconomic measurements included factors like employment situation, social class, income, housing characteristics, composite indicators and area level indicators. Low socioeconomic level (Sea S) in industrialized nations is linked to an increased risk of cardiovascular disease and death. Low and Middle Income (LMIC) countries account for over 80% of all CVD cases worldwide.

An extensive study conducted in the United States and Finland found that low-income cohorts continued to have a higher risk of non-fatal MI and sudden cardiac death even when smoking and alcohol consumption were considered. After adjusting for cardiovascular risk variables, low SES was associated with higher incidence rates of Acute Myocardial Infarction (AMI) (HR=1.16, 95 percent Confidence Interval (CI=1.14-1.19) and stroke (HR=1.13, 95 percent CI=1.11-1.14).

Due to the limitations of conventional statistical methods, such as potential confounders or reverse causalities, the stated associations between SES and MI could not be accurately determined. It is unclear how SES and myocardial infarction are related causally.

Correspondence to: Yongfeng Shi, Department of Cardiology, The Second Hospital of Jilin University, Changchun, China; E-mail: Shiyf@jlu.edu.cn

Received: 08-Nov-2023, Manuscript No. EGM-23-27956; **Editor assigned:** 13-Nov-2023, PreQC No. EGM-23-27956 (PQ); **Reviewed:** 27-Nov-2023, QC No. EGM-23-27956; **Revised:** 04-Feb-2025, Manuscript No. EGM-23-27956 (R); **Published:** 11-Feb-2025, DOI: 10.35248/2165-7548.25.15.335

Citation: Luo Q, Liu M, Sun X, Li L, Wang G, Shi Y, et al. (2025) A Mendelian Randomization Study Investigated the Association between Socioeconomic Status and the Risk of Myocardial Infarction. Emergency Med. 15:335.

Mendelian Randomization (MR) is an approach that can assist people in getting around the constraints above. Similar to Randomized Controlled Trials (RCTs), where alleles are randomly distributed at conception by Mendel's second rule, MR decreases systematic biases in these circumstances by choosing genetic variants associated with exposure as Instrumental Variables (IVs). If a direction, such as SES, contributes to an event, such as myocardial infarction, then a variable that affects SES should be correctly expected to contribute to myocardial infarction. A different method, through which this variant can alter MI, such as horizontal pleiotropy, should first be ruled out.

In this study, we applied a two sample MR to find the causal link between SES and the risk of myocardial infarction using data from large scale Genome-Wide Association Studies (GWAS) of SES and MI [2].

MATERIALS AND METHODS

Since this was a re-analysis of information that had already been acquired and published, no further ethics approval was necessary. Using a two sample MR design, the genetic tools for the exposure and the outcome were gathered from different GWAS data sources. We carried out two sample MR analyses, first identifying the causal effect of the socioeconomic determinants on SES and then investigating the relationship between SES and MI. This analysis utilized several genetic variants derived from publicly available GWAS summary data (Figure 1) [3].

Data source

Public GWAS sources were used to assemble information on the Townsend Index of Deprivation (TID), family income, years of full-time education completed, age and physically demanding occupation. The UK Biobank provided the genetic information for the TID, which includes factors like being unemployed, not having a car, not having a home and living in a small space (https://gwas.mrcieu.ac.uk/datasets/ukb-b-10011/). A greater TID corresponds to a lower socioeconomic status. Additionally, a GWAS of self-reported household income was carried out using the UK Biobank (https://gwas.mrcieu.ac.uk/datasets/ukb-b-7408/), which was established as the average total household income from 2006 to 2010 before tax reduction. Additionally, a GWAS of participants in full-time education was derived from the UK Biobank, which contained 226899 European participants (https://gwas.mrcieu.ac.uk/datasets/ukb-a-505/). Furthermore, GWAS data from the MRC-IEU consortium were obtained from UK Biobank (https://gwas.mrcieu.ac.uk/datasets/ukb-b-2002/), which included 263615 European populations (Table 1) [4].

Table 1: Data sources of exposures and outcome GWAS data.

Trait	Year	Population	Sample size	Consortium	Website
TID	2018	European	462464	MRC-IEU	https://gwas.mrcieu.ac.uk/datasets/ukb-b-10011/
Income	2018	European	397751	MRC-IEU	https://gwas.mrcieu.ac.uk/datasets/ukb-b-7408/
Education	2017	European	226899	Neale Lab	https://gwas.mrcieu.ac.uk/datasets/ukb-a-505/
Heavy	2018	European	263615	MRC-IEU	https://gwas.mrcieu.ac.uk/datasets/ukb-b-2002/
MI	2021	European	395795	Meta-analysis	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST01

Note: TID: Townsend Index of Deprivation at recruitment; Income: Self-reported; household income, Education: Age completed full-time education; Heavy: Jobs involve heavy manual work or physical work; MI: Myocardial Infarction

The outcome variable data for MI was obtained from a GWAS analysis study that included 14825 myocardial cases and 44000 controls of European ancestry in the UK Biobank (https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST011364/), as well as the meta-analysis with CARDIoGRAMplusC4D.

Instrumental variable selection

The following assumptions guided the selection of the recovered genetic variations as IVs to estimate the causative effects of SES markers on the risk of MI:

- Being able to predict SES.
- Being free of confounding variables.

• Not having any association with MI unless through SES.

Genetic tools that satisfied a $p<5 \times 10^{-8}$ genome-wide significance threshold was chosen from the relevant genome-wide association studies. Linkage Disequilibrium (LD) between SNPs, defined as LD r2 0.001 and clump distance 10,000 kb, was assessed using the 1000 Genomes European reference panel (https://www.internationalgenome.org). We selected the SNPs in linkage disequilibrium with the most vital relationships with the exposure. The remaining independent SNPs that had attained GWAS-wide significance served as the genetic tools. SNPs missing from an outcome dataset were replaced with acceptable proxies (minimum linkage disequilibrium LD r2=0.8) where they were available. All palindromic SNPs and SNPs without an imputed replacement were removed.

Our genetic tools included 18 SNPs for the TID, 45 SNPs for family income, 20 SNPs for age at which one has finished an entire course of study and 24 SNPs for hard physical labor (Tables 2 and 3) [5].

Table 2: The MR analysis between SES factors and MI using the IVW method.

Exposure	Outcome	nSNP	Beta	SE	P	OR (95% CI)
Education	MI	20	-0.56	0.21	0.0096	0.57 (0.38-0.87)
TID	MI	18	0.72	0.32	0.0232	2.05 (1.10-3.82)
Heavy	MI	24	0.6	0.21	0.004	1.82 (1.21-2.75)
Income	MI	45	-0.89	0.12	8.82×10^{-14}	0.41 (0.32-0.52)

Note: TID: Townsend Index of Deprivation at recruitment; Income: Self-reported household income; Education: Age of completed full-time education; Heavy: Jobs involve heavy manual work or physical work

Table 3: The MR analysis between SES factors and MI using the IVW method after outlier removal and tightening the threshold of the p-value of exposure.

Exposure	Outcome	nSNP	Beta	SE	P	OR (95% CI)
Education	MI	20	-0.56	0.21	0.0096	0.57 (0.38-0.87)
TID	MI	17	0.54	0.27	0.0507	1.71 (1.00-2.93)
Heavy	MI	12	0.74	0.26	0.0054	2.09 (1.24-3.51)
Income	MI	45	-0.89	0.12	8.82×10^{-14}	0.41 (0.32-0.52)

Moreover, F-statistics was 24.82 for full-time education age, 57.93 for family income, 29.74 for heavy physical work and 33.96 for TID, more significant than the traditional value of 10, demonstrating that the tools' ability to predict the SES components was quite vital.

Statistical analyses

After coordinating the impact alleles across the GWASs of SES factors and MI, our study used MR techniques, such as the Inverse Variance Weighted (IVW), weighted median and MR-Egger, to generate MR estimates of SES variables for MI. The IVW technique is our primary method of analysis to determine the causal impact between SES factors and MI (Figure 1). The relationship with the p-value of 0.0125 or less (0.05/4 exposures) was significant, while the association with the p values of 0.0125 to 0.05 was suggestive [6].

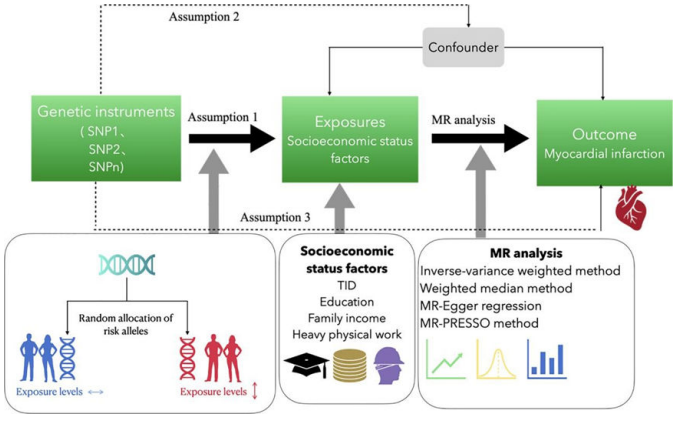

Figure 1: Study design overview of the Mendelian randomization study revealing the causal relationship between SES and MI.

The MR-Egger and weighted median techniques, which might provide more reliable estimates in a broader range of scenarios

but are less effective, were employed to supplement IVW calculations (wider CIs). If these techniques' estimates in our study were inconsistent, a stricter instrument p-value threshold was selected [7].

Sensitivity analysis is crucial in MR research for identifying underlying pleiotropy and heterogeneity for MR estimations might be gravely violated. We used heterogeneity markers (Cochran Q-derived p<0.05) from the IVW approach to show possible horizontal pleiotropy. Directional pleiotropy was identified using the MR-Egger regression intercept (directional pleiotropy was defined as the existence of p<0.05). MR-Pleiotropy Residual Sum and Outlier methods (MR-PRESSO) were also used to assess and correct horizontal pleiotropy. The three parts of MR-PRESSO are:

- Horizontal pleiotropy detection.
- Horizontal pleiotropy correction by removing outliers.
- Testing for statistically significant differences between causal estimates before and after outlier correction.

Compared to IVW and MR-Egger, it is less biased and more accurate when the proportion of horizontal pleiotropy variations is less than 10%.

The impact of a single SNP on the MR calculation was also assessed using the leave-one-out method. The possible directional pleiotropy was evaluated using a funnel plot, a tool also used in meta-analyses to identify publication bias [8].

The R (version 4.2.0) packages two SampleMR (version 0.5.6) and MRPRESSO (version 1.0) were used to conduct the analyses.

RESULTS

The causal effect of TID on MI

We discovered strong evidence of a possible relationship between TID and the risk of MI using the IVW method (OR=2.05, 95 percent CI=1.10-3.82, p=0.023). However, neither the weighted median strategy (OR=1.37, 95 percent CI=0.72-2.58, p=0.339) nor the MR-Egger regression method (OR=0.18, 95 percent CI=0.00-7.49, p=0.383) yielded statistically significant results [9].

A Cochran Q-test generated a p-value of 0.005 for MR-Egger and a p-value of 0.002 for IVW indicated heterogeneity. MR-PRESSO also reported similar findings (p-value for the test of globe heterogeneity=0.0042). One outlier (rs1483246) for TID was eliminated from the genetic tools. The p-value for the distortion test by the MR-PRESSO technique was then 0.313. After removing outliers using MR-PRESSO, there was no discernible correlation between TID and MI using the IVW approach (OR=1.71, 95 percent CI=0.998-2.93, p=0.051). A Cochran Q-test determined a p-value of 0.07 for MR-Egger and a p-value of 0.06 for IVW and heterogeneity was not noticed. In addition, no evidence of a significant intercept (Intercept=0.033, se=0.026, p=0.214) was found, suggesting no directional pleiotropy [10].

There was no causal relationship between TID and MI (Figure 2). The leave-one-out sensitivity analysis revealed that no one SNP significantly violated the overall effect of TID on MI (Figure 3) [11].

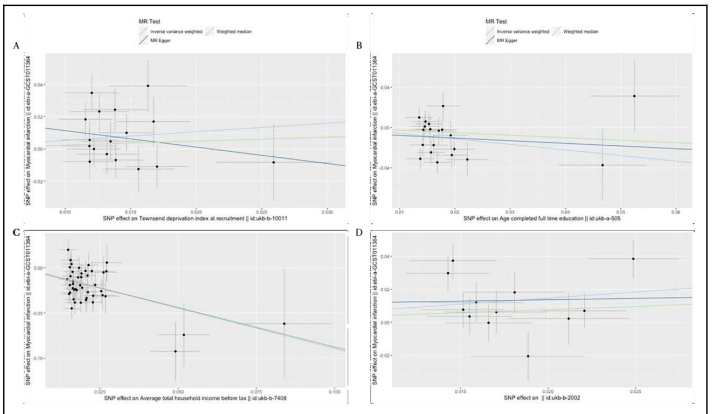

Figure 2: Scatter plots of SNPs associated with SES factors and MI. A scatter plot of SNPs associated with TID and MI risk after outliers removal with MR-PRESSO; B scatter plot of SNPs associated with the age of completed full-time education and MI risk; C scatter plot of SNPs associated with the average total self-reported household income and MI risk; D scatter plot of SNPs associated with heavy manual work and MI risk after outliers removal and tightening threshold the p-value of exposure.

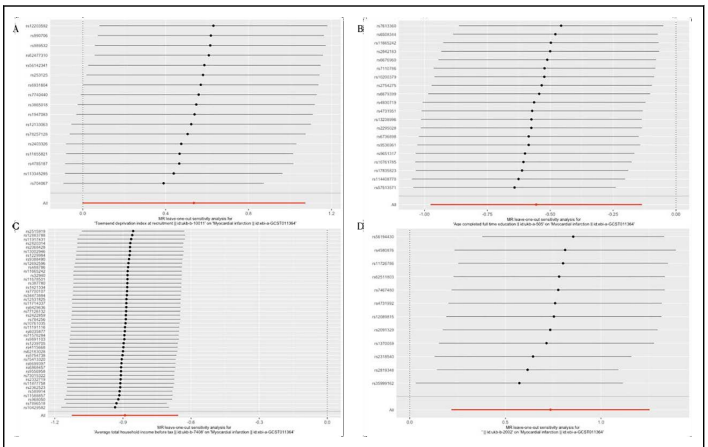

Figure 3: Leave-one-out of SNPs associated with SES status and their risk of MI. A leave-one-out of SNPs associated with TID and MI risk after outliers removal with MR-PRESSO; B leave-one-out of SNPs associated with the age of completed full-time education and MI risk; C leave-one-out of SNPs associated with the average total self-reported household income and MI risk; D leave-one-out of SNPs associated with heavy manual work and MI risk after outliers removal and tightening threshold the p-value of exposure.

The causal effect of education on MI risk

Twenty SNPs that were substantially and independently related to the age at which full-time education was completed were identified. Age of full-time education had a causal relationship with MI, supported by the IVW's findings (OR=0.57, 95%CI=0.38-0.87, p=0.0096). Other MR approaches include MR-Egger (OR=0.77, 95 percent CI=0.14-4.32, p=0.77) and Weighted median (OR=0.78, 95 percent CI=0.47-1.28, p=0.32) also produced results that were consistent but not statistically significant. The p-value obtained from the Cochran Q-test was

0.027, showing that heterogeneity had been noticed. A similar outcome was also provided by MR-PRESSO (the p-value in the global heterogeneity test was 0.032). Furthermore, using the MR-PRESSO approach, no outlier was discovered. No significant intercept could be demonstrated (intercept=-0.005, se=0.015, p=0.74), suggesting no directional pleiotropy was found [12].

The causal effect between family income and MI risk

45 SNPs had a significant and independent correlation with self-reported household income. Using the 45 SNPs linked to family income, we identified a potentially causal association between family income and the risk of MI. The finding was statistically significant (OR=0.41, 95% CI=0.32-0.52, p=8.82 × 10^{-14}). Similar risk estimates were produced with the weighted median method (OR=0.42, 95% CI=0.31-0.56, p=3.90 × 10^{-9}). The MR-Egger regression result (OR=0.42, 95 percent CI=0.15-1.13, p=0.093) did not show a statistically significant trend but a consistent tendency. Heterogeneity was discovered using a Cochran Q-test, which produced p-values of 0.0056 for MR-Egger and 0.0074 for IVW. Similar results were also demonstrated using MR-PRESSO (the p-value in the global heterogeneity test was 0.015). Moreover, no outlier was found using the MR-PRESSO method. The absence of a significant intercept (intercept=-0.00039, se=0.0099, p=0.97) indicates that no directional pleiotropy was discovered [13].

The causal effect between heavy physical work and MI risk

A substantial correlation between heavy physical labor and 24 SNPs was found. Using the IVW method, we identified a potential causal association between severe physical work and MI (OR=1.82, 95 percent CI=1.21-2.75, p=0.004). The weighted median method yielded identical risk estimates (OR=1.43, 95 percent CI=0.89-2.29, p=0.14) even though the association was not statistically significant. Inconsistent results were obtained using the MR-Egger approach (OR=0.67, 95 percent CI=0.096-4.69, p=0.69) [14].

We lowered the instrument p-value cutoff to 1 × 10^{-8} and selected 13 SNPs as instrument tools since the MR estimations of MR-Egger and IVW varied. According to the MR estimations by the IVW technique, the genetically predicted increase in hard physical labor was significantly associated with an increased risk of MI (OR=1.79, 95 percent CI=1.02-3.13, p=0.042). Using the MR-Egger regression (OR=1.41, 95 percent CI=0.05-39.7, p=0.84) and Weighted median techniques (OR=1.42, 95 percent CI=0.81-2.50, p=0.22), comparable risk estimates were found even though the association was not statistically significant. Heterogeneity was discovered using a Cochran Q-test, which showed p-values of 0.0022 for MR-Egger and 0.0039 for IVW [15].

MR-PRESSO also demonstrated a comparable result (the p-value in the global heterogeneity test was 0.0072). The MR methods were again used to assess the association between physical work and the risk of MI after removing one outlier (rs1081158). The IVW technique substantially increased the risk of MI through intense physical work (OR=2.09, 95% CI=1.24-3.51, p=0.0054). While utilizing the weighted median technique (OR=1.47, 95% CI=0.84-2.58, p=0.18) and MR-Egger regression (OR=1.18, 95% CI=0.06-22.82, p=0.91), comparable risk estimates were discovered; however, the connection was not statistically significant. The Cochran Q-test found heterogeneity with p-values of 0.024 for MR-Egger and 0.034 for IVW. MR-PRESSO also provided similar findings (the p-value in the global heterogeneity test was 0.044). Moreover, no outlier was discovered. Furthermore, there was no indication of a significant intercept (intercept=0.01; SE=0.027; p=0.71), demonstrating that no directional pleiotropy was seen. No single SNP strongly violated the overall effect of heavy physical work on MI risk in the leave-one-out sensitivity analysis [16].

DISCUSSION

This study examined whether genetically predicted SES determinants cause an increase in the incidence of MI using a two-sample MR method. Four large GWASs chose candidate IVs for TID, education, family income, and heavy physical work. The IVs had a better possibility of correctly predicting the SES components (F-statistics>10). We demonstrated that a genetic predisposition to the socioeconomic position, including full-time completed education age, family income, and heavy physical work directly associated with MI risk (Figure 4). Genetically predicated TID was not associated with MI risk [17].

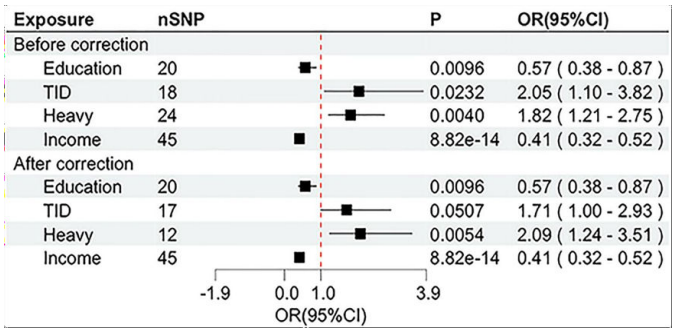

Figure 4: Forest plot of MR analysis between SES factors and MI risk before and after correction. Before correction: MR analysis before outlier removal and tightening threshold of the p-value of exposure. After modification: MR analysis before outlier removal and tightening entry of the p-value of exposure.

According to reports, due to their heightened vulnerability, individuals with ST-Segment Elevation Myocardial Infarction (STEMI) in rural areas and lower SES groups require specific attention. Additionally, a large observational study revealed that those with low SES had a greater frequency of cardiovascular illness. Social determinants of health have been studied in the incidence and survival of myocardial infarctions, including socioeconomic status (income, education), neighborhood disadvantage, immigrant status, social support and social network [18].

Our work offers a deeper understanding of earlier observational findings using the two sample MR methodology. The following factors may have a role in the association between SES and myocardial infarction. Living in an area with less financial

resources may limit one's ability to receive routine or follow-up care and postpone the treatment of an acute illness. Additionally, chronic stress, a lack of social networks and access to health information are a few plausible socio-behavioral pathways by which individual-level SES may still affect health outcomes for the elderly. Educational achievement is an additional crucial factor because, in high-income nations, there is a long-established negative relationship between educational attainment and cardiovascular disease. In a cohort study, Chaix et al. examined the association between neighborhood socioeconomic deprivation and risk of myocardial infarction in a population of 52,084 adults in the Scania area of Sweden. The incidence of myocardial infarction increased together with the level of socioeconomic deprivation in the area. High vs. low neighborhood socioeconomic deprivation resulted in a hazard ratio of 1.7 (95% CI=1.4-2.0) [19].

According to our research, the risk of MI is inversely correlated with family income. This study's findings are in line with those of previous observational studies. Stjarne et al. conducted population-based case-control research in Stockholm county, Sweden, to examine the relationship between socioeconomic resources and the risk of acute myocardial infarction. The quantity of socioeconomic resources nearby influences the relative risk of myocardial infarction context-dependently. Compared to high-income communities, the incidence rate ratio in low-income areas was 1.88 (95 percent confidence interval=1.25-2.84) for women and 1.52 (95 percent CI=1.16-1.99) for men. Population-based cohort research in four American towns by Rose et al. examined the relationship between neighborhood median family income and risk of myocardial infarction. There was a greater risk of myocardial infarction among inhabitants of low household income areas than among residents of higher household income neighborhoods, regardless of race or gender. Our MR analysis confirmed these earlier findings and showed a causal relationship between family income and MI risk. Our findings indicated that residents with low incomes should receive special consideration. An established association between educational attainment and CVD has existed for many years and recent population-based research continues to show the importance of this link and its underlying mechanisms. Numerous studies have shown that those with lower educational levels have a greater risk of AMI. Nearly 90,000 people in Australia and New Zealand were examined in comprehensive research by Woodward et al., and it was shown that those with elementary education had a higher risk of Cardiovascular Disease (CVD), cardiovascular mortality and all-cause death than those with tertiary education. Poorer long-term outcomes following AMI are also predicted by lower educational attainment. Likewise, our study confirmed that lower completed full-time education age could increase the risk of MI. Health may be impacted by education in several different ways. People with lower levels of education typically have more CVD risk factors. Thus more attention should be given to people with a low level of education [20].

From 1984 to 2000, a cohort of 1755 males from eastern Finland, ranging in age from 42 to 65, was examined. According to the study, there is an elevated risk of cardiovascular disease in males who engage in heavy physical work. Thirty seven thousand three hundred men and women participated in the Norwegian HUNT study, with a median follow-up of 12.4 years. The research showed that people with heavy physical work and metabolic

Syndrome had an HR of 3.02 (95% CI=1.93-4.75) for cardiovascular death. Our MR analysis showed that backbreaking physical work was causally associated with MI risk.

The aforementioned observational study on the association between SES variables and MI is not a causal link because of bias. Different levels of adjustment have been made for these risk factors in earlier research. Previous observational studies had a tough time eliminating confounding risk factor violations. However, using MR analysis and a superior study design, we definitively revealed causation apart from bias in the current studies.

Our study has several advantages. Our study may initially approximate randomized controlled trials in observational settings due to the MR method. Randomized controlled trials are frequently used to investigate causes but are expensive and typically challenging. However, MR studies can avoid confounding bias when SNPs are administered randomly. In contrast to previous observational studies, MR can also control the reverse causal impact. Second, according to our results, individuals with low socioeconomic status should be paid more attention to prevent myocardial infarction. The government should pay more attention to increasing investment in education, improving people's living standards, improving the level of social-environmental governance and reducing the risk of myocardial infarction.

CONCLUSION

There were, however, certain restrictions. Initially, the European population served as the source of all GWAS data. If our results would hold in other individuals remained to be seen. Second, since MR analyses developed causal hypotheses by taking advantage of the genetic variations' random distribution, it proved challenging to separate mediation and pleiotropy using MR techniques entirely. Our genome's significant variations likely impact one or more phenotypes. Thirdly, this study was a lack of mediator analysis. Our MR analysis supports the hypothesis that low SES levels could increase MI incidence.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

All data used in the current investigation are GWAS summary data that are publicly available.

COMPETING INTERESTS

The authors declare that they have no competing interests.

FUNDING

This research was sponsored by the Education Department of Jilin Province (Grant No: JJKH20211197KJ) and the Beijing United Heart Foundation (Grant No: 2021YX0117).

AUTHORS' CONTRIBUTIONS

Design: Qiang Luo, Meijia Liu, Xueqing Sun, and Yongfeng Shi; Conduct/data collection: Xueqing Sun and Longbo Li;

Analysis: Meijia Liu and Yongfeng Shi; Supervision: Yongfeng Shi and Bin Liu;

Writing manuscript: Qiang Luo, Meijia Liu, Xueqing Sun, and Guan Wang.

ACKNOWLEDGEMENTS

We wish to acknowledge the participants and investigators of the UK Biobank, IEU Open GWAS Project and CARDIoGRAMplusC4D consortium.

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