Journal of Pain Research

Dovepress
Taylor & Francis Group

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ORIGINAL RESEARCH

Association Between Educational Attainment and Chronic Pain: A Mediation Mendelian Randomization Study

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Background: The underlying association between educational attainment (EA) and chronic pain (CP) risk is not clear. This study aimed to investigate the causal relationship of EA with CP using Mendelian randomization (MR).

Methods: Single nucleotide polymorphisms (SNPs) for EA were selected from the Social Science Genetic Association Consortium (SSGAC). Inverse-variance weighted (IVW), weighted median, penalized weighted median, maximum likelihood (ML), and MR-Egger methods were used to estimate causal effects. Two sample MR analyses were undertaken to assess whether EA has a causal effect on CP. We also performed mediation analyses to estimate the mediation effects.

Results: A genetically predicted higher EA was associated with a decreased risk of multisite chronic pain (MCP) (odds ratio [OR] = 0.772, 95% confidence interval [CI] 0.732–0.816 per one standard deviation of longer education, $P < 0.05$), and the Genome-wide association studies (GWAS) data for chronic widespread pain (CWP) supported the result mentioned above. Potential mediators included body mass index (BMI) (OR = 1.176, 95% CI 1.091–1.267, $P < 0.05$), smoking (OR = 1.054, 95% CI 1.028–1.081, $P < 0.05$), and depression (OR = 1.201, 95% CI 1.147–1.258, $P < 0.05$) have all been proven to be causally associated with MCP. The proportions of the effects of genetically predicted EA mediated through genetically predicted BMI, smoking, and depression were 17.1%, 23.6%, and 9.2%, respectively.

Conclusion: Genetically predicted higher educational attainment reduces multisite chronic pain risk, partially mediated by body mass index (17.1%), smoking (23.6%), and depression (9.2%), highlighting education's protective role and its potential in chronic pain prevention strategies.

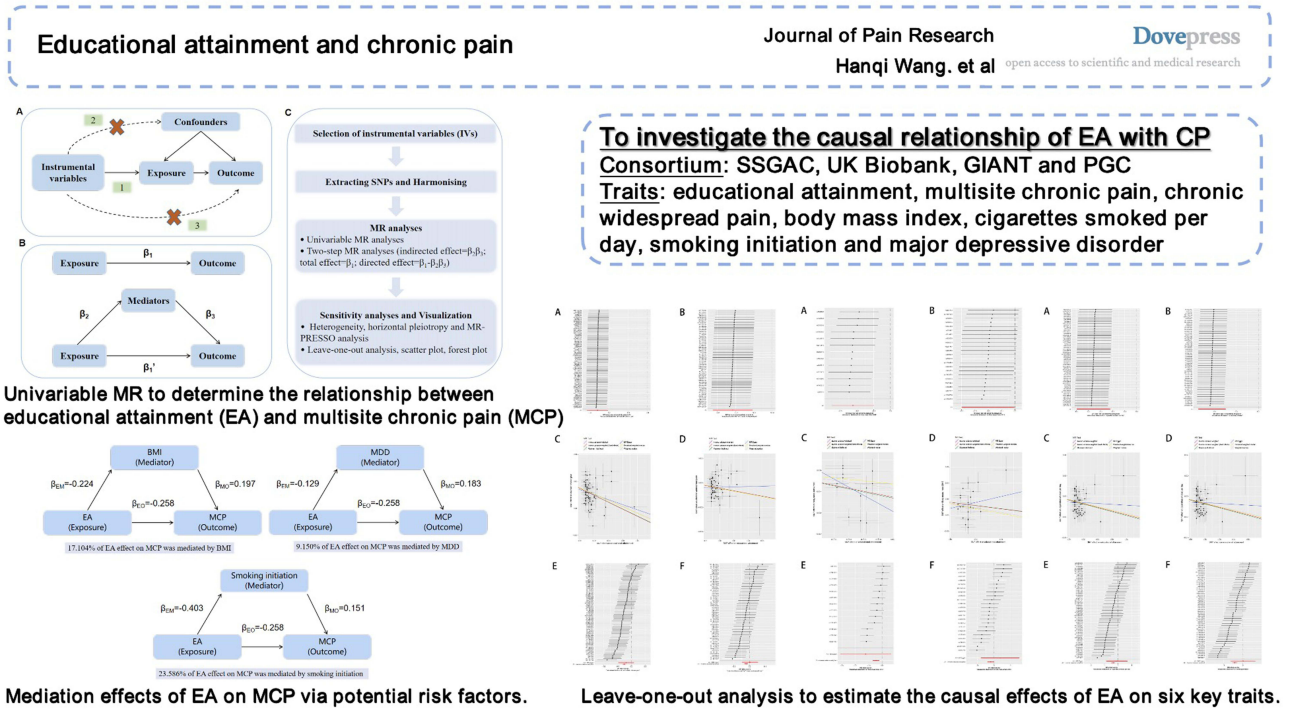
Keywords: educational attainment, chronic pain, Mendelian randomization, risk factors

Introduction

Chronic pain (CP) is commonly defined as pain that lasts >3 months.[1] According to data from the National Health Interview Survey in 2016, about 20.4% of American adults reported having CP,[2] a rate that is comparable to those of European ancestry.[3] Chronic pain not only poses a major challenge to patients' physical health but also seriously affects their mood, cognitive function, and quality of life.[4,5] According to evidence from the Medical Expenditure Panel Survey (MEPS), the estimated national cost of CP ranged from $560 to $635 billion,[6] which was still increasing. Therefore, chronic pain not only causes great distress to patients but also has a profound impact on the social health system and economic system, becoming an important public health issue worldwide. Currently, the treatment of chronic pain primarily employs a multimodal, integrated management strategy, including pharmacological treatments (such as nonsteroidal anti-inflammatory drugs, opioids, and adjunctive analgesics),[7,8] physical therapy (such as exercise rehabilitation and neuromodulation techniques),[9,10] psychological interventions (such as cognitive behavioral therapy),[11,12] and interventional treatments (such as nerve blocks and spinal cord stimulation).[13,14] However, existing treatments often face challenges such as significant individual variability in response, limited long-term effectiveness, and the risk of drug dependence.[15,16] Against this backdrop, early prevention targeting high-risk populations has become an important focus in clinical research.[17,18]

Received: 6 January 2025
Accepted: 19 March 2025
Published: 3 April 2025

Graphical Abstract



Whereas the causal effects of some risk factors (obesity, psychological factors and unhealthy lifestyle, etc) are generally accepted and reflected in disease prevention strategies, substantial uncertainty still surrounds other potential factors. Many studies have indicated the relationship between educational attainment (EA) and chronic pain[19,20] in the past few decades. Current evidence pointed out that individuals with lower levels of education are more likely to experience chronic pain compared to those with higher educational attainment.[21] However, this association may not be due to a causal effect, but rather could be a result of the methodological constraints inherent in traditional observational studies. Meanwhile, increasing evidence suggests that various adverse health outcomes, including obesity, smoking, and depression, are co-morbid with chronic pain.[22–26] These factors are believed to potentially play a role in the relationship between educational attainment and chronic pain. Therefore, clarifying the causal relationship between education level and chronic pain, while exploring potential mediating factors, is crucial for advancing our understanding of the underlying causes of chronic pain and for the development of novel population-based strategies for its prevention.

Although randomized controlled trials (RCTs) are widely regarded as the "gold standard" for assessing causal relationships, their high costs, long research timelines, and the need for multidisciplinary collaboration often make their implementation challenging. Therefore, there is an urgent need for a new research method that can avoid the limitations of traditional observational studies and RCTs while providing more reliable evidence for causal inference.

Mendelian randomization (MR) is a method that is used to evaluate the causal relationship between exposures and outcomes as an adjuvant to traditional epidemiological methods. Genetic variants were randomly allocated from parents to offspring at conception, minimizing confounding and ruling out reverse causality.[27] This method enables researchers to more accurately evaluate the causal relationship between exposures and outcomes. Particularly in situations where random assignment is not possible, MR offers a more reliable alternative. MR uses genetic variants to conduct causal inference, and the role of genetic variants in chronic pain susceptibility has been confirmed in multiple studies. For instance, the allele at the rs734784 locus in the KCNS1 gene has been associated with increased risk of various chronic pain conditions such as neuropathic pain and osteoarthritis pain, potentially involving abnormal potassium channel

function leading to central nervous system sensitization.[28] Similarly, the allele at the rs1042713 locus in the ADRB2 gene is linked to elevated risk of chronic widespread pain (CWP), possibly through influencing stress response and neuroendocrine regulation, thereby promoting chronic pain.[29]

This study used univariate MR analysis to determine whether exposure and outcome were causally associated. In addition, MR mediation analyses were performed to explore whether the phenotypes of risk factors could mediate the effect of education on the probability of developing chronic pain, so as to explore the early identification of mediating factors and provide clinicians with new evidence for personalized chronic pain intervention. At the same time, it aims to improve people's awareness and provide support for health policy formulation, especially health promotion and intervention strategies for low-education groups. We hypothesize that there is a causal relationship between educational attainment and chronic pain, and risk factors mediate the association between them.

Methods

Because this MR study was performed based on publicly available Genome-wide association studies (GWAS) summary statistics, the Research Ethics Committee of the First Hospital of Jiaxing University deemed this work exempt from the Ethics Committee review. Considering that participant consent has been obtained by previously published studies included in this project, the Research Ethics Committee agreed to exempt the written informed consent. Data analyses started in February 2023 and was completed in May 2023.

Study Design

First, we performed a univariable MR analysis to determine whether there is a causal relationship between EA and CP. Based on the results of previous observational studies, we selected three possible risk factors to investigate the underlying mechanisms between EA and CP.[22,23,25] The following phase involved a two-step MR analysis for those risk factors that may contribute to CP (Figure 1B). Specifically, we used univariable MR to describe the potential association between education and the factors we highlighted and to infer the causal relationship between three phenotypes of risk

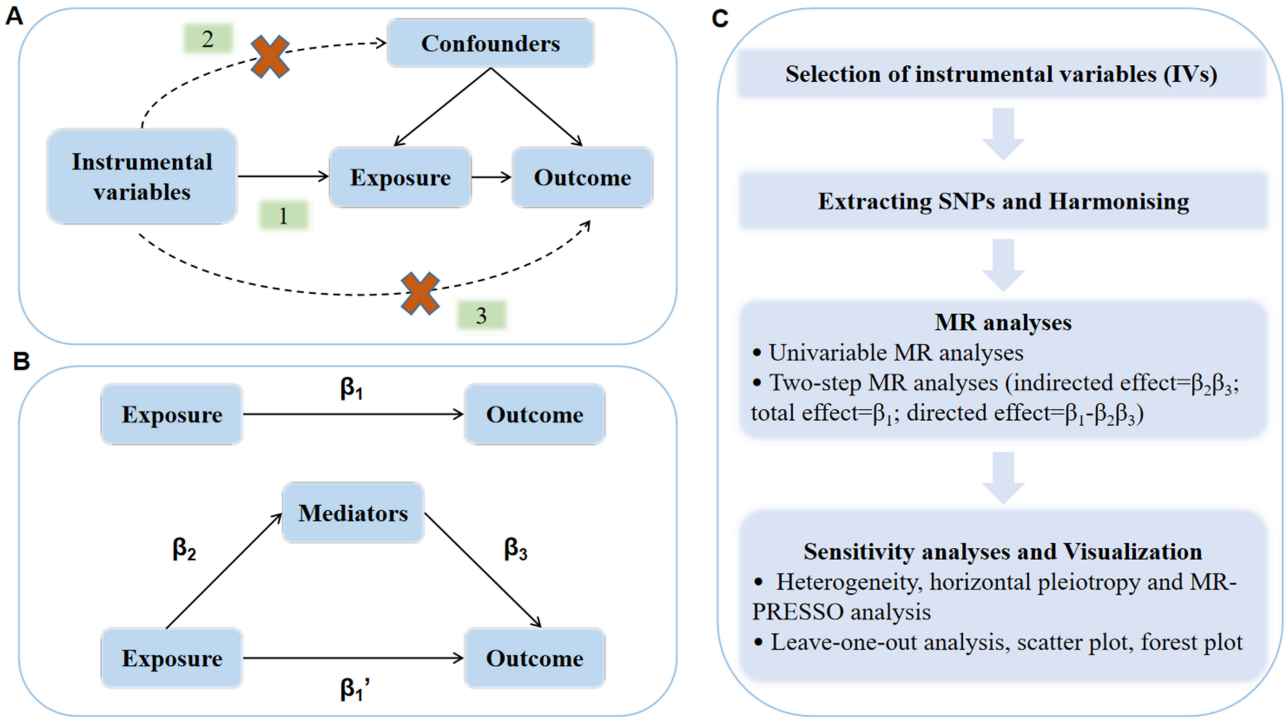


Figure 1 Schematic representation of the study design. (**A**) The core assumptions for Mendelian randomization analysis are as follows: (1) Genetic variants are strongly associated with the exposure (usually $P < 5e\text{-}08$), (2) Genetic variants are associated with the outcome through the exposure, and (3) Genetic variants are independent of the confounders. (**B**) In Mendelian analyses, the total effect (β_1) can be divided into direct effect (β_1') and indirect effect ($\beta_2\beta_3$). (**C**) The specific steps of this study.

https://doi.org/10.2147/JPR.S515921

factors for CP. Two significant GWAS summary statistics were matched with each phenotype considering the repeatability of the results to confirm the robustness of the causal inference. Finally, mediation analyses determined how each risk factor mediated the relationship between EA and CP. Figure 1C shows the schematic diagram.

Data Sources of EA and CP

Okbay et al[28] have conducted a large meta-analysis of GWAS for individuals of European descent over the age of 30. Educational attainment was measured in the analysis as the number of years of schooling completed (n = 293,723, mean = 14.3, sd. = 3.6). The genetic instruments of multisite chronic pain (MCP) were obtained from GWAS summary statistics performed in UK Biobank with a total of 387,649 individuals of European ancestry stratified by gender.[29] MCP was regarded as a quasi-quantitative variable, and phenotypic values ranged from 0 to 7 due to the numbers of body sites. Age, sex, and genotyping array were adjusted by the original investigators. The GWAS summary statistics of CWP derived from UK biobank, when self-reported of pain all over the body lasting for more than 3 months; simultaneous pain that lasting for 3 months or more in the knee, shoulder, hip, and back, accompanied by fibromyalgia, can be defined as CWP.[30] Table 1 lists characteristics of GWAS summary statistics included in this study.

Selection of Genetic Variants

Genetic variants were retrieved using rigorous steps for GWAS summary statistics of EA to eliminate the bias and instability caused by weak instrumental bias. These fundamental assumptions must be met when using single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) in MR analysis[31] (Figure 1A): (1) IVs are strongly associated with the selected exposures; (2) IVs are associated with the outcome only through the exposure; and (3) IVs are not associated with confounders affecting the outcome. SNPs associated with EA and any other significant risk factor across the genome ($P < 5e\text{-}08$) were filtered out. A strict measure of clumping with a threshold of $r^2 < 0.001$ and window size = 10,000 kb was also conducted to reduce the impact of linkage disequilibrium (LD). To investigate whether other confounders influenced genetic variants, we examined all the selected IVs in Phenoscanner.

MR Analysis

Prior to the performance of MR analyses, genetic variations from GWAS summary statistics for chronic pain were thought to be harmonized so that the effect allele of each SNP was consistent throughout the datasets mentioned above.

Inverse-variance weighted (IVW) is the primary method for estimating the causal relationship between exposure and outcome in two-sample MR analysis. The IVW method was essentially a meta-analysis technique that combined the effect of

Table 1 Characteristics of GWAS Summary Statistics

Traits	Consortium	Authors	Population	Samples
Educational attainment	SSGAC	Okbay et al	European	2,93,723
Multisite chronic pain	UK Biobank	Johnston et al	European	3,87,649
Chronic widespread pain	UK Biobank	Rahman et al	European	6,914/242,929
Body mass index 2018	GIANT	Yengo et al	European	6,81,275
Body mass index 2015	GIANT	Locke et al	European	3,39,224
Cigarettes smoked per day	GSCAN	Liu et al	European	2,49,752
Smoking initiation	GSCAN	Liu et al	European	311,629/321,173
Major depressive disorder 2019	PGC	Howard et al	European	246,363/561,190
Major depressive disorder 2018	PGC	Wray et al	European	59,851/113,154

Abbreviations: GWAS, Genome-wide association study; PGC, psychiatric genomics consortium; SSGAC, Social Science Genetic Association Consortium; GIANT, Genetic Investigation of Anthropometric Traits; GSCAN, GWAS and Sequencing Consortium of Alcohol and Nicotine use.

each SNP to obtain causal estimates.[32] The odds ratios (ORs) and 95% confidence intervals (95% CIs) were computed using the estimates. However, to establish the heterogeneity of genetic variations based on the findings of the hypothesis test, we employed Cochran's Q test to produce Q statistics. Subsequently, we then conducted several sensitivity analyses, including weighted median, MR-Egger, maximum likelihood (ML), and penalized weighted median to assess the robustness of the MR analysis results. In addition to IVW, we used a weighted median technique, which provided a steady estimate even when up to 50% of the genetic variations were ineffective IVs.[33] Furthermore, the penalized weighted median method was less biased when a few genetic variants were invalid. A rough estimate of unbiased causal estimates can be obtained using MR-Egger regression. It was fairly credible as a tool to examine the robustness of the results of MR analyses when the instrument strength independent of the direct effect (InSIDE) assumption was satisfied.[34] Another method that can estimate the parameters of a probability distribution by maximizing the likelihood function is ML.[35] After excluding outliers with horizontal pleiotropy characteristics using MR-PRESSO analysis,[36] we would reevaluate the causal effects in univariable analyses.

Additionally, we performed a leave-one-out analysis to determine whether the MR results were caused by SNP. Then, we eliminated each SNP one at a time to reevaluate the causal estimates. Complementary analyses, including scatter and forest plots, were used to visualize the heterogeneity in the causal effects of various genetic instruments.

Potential Risk Factors

Potential risk factors may affect the underlying mechanisms of EA on CP. Based on the results of previous observational studies, we further examined three potential risk factors for obesity (eg, BMI), lifestyle factors (eg, smoking), and mood disorders (eg, depression). Instrument variables for BMI were derived from the largest meta-analysis of GWASs, which included the summary statistics from the Genetic Investigation of ANthropometric Traits (GIANT) consortium and the dataset conducted in UK Biobank participants of European ancestry, reaching 681,275 individuals.[37] The relationship findings for up to 339,224 individuals from 125 studies[38] included in another meta-analysis for BMI were made public by the GIANT consortium. Liu et al[39] reported the GWAS summary statistics on several smoking-related phenotypes in 1.2 million participants. Smoking initiation was a binary phenotype. Any participant reporting ever being a regular smoker in their life (current or former) were coded "2", while any participant who reported never being a regular smoker in their life were coded "1". A debilitating psychiatric illness known as major depressive disorder (MDD) is typically associated with low mood and anhedonia. Howard et al[40] meta-analyzed data on 807,553 participants from the three largest depression-related GWAS. This GWAS dataset was adjusted for age, sex, genotyping array, and ancestry factors. A meta-analysis by Wray et al[41] released by the psychiatric genomics consortium (PGC) provided further GWAS summary statistics for MDD.

Mediation Effects

We combined the total effect from the univariable MR analysis of education on CP with the causal estimates from the two-step MR to estimate the indirect effect of EA on CP via different risk factors.

As shown in Figure 1B, we assumed there was a relationship between EA, CP, and underlying risk factors. A univariate MR analysis indicated that EA had a causal association on CP, estimated to be β_1, which was also considered the overall effect of exposure on the outcome. In contrast, the causal estimates of education on risk factors and those factors on CP were β_2 and β_3, respectively. Therefore, the product of β_2 and β_3 can be used to calculate the indirect effects of risk factors. The indirect effects were calculated using the coefficient product method, and the standard error (SE) and CI for the mediation effect were calculated using the Delta method.[42]

Statistical Analysis

R software (Version 4.0.5, RStudio Inc., USA) was used to conduct the statistical analysis. The R packages "TwoSampleMR" (version 0.5.6) and "MRPRESSO" (Version 1.0), which were loaded to conduct all MR analyses, were used for identifying the outliers. $P < 0.05$ was considered statistically significant. F statistics were calculated using the formula: $F = \beta^2/SE^2$ [43,44] to evaluate the strength of IVs. The F value <10 may indicate that IVs were weak instruments.

Results

Extraction of Instrumental Variables

Summary information for SNPs is shown in Supplementary Table S1 following a rigorous genetic variants screening. The GWAS dataset was filtered for EA, leaving 75 independently related SNPs. A total of 489 SNPs were strongly associated with BMI,[37] and 74 independent SNPs were found in another summary statistics for the repeatability test[38] regarding risk factors. The smoking-related GWAS datasets extracted 21 and 80 SNPs for "Cigarettes smoked per day" and "smoking initiation." Genetic variants associated with MDD were selected from two summary statistics published in 2019 and 2018 with 49 and 5 SNPs, respectively. We extracted the IVs using a more logical framework because the existence of proxies may cause deviation in causal inference. Additionally, Supplementary Table S2–S3 demonstrate the data extraction process and the data harmonization results. The F statistics of these genetic variants ranged from 32.439 to 74.600 (Supplementary Table S5), demonstrating the little possibility of weak instrument bias.

Causal Estimates of EA on CP

Univariable MR analysis revealed that individuals with lower EA had a higher risk of developing multisite MCP (OR=0.772, 95% CI 0.732 to 0.816, P=1.502E-20) and CWP (OR=0.979, 95% CI 0.968 to 0.989, P=8.929E-05). Four sensitivity analysis methods (Supplementary Table S5 and S9) were evaluated with similar results, including MR-Egger, weighted median, maximum likelihood, and penalized weighted median. The Cochran's Q statistic allowed for the detection of heterogeneity in each univariable MR study, while the MR-Egger intercept provided no conclusive proof of the existence of horizontal pleiotropy. Significant outliers were identified using the MR-PRESSO method. We excluded IVs considered to have the trait of horizontal pleiotropy before investigating the causal effects of EA on CP (EA on MCP: rs111321694, rs11222416, rs12036042, rs4565697; EA on CWP: rs773107). Supplementary Table S4–S7 contains more detailed information. Supplementary Figure S1 displayed the results of visualization for the causal estimates of the genetically predicted EA on CP.

Causal Estimates of EA on Risk Factors

We also discovered evidence that a lower risk of BMI (BMI 2018: beta=−0.224, 95% CI −0.350 to −0.099, P=4.530E-04; BMI 2015: beta=−0.202, 95% CI −0.400 to −0.005, P=4.490E-02), smoking (Cigarettes smoked per day: beta=−0.357, 95% CI −0.496 to −0.219, P=4.391E-07; Smoking initiation: OR 0.669, 95% CI 0.592 to 0.755, P=8.899E-11), and depression (MDD 2019: OR 0.879, 95% CI 0.787 to 0.980, P=2.060E-02; MDD 2018: OR 0.814, 95% CI 0.666 to 0.994, P=4.400E-02) was genetically associated with EA. Supplementary Table S4-S7 and Supplementary Figure S2–S4 showed the results of sensitive analyses and visualization for EA on risk factors.

Causal Estimates of Risk Factors on CP

We calculated the causal effects of three potential risk factors for CP using univariable MR analyses. The findings indicated that a higher genetically predicted BMI (MCP: OR 1.217, 95% CI 1.189 to 1.246, P=5.003E-61; CWP: OR 1.023, 95% CI 1.019 to 1.027, P=1.286E-35), "smoking initiation" (MCP: OR 1.164, 95% CI 1.122 to 1.207, P=3.009E-16; CWP: OR 1.016, 95% CI 1.009 to 1.023, P=4.491E-06), and MDD (MCP: OR 1.201, 95% CI 1.147 to 1.258, *P*=1.071E-14; CWP: OR 1.021, 95% CI 1.013 to 1.029, P=2.742E-07) was associated with a higher risk of CP. The outcomings for other methods, such as weighted median (BMI on MCP: OR 1.182, 95% CI 1.149 to 1.216, P=3.425E-31; Smoking initiation on MCP: OR 1.167, 95% CI 1.120 to 1.215, P=2.069E-13; MDD on MCP: OR 1.139, 95% CI 1.084 to 1.196, P=2.376E-07) and MR-Egger (BMI on MCP: OR 1.176, 95% CI 1.091 to 1.267, P=2.589E-05; Smoking initiation on MCP: OR 1.198, 95% CI 1.000 to 1.436, P=5.371E-02; MDD on MCP: OR 1.482, 95% CI 1.155 to 1.901, P=3.589E-03), were qualitatively consistent with the causal relationship by IVW analysis. Table 2 and Supplementary Table S5 also contain lists of the outcomes of other MR methods. Additionally, we performed the two-sample MR analyses again using at least one independent summary statistic and obtained robust and reliable outcomes. According to Egger, intercept analysis failed to detect any pleiotropy, indicating that no horizontal pleiotropy was found in the causal estimates. We discovered no outliers in the univariable MR analysis of smoking initiation and MDD on CWP. Additionally, the limited number of SNPs

Table 2 Causal Effects of Risk Factors on Chronic Pain in Univariable MR Analyses

Risk Factors	Multisite Chronic Pain				Chronic Widespread Pain			
	Beta / OR	95%_LCI	95%_UCI	*P* value	Beta / OR	95%_LCI	95%_UCI	*P* value
BMI 2018								
IVW	1.217	1.189	1.246	5.003E-61	1.023	1.019	1.027	1.286E-35
MR-Egger	1.176	1.091	1.267	2.589E-05	1.014	1.003	1.025	1.660E-02
Weighted median	1.182	1.149	1.216	3.425E-31	1.022	1.019	1.027	1.003E-15
Maximum likelihood	1.220	1.199	1.240	9.354E-119	1.023	1.016	1.027	4.907E-44
Penalised weighted median	1.158	1.125	1.193	4.392E-23	1.022	1.020	1.026	2.529E-15
BMI 2015								
IVW	1.093	1.056	1.132	3.812E-07	1.012	1.006	1.018	7.735E-05
MR-Egger	1.053	0.951	1.166	3.260E-01	1.003	0.989	1.017	7.230E-01
Weighted median	1.085	1.040	1.132	1.767E-04	1.006	0.998	1.014	1.380E-01
Maximum likelihood	1.096	1.068	1.126	1.333E-11	1.012	1.007	1.017	3.758E-07
Penalised weighted median	1.086	1.041	1.133	1.266E-04	1.006	0.998	1.014	1.420E-01
Cigarettes smoked per day								
IVW	1.054	1.021	1.089	4.784E-05	1.011	1.005	1.020	4.532E-05
MR-Egger	0.991	0.924	1.063	8.090E-01	1.005	0.992	1.019	4.635E-01
Weighted median	1.036	0.996	1.076	7.526E-02	1.013	1.005	1.021	1.386E-03
Maximum likelihood	1.056	1.029	1.084	4.058E-05	1.011	1.006	1.017	4.584E-05
Penalised weighted median	1.032	0.997	1.069	7.293E-02	1.013	1.005	1.020	8.024E-04
Smoking initiation								
IVW	1.164	1.122	1.207	3.009E-16	1.016	1.009	1.023	4.491E-06
MR-Egger	1.198	1.000	1.436	5.371E-02	1.033	0.997	1.070	8.223E-02
Weighted median	1.167	1.120	1.215	2.069E-13	1.018	1.010	1.026	4.641E-06
Maximum likelihood	1.172	1.142	1.204	2.941E-32	1.016	1.011	1.022	7.884E-10
Penalised weighted median	1.171	1.124	1.220	5.594E-14	1.019	1.011	1.027	5.381E-06
MDD 2019								
IVW	1.201	1.147	1.258	1.071E-14	1.021	1.013	1.029	2.742E-07
MR-Egger	1.482	1.155	1.901	3.589E-03	1.008	0.967	1.051	7.002E-01
Weighted median	1.139	1.084	1.196	2.376E-07	1.019	1.010	1.028	4.186E-05
Maximum likelihood	1.218	1.179	1.258	1.014E-32	1.022	1.015	1.028	4.223E-11
Penalised weighted median	1.128	1.074	1.185	1.290E-06	1.019	1.010	1.028	5.474E-05

(*Continued*)

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Table 2 (Continued).

Risk Factors	Multisite Chronic Pain				Chronic Widespread Pain			
	Beta / OR	95%_LCI	95%_UCI	*P* value	Beta / OR	95%_LCI	95%_UCI	*P* value
MDD 2018								
IVW	1.105	1.031	1.185	8.477E-05	1.013	1.002	1.024	2.036E-02
MR-Egger	0.894	0.659	1.214	5.477E-01	1.010	0.944	1.081	8.230E-01
Weighted median	1.091	1.016	1.172	1.682E-02	1.012	0.999	1.026	7.492E-02
Maximum likelihood	1.110	1.051	1.171	1.551E-04	1.013	1.002	1.024	2.255E-02
Penalised weighted median	1.091	1.020	1.168	1.121E-02	1.012	0.999	1.027	7.811E-02

Abbreviations: MR, Mendelian randomization; IVW, inverse-variance weighted; OR, odds ratio; CI, confidence interval.

included in the MR analysis prevented us from performing the identification process of outliers in CWP based on GWAS summary statistics of the validation dataset for MDD. No single SNP was found to be the key driver of the overall results in the primary MR analysis, according to leave-one-out analyses (Supplementary Figure S5-S10).

Mediation Effects

We selected the GWAS summary statistics with the largest sample sizes for the underlying risk factors and CP to estimate the mediation effects. Mediation analyses quantified the effects of educational attainment on chronic pain outcomes via three risk factors. As shown in Figure 2 and Supplementary Table S8, the mediation effects of EA on MCP mediated by BMI, smoking initiation, and MDD were −0.044 (−0.073 to −0.016), −0.061 (−0.110 to −0.012), and −0.024 (−0.040 to −0.007), respectively. The percentage of mediation effects of EA via BMI, smoking initiation, and MDD were approximately 17.104%, 23.586%, and 9.150%, respectively.

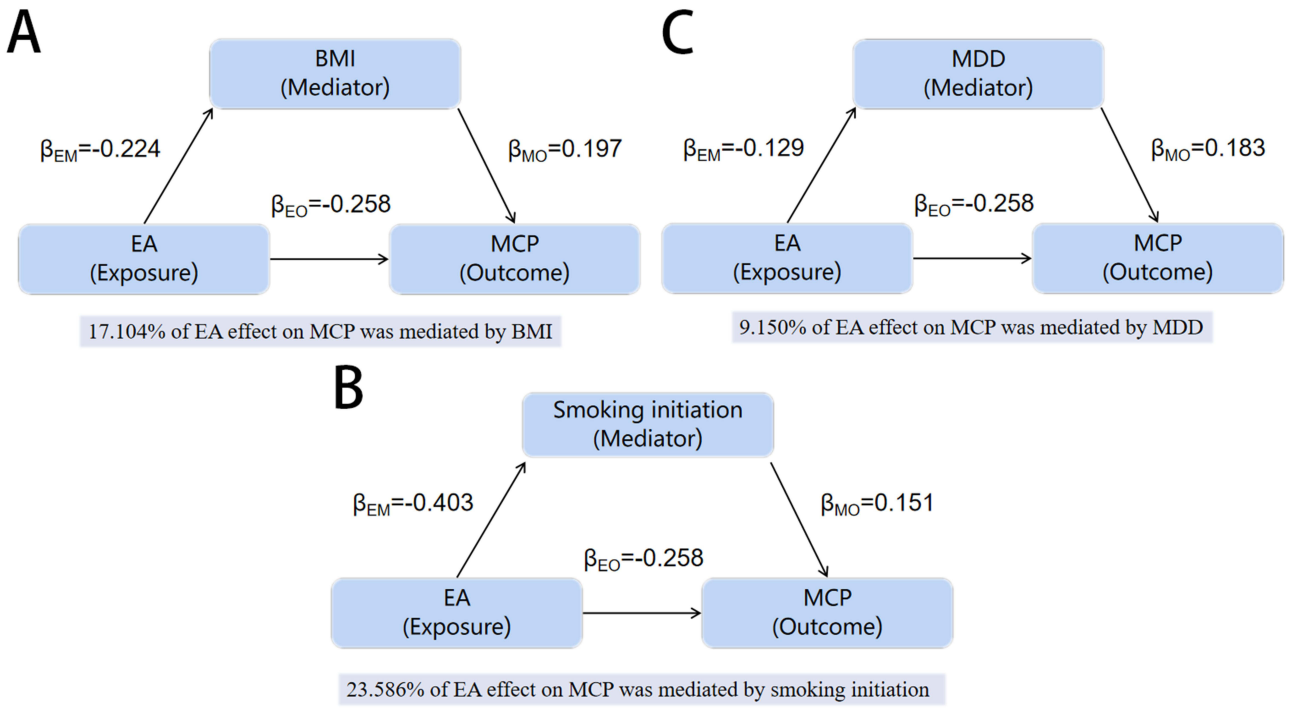

Figure 2 Mediation effects of educational attainment (EA) on multisite chronic pain (MCP) via potential risk factors. (**A**) Causal effect of EA on MCP mediated by body mass index (BMI). (**B**) Causal effect of EA on MCP mediated by smoking initiation; (**C**_ Causal effect of EA on MCP mediated by major depressive disorder (MDD).

Discussion

The innovation of this study lies in its pioneering use of the Mendelian randomization framework, which leverages genetic variations as instrumental variables to effectively mitigate confounding factors such as demographics, environmental influences, and other common confounders. This approach provides more reliable causal inferences. Furthermore, we employed multiple latest GWAS summary statistics to validate the stability of our results, further substantiating the causal impact of education attainment on chronic pain and the mediating effects of related risk factors. The results showed that low education level was significantly causally associated with the occurrence of chronic pain (EA on MCP: OR=0.772, 95% CI 0.732 to 0.816, P=1.502E-20; EA on CWP: OR=0.979, 95% CI 0.968 to 0.989, P=8.929E-05). The mediating percentages of BMI, "smoking initiation", and MDD were approximately 17.104%, 23.586%, and 9.150%, respectively.

This finding not only aligns with the associations reported in previous studies but also further suggests a direct causal relationship. Several prior observational studies have reported similar results. Smith et al[45] conducted a study in the Grampian region of Scotland to investigate the effects of CP on general health. After adjusting relevant variables, they discovered that individuals with secondary school certificates had a 0.5–1.2-fold higher risk of CP than those with higher education. In addition, the risk of CP increased by 1.0–1.6-fold in those with no qualifications. Macky et al[46] also found that low education level was an independent risk factor for CP among 262 subjects.

There are several potential mechanisms that may explain why lower educational attainment increases susceptibility to chronic pain. Firstly, individuals with lower education levels typically have limited health literacy and lack resources for effective pain prevention and management. They may have insufficient knowledge of strategies to avoid or treat chronic pain, or engage in physically demanding or high-risk occupations, thereby increasing their risk of pain-related disorders. Additionally, individuals with lower educational attainment are more prone to pain catastrophizing—a cognitive tendency to perceive pain in an excessively negative way, which intensifies the sensation of pain.[47] After controlling for factors such as depression, the association between lower education and pain significantly weakened, suggesting that emotional and cognitive factors (eg, depression) partially mediate the effect of education level on pain.[47] In line with this, our Mendelian randomization analysis indicates that approximately 9% of the education–pain relationship can be explained by MDD. Depression not only reduces an individual's pain tolerance but also impairs their ability to cope with pain, thereby exacerbating chronic pain symptoms.[48,49]

The lifestyle factors associated with education level also represent crucial pathways linking education to chronic pain. Lower educational attainment is often closely linked to unhealthy behaviors such as obesity, sedentary lifestyle, smoking, and alcohol consumption, all of which have been established as risk factors for chronic pain.[50–52] Our study findings support this explanation; specifically, we found that approximately 17% of the total effect of low education on multisite chronic pain is mediated through higher BMI, while about 24% of the effect is mediated by an increased tendency to smoke. These findings indicate that lifestyle differences significantly contribute to the increased burden of chronic pain among lower educated groups. Obese individuals are more likely to experience a pro-inflammatory state characterized by a higher prevalence of CP.[53,54] Briggs et al[55] originally reported that low back pain (LBP) risk may be increased by high levels of C-reactive protein, particularly in obese individuals. Chronic inflammation may increase the sensitivity of neural pathways, thereby leading to persistent pain. Regardless of the specific mechanisms involved, our findings suggest that weight control could be an effective strategy for reducing the risk of chronic pain, particularly in populations with high obesity rates and low educational attainment.[11]

Interestingly, nicotine has an analgesic effect in experimental studies,[56] but it appears paradoxical since epidemiological research found smoking to be a high-risk factor for CP. The results of our MR analysis confirmed the findings of observational studies that individuals who regularly smoked had a higher risk of developing CP than individuals who had never smoked (OR: 1.016–1.164). Still, whether individuals who underwent smoking cessation could benefit from experiencing CP is unclear. Shi et al[24] have noted that although it has not been shown, recovering from the effects of long-term exposure to nicotine may alleviate CP. Another meta-analysis[57] showed that there is currently insufficient evidence to conclude that smoking cessation has any clinically significant effects on individuals with CP. Nonetheless, given the many overall health benefits of smoking cessation and the established association between smoking and pain, it is recommended that smoking cessation measures be actively promoted among patients with chronic pain. In the long

term, quitting smoking may contribute to improved overall health and potentially prevent the exacerbation of pain or the development of related pain disorders.[24]

This study has some limitations. First, we had to account for memory bias because the estimates of genetic associations such as CP and smoking were collected through self-reports or questionnaires. Second, the MR analysis was performed using data from individuals with European ancestry. We should be cautious with interpreting and generalizing other ethnicities because different races have distinct lifestyles and cultural backgrounds. Third, the non-collapsibility of OR[58] may cause biased estimates for the proportions of mediation effects.

Conclusion

This Mendelian randomization analysis indicates a causal association between lower educational attainment and a higher risk of chronic pain, with BMI, smoking, and depression serving as mediators of the effect of education attainment on chronic pain. These findings underscore the need to focus on lifestyle and mental health in the prevention and management of chronic pain.

Abbreviations

EA, Educational attainment; CP, Chronic pain; MR, Mendelian randomization; SNPs, Single nucleotide polymorphisms; SSGAC, Social Science Genetic Association Consortium; IVW, Inverse-variance weighted; ML, Maximum likelihood; MCP, Multisite chronic pain; OR, Odds ratio; CI, Confidence interval; GWAS, Genome-wide association studies; CWP, Chronic widespread pain; BMI, Body mass index; MEPS, Medical Expenditure Panel Survey; RCTs, Randomized controlled trials; CWP, Chronic widespread pain; IVs, Instrumental variables; LD, Linkage disequilibrium; GIANT, Genetic Investigation of ANthropometric Traits; MDD, Major depressive disorder; PGC, Psychiatric genomics consortium; SE, Standard error; LBP, Low back pain.

Data Statement

Publicly available datasets were analyzed in this study. Further inquiries can be directed to the corresponding author.

Acknowledgments

We are grateful to the SSGAC, UK Biobank, GIANT, GSCAN and PGC for making this research possible.

Funding

There is no funding to declare.

Disclosure

The authors declare no conflicts of interest.

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