Journal of Pain Research

Dovepress
Taylor & Francis Group

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ORIGINAL RESEARCH

Impact of Socioeconomic Status on the Risk of Intervertebral Disc Degeneration and Low Back Pain in the European Population and the Mediating Role of Obesity-Related Traits: Evidence from a Mendelian Randomization Study

Zhou Long[1], Qian Qin[2]

[1]Department of Neurosurgery, Third Xiangya Hospital, Central South University, Changsha, Hunan, 410013, People's Republic of China; [2]Department of Anesthesiology, Third Xiangya Hospital, Central South University, Changsha, Hunan, 410013, People's Republic of China

Correspondence: Qian Qin, Department of Anesthesiology, Third Xiangya Hospital, Central South University, 138 Tongzipo Road, Yuelu District, Changsha, Hunan, 410013, People's Republic of China, Email qinqian5727@163.com

Objectives: To identify the causal effect of socioeconomic status (SES) on intervertebral disc degeneration (IVDD) and low back pain risk through Mendelian Randomization (MR) analysis, and to evaluate the mediating role of obesity-related traits in these causal associations.

Methods: Genome-wide association summary statistics for SESs ([i] years of schooling, [ii] occupational attainment, [iii] Townsend deprivation index, [iv] job involves heavy manual or physical work, and [v] average total household income before tax), obesity-related traits ([i] body mass index [BMI], [ii] waist circumference, and [iii] hip circumference), IVDD, and low back pain, were obtained from public databases. Inverse variance weighted (IVW) was the primary causal inference approach. Through two-step mediation MR analysis, key obesity-related traits mediating the causal effect of SES on the risk of IVDD and low back pain were identified.

Results: This MR study supported that years of schooling reduced the risk of IVDD and low back pain, while the Townsend deprivation index and jobs involving heavy manual or physical work increased the risk of IVDD and low back pain. Additionally, occupational attainment and average total household income before tax reduced the risk of low back pain. Mediation MR analysis indicated that BMI and waist circumference mediated the causal effect of years of schooling, and BMI mediated the causal impact of average total household income before tax.

Conclusions: This MR study provided evidence for the causal effect of genetically determined SES on the risk of IVDD and low back pain and revealed the potential mediating effect of obesity-related traits.

Keywords: mediation mendelian randomization analysis, socioeconomic status, obesity, intervertebral disc degeneration, low back pain, causal inference

Introduction

Low back pain is typically characterized by discomfort, muscle tension, or stiffness located below the rib margin and above the lower buttocks, with or without accompanying leg pain.[1] In 2020, low back pain remained the leading global cause of years lived with disability (YLDs), affecting 619 million people.[2] Although age-standardized rates decreased by about 10% from 1990 to 2020, the burden is projected to rise, with over 800 million cases expected by 2050.[2] Among the numerous causes of low back pain, symptomatic intervertebral disc degeneration (IVDD) is considered a major contributing factor.[3] IVDD is a pathological condition arising from the degeneration and aging of the vertebral body, intervertebral discs, ligaments, and other spinal structures, leading to spinal stenosis or intervertebral disc herniation.[4] It is characterized by progressive loss of proteoglycans and water in the nucleus pulposus, which initiates spinal changes and contributes to nucleus pulposus

Received: 15 October 2024
Accepted: 12 March 2025
Published: 26 March 2025

protrusion, fibrous ring tears, disc narrowing, and ultimately low back pain.[5] When intervertebral disc protrusion caused by IVDD compresses the spinal cord or nerve roots, it can lead directly to symptoms of low back pain.[6]

Low back pain and IVDD are major global health burdens, severely reducing quality of life and driving significant clinical and economic costs worldwide. In high-income countries, low back pain results in an annual hospitalization rate of 3.2% and substantial economic burden, with direct and total costs per patient estimated at $9231 and $10,143.1, respectively.[7] In contrast, in low- and middle-income countries, low back pain leads to significantly higher hospitalization rates of 13.4%–18.7% annually, with an economic burden of $2.2 billion per year and $1226.25 per patient.[8] It is widely recognized that approximately 80% of people will experience low back pain during their lifetime, often severe enough to require medical intervention and cause a loss of productive workdays.[3] Identifying modifiable risk factors influencing IVDD and low back pain is critical for developing targeted interventions and policies aimed at alleviating these global health burden. Several risk factors contribute to low back pain and IVDD, including heavy physical labor,[9] prolonged sitting,[10] obesity,[11,12] smoking,[13,14] and psychosocial stress such as depression.[15] These factors are more prevalent in lower socioeconomic status (SES) populations due to greater exposure to physical demands, unhealthy lifestyles, and limited healthcare access,[16] underscoring SES as a key determinant of risk.

SES is a multifaceted construct that encompasses an individual's economic resources, social position, educational attainment, and Townsend deprivation index, which has been widely recognized as a significant determinant of health outcomes across various diseases and conditions.[17] Previous research indicates an association between SES disparities and the prevalence of low back pain and IVDD.[18,19] However, these findings largely stem from observational studies, which are susceptible to confounding and thus unable to clarify causal relationships. Additionally, low SES populations often face challenges such as limited access to healthy food, fewer opportunities for physical activity, and higher levels of stress, all of which contribute to higher rates of obesity.[20–22] Obesity, in turn, is a well-established risk factor for IVDD and low back pain.[23] Excessive weight increases biomechanical stress on the spine and contributes to chronic systemic inflammation, which may accelerate the degeneration of intervertebral discs and exacerbate back pain.[24] Given these pathways, obesity may act as a mediator in the causal relationship between SES and IVDD or low back pain. However, the degree to which obesity mediates these effects has not been fully clarified. Randomized controlled trials (RCTs) are considered the gold standard for supporting causal inference in epidemiological studies. However, due to issues such as time, cost, and medical ethics, some RCTs are difficult to implement.

To address these limitations, Mendelian randomization (MR) emerges as a robust genetic epidemiology method that employs genetic variants as instrumental variables (IVs) to explore causal links between exposures and outcomes.[25] This approach leverages the random assortment of genetic variants during meiosis to mimic a randomized controlled trial, thereby minimizing confounding factors and reverse causation.[26] Single nucleotide polymorphisms (SNPs) are commonly used as IVs in MR studies to proxy diverse exposure levels.[27] The widespread availability of summary-level statistics from genome-wide association studies (GWAS) facilitates the implementation of MR analyses.[28] This study aimed to conduct an MR analysis to provide robust evidence of the causal influence of SES factors on prevalent spinal conditions, highlighting the practical significance of addressing SES inequalities in guiding targeted interventions, informing healthcare policies, and ultimately mitigating the burden of IVDD and low back pain on a global scale.

Methods

Overall Study Design

Figure 1 illustrates the overall workflow of the present study. This study was conducted within the framework of two-sample MR analysis and two-step mediation MR analysis. Specifically, in this MR study, SES were the exposures, obesity-related traits were the candidate mediators, and low back pain and IVDD were the outcomes. First, the GWAS summary-level statistics for five SES ([i] years of schooling, [ii] occupational attainment, [iii] Townsend deprivation index, [iv] job involves heavy manual or physical work, and [v] average total household income before tax), three obesity-related traits ([i] body mass index [BMI], [ii] waist circumference, and [iii] hip circumference), IVDD, and low back pain were downloaded from public databases. Next, a two-sample MR analysis was conducted to assess (i) the causal effect of SES on IVDD and low back pain, (ii) the causal effect of SES on obesity-related traits, and (iii) the causal

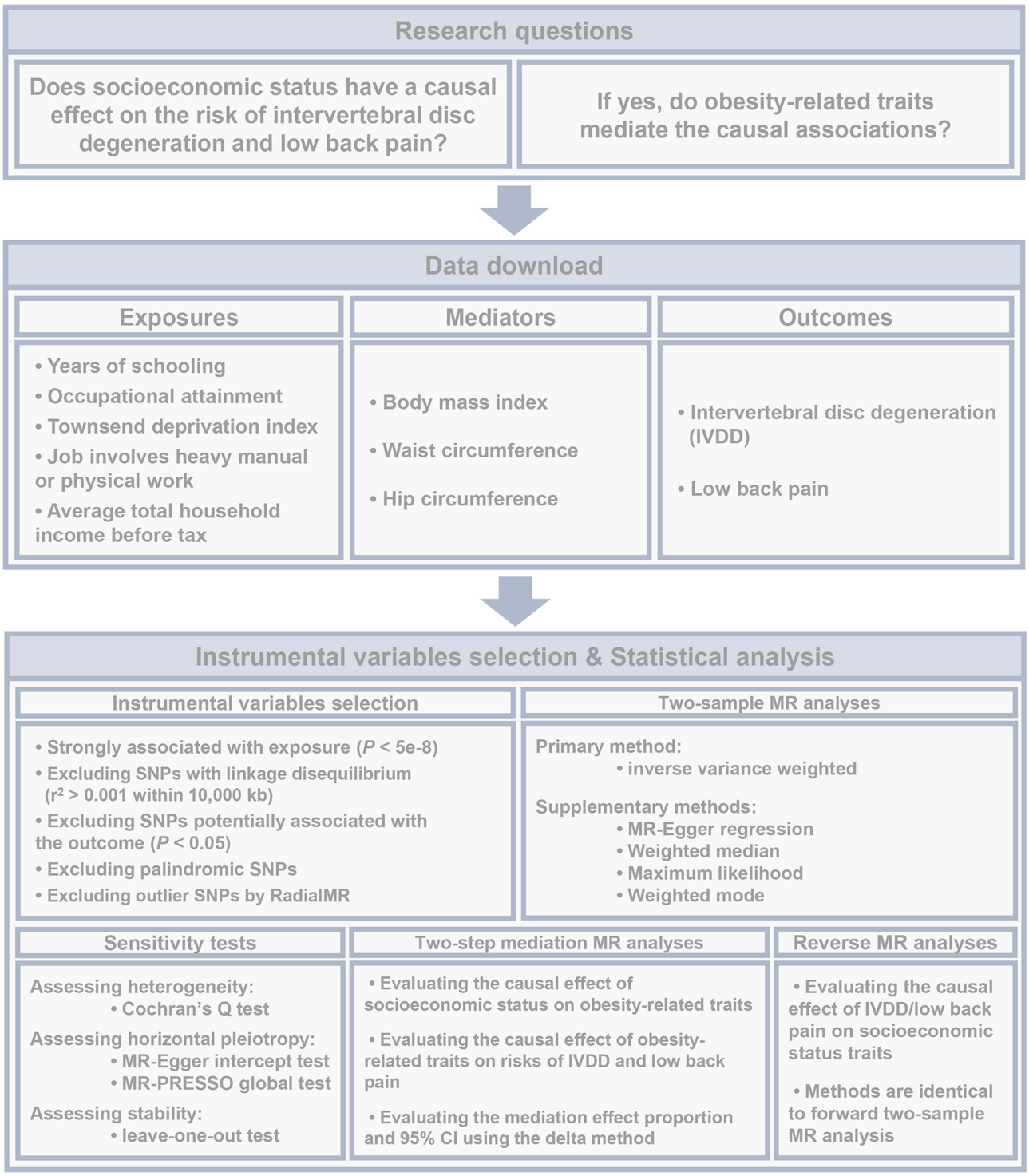

Figure 1 Overall study procedure.

effect of obesity-related traits on IVDD and low back pain. Next, various sensitivity tests were conducted to comprehensively assess the causal estimations. Finally, within the framework of a two-step MR analysis, the mediating effect of obesity-related traits on the relationship between SES and IVDD and low back pain was determined. Detailed information for each step is provided in the following subsections. This study was performed based on the "TwoSampleMR" package in R software.

https://doi.org/10.2147/JPR.S501083

GWAS Summary Level Statistics

The download links for all GWAS summary statistics included in this MR study are shown in Supplementary Table S1. The GWAS summary statistics for years of schooling (n = 766,345) were obtained from the IEU Open GWAS database, derived from a large-scale GWAS meta-analysis by SSGAC consortium.[29] The GWAS summary statistics for occupational attainment (n = 248,847) were sourced from a GWAS study by Ko et al.[30] The GWAS summary statistics for Townsend deprivation index (n = 462,464), job involving heavy manual or physical work (n = 263,615), and average total household income before tax (n = 397,751) were obtained from the MRC-IEU Consortium's curated data in the IEU OpenGWAS project database.[31] The GWAS summary-level statistics for BMI (n = 806,834) were derived from a GWAS meta-analysis by Pulit et al.[32] The GWAS summary-level statistics for waist circumference (n = 407,661) and hip circumference (n = 407,662) were obtained from the IEU Open GWAS database, derived from a large GWAS analysis conducted by Mbatchou et al.[33] The GWAS summary-level statistics for low back pain and IVDD were obtained from the FinnGen database's R11 release.[34] The data for low back pain included 37,567 cases and 322,314 controls, while the data for IVDD included 46,205 cases and 322,314 controls. Definitions of all traits included in the present study are detailed in Supplementary Table S1.

Screening Genetic Instrumental Variables

First, the most relevant SNPs were screened from the GWAS summary statistics of the corresponding exposure (based on the genome-wide significance threshold $P < 5e\text{-}8$). Subsequently, to ensure the independence of the IVs, SNPs with linkage disequilibrium were excluded (based on a threshold of $r^2 < 0.001$ within 10,000 kb). Next, to minimize the effect of horizontal pleiotropy, SNPs potentially associated with the outcome ($P < 0.05$) were excluded from the IVs. In addition, palindromic SNPs were excluded from the IVs. Next, the RadialMR R package was used to further remove outlier SNPs. Finally, the *F*-statistics of each IV were calculated and only IVs with *F*-statistics > 10 were retained, thus eliminating the bias of weak genetic instruments. Supplementary Tables S2–S11 detail the IVs used for conducting MR analyses to evaluate the causal effects of five of SES on risk of IVDD and low back pain. Supplementary Tables S12–S26 detail the IVs used for conducting MR analyses to evaluate the causal effects of five of SES on three obesity-related traits. Supplementary Tables S27–S32 detail the IVs used for conducting MR analyses to evaluate the causal effects of three obesity-related traits on risk of IVDD and low back pain.

Two-Sample MR Analysis

The primary method for causal inference was Inverse-variance weighted (IVW), which integrates the final causal effect through a meta-analysis of causal inferences based on the Wald ratio method using individual IVs.[35] Before performing MR analysis, Cochran's Q test was conducted to evaluate heterogeneity among causal inferences derived from different individual IVs. If no heterogeneity was found ($P > 0.05$), the fixed-effects model-based IVW served as the primary approach. In cases of detected heterogeneity ($P < 0.05$), the random-effects model-based IVW was chosen as the primary method. Additionally, four supplementary methods—MR-Egger regression, weighted median, maximum likelihood, and weighted mode—were employed alongside IVW. Causal inference was reported using odds ratio (OR) and 95% confidence interval (CI). A significant causal association was indicated if the *P*-value from IVW estimation was less than 0.05 and OR values from the supplementary methods aligned with IVW results.

Sensitivity Tests

The reliability of MR estimation was further evaluated through various sensitivity tests. Horizontal pleiotropy, which refers to the possibility of IVs affecting the outcome through paths other than exposure, was assessed using the MR-Egger intercept test and MR-PRESSO global test. A *P*-value greater than 0.05 suggested that horizontal pleiotropy did not significantly influence MR analysis. Additionally, the leave-one-out test involved repeated MR analyses after sequentially removing each IV to assess whether any outlier IVs significantly altered the results, thereby examining the stability of estimation.

Two-Step Mediation MR Analysis

A two-step mediation MR analysis further evaluated the obesity-related traits that might have mediated the causal effect of SES on IVDD and low back pain. Specifically, if an obesity-related trait was significantly influenced by a particular SES and, in turn, significantly affected IVDD or low back pain in a matching direction, then that obesity-related trait was considered a potential key mediator. The proportion of mediation effect and the corresponding 95% CI was assessed using the delta method.[36] Specifically, β_1 represents the causal effect of SES on the obesity-related trait (with a standard error of SE(β_1)), β_2 represents the causal effect of the obesity-related trait on IVDD/low back pain (with a standard error of SE(β_2)), β_3 represents the causal effect of the SES on IVDD/low back pain (with a standard error of SE (β_3)). Mediating proportion $= \frac{\beta_1 \times \beta_2}{\beta_3}$; 95% *CI* of mediating proportion $= \frac{\beta_1 \times \beta_2 \pm 1.96 \times \sqrt{\beta_1^2 \times (\mathrm{SE}(\beta_2))^2 + \beta_2^2 \times (\mathrm{SE}(\beta_1))^2}}{\beta_3}$.

Reverse MR Analysis

To comprehensively understand the relationship between low back pain/IVDD and SESs, we further conducted a reverse MR analysis to assess the causal effect of low back pain/IVDD on SESs. The methodology for IV selection and the approach employed for MR analysis were consistent with those utilized in the forward MR analysis.

Results

Causal Impact of SES on IVDD and Low Back Pain

Figure 2 shows the causal effects of five types of SES on risk of IVDD and low back pain evaluated by the IVW method. Years of schooling (OR = 0.75, 95% CI: 0.69–0.82, P = 1.49E-10) were significantly negatively associated with the risk of IVDD, whereas Townsend deprivation index (OR = 1.48, 95% CI: 1.08–2.01, P = 1.36E-02) and job involving heavy manual or physical work (OR = 1.45, 95% CI: 1.06–2.00, P = 2.16E-02) were significantly positively associated with the risk of IVDD. In addition, years of schooling (OR = 0.67, 95% CI: 0.61–0.74, P = 1.95E-15), occupational attainment (OR = 0.90, 95% CI: 0.83–0.98, P = 1.82E-02), and average total household income before tax (OR = 0.80, 95% CI: 0.67–0.94, P = 7.10E-03) were significantly negatively associated with the risk of low back pain, while Townsend deprivation index (OR = 1.89, 95% CI: 1.31–2.72, P = 6.29E-04) and job involving heavy manual or physical work (OR = 1.38, 95% CI: 1.03–1.84, P = 3.19E-02) were significantly positively associated with the risk of low back pain. The direction of MR estimation determined by the four additional MR methods was consistent with IVW (Table 1). Cochran's Q test indicated no significant heterogeneity among the IVs (P > 0.05) (Figure 2 and Supplementary Table S33). The MR-Egger intercept and MR-PRESSO global test showed that the MR estimates were not significantly influenced by pleiotropy (P > 0.05) (Figure 2 and Supplementary Table S34). Leave-one-out test results indicated that significant causal estimations were not affected by outlier IVs (Supplementary Figures S1–S8).

MR analysis				Sensitivity test			
Exposure	Outcome	OR (95% CI)	*P*− value	P_{Q_ivw}	P_{Q_Egger}	$P_{Egger\text{-}intercept}$	P_{PRESSO}
Years of schooling	IVDD	0.75 (0.69, 0.82)	1.49E−10	0.497	0.477	0.899	0.509
	Low back pain	0.67 (0.61, 0.74)	1.95E−15	0.908	0.909	0.318	0.921
Occupational attainment	IVDD	0.92 (0.84, 1.00)	5.14E−02	0.121	0.096	0.605	0.152
	Low back pain	0.90 (0.83, 0.98)	1.82E−02	0.333	0.292	0.573	0.364
Townsend deprivation index	IVDD	1.48 (1.08, 2.01)	1.36E−02	0.667	0.720	0.234	0.671
	Low back pain	1.89 (1.31, 2.72)	6.29E−04	0.480	0.405	0.746	0.514
Job involves heavy manual or physical work	IVDD	1.45 (1.06, 2.00)	2.16E−02	0.705	0.615	0.749	0.754
	Low back pain	1.38 (1.03, 1.84)	3.19E−02	0.293	0.232	0.834	0.311
Average total household income before tax	IVDD	0.90 (0.77, 1.04)	1.61E−01	0.381	0.486	0.086	0.403
	Low back pain	0.80 (0.67, 0.94)	7.10E−03	0.744	0.706	0.727	0.743

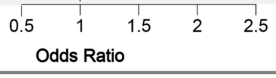

Figure 2 Causal effects of SES on risks of IVDD and low back pain identified by IVW method.

https://doi.org/10.2147/JPR.S501083

Table 1 Results of MR Analysis Assessed by Five Diverse MR Methods (Evaluating the Causal Effects of Socioeconomic Status on IVDD and Low Back Pain)

Exposure	Outcome	Method	OR (95% CI)	*P*-value
Years of schooling	IVDD	IVW	0.75 (0.69, 0.82)	1.49E-10
		MR Egger	0.77 (0.54, 1.09)	1.37E-01
		Weighted median	0.72 (0.63, 0.83)	2.92E-06
		Maximum likelihood	0.75 (0.68, 0.82)	1.50E-10
		Weighted mode	0.61 (0.44, 0.85)	4.23E-03
Years of schooling	Low back pain	IVW	0.67 (0.61, 0.74)	1.95E-15
		MR Egger	0.82 (0.54, 1.23)	3.42E-01
		Weighted median	0.64 (0.55, 0.73)	6.66E-10
		Maximum likelihood	0.67 (0.61, 0.74)	4.32E-15
		Weighted mode	0.60 (0.41, 0.88)	1.03E-02
Occupational attainment	IVDD	IVW	0.92 (0.84, 1.00)	5.14E-02
		MR Egger	0.85 (0.62, 1.16)	3.21E-01
		Weighted median	0.89 (0.78, 1.01)	7.73E-02
		Maximum likelihood	0.91 (0.84, 1.00)	4.83E-02
		Weighted mode	0.84 (0.71, 1.00)	8.19E-02
Occupational attainment	Low back pain	IVW	0.90 (0.83, 0.98)	1.82E-02
		MR Egger	0.84 (0.64, 1.10)	2.28E-01
		Weighted median	0.89 (0.79, 1.01)	7.54E-02
		Maximum likelihood	0.91 (0.83, 0.99)	2.21E-02
		Weighted mode	0.83 (0.67, 1.01)	8.48E-02
Townsend deprivation index	IVDD	IVW	1.48 (1.08, 2.01)	1.36E-02
		MR Egger	8.11 (0.55, 119.57)	1.51E-01
		Weighted median	1.69 (1.09, 2.61)	1.84E-02
		Maximum likelihood	1.50 (1.09, 2.05)	1.22E-02
		Weighted mode	1.99 (0.97, 4.07)	8.07E-02
Townsend deprivation index	Low back pain	IVW	1.89 (1.31, 2.72)	6.29E-04
		MR Egger	3.13 (0.15, 63.76)	4.73E-01
		Weighted median	2.25 (1.37, 3.70)	1.36E-03
		Maximum likelihood	1.94 (1.33, 2.82)	6.04E-04
		Weighted mode	2.68 (1.18, 6.09)	3.66E-02
Job involves heavy manual or physical work	IVDD	IVW	1.45 (1.06, 2.00)	2.16E-02
		MR Egger	1.11 (0.21, 5.73)	9.08E-01
		Weighted median	1.52 (1.01, 2.31)	4.56E-02
		Maximum likelihood	1.46 (1.06, 2.02)	2.17E-02
		Weighted mode	1.61 (0.96, 2.68)	1.07E-01
Job involves heavy manual or physical work	Low back pain	IVW	1.38 (1.03, 1.84)	3.19E-02
		MR Egger	1.71 (0.23, 12.91)	6.12E-01
		Weighted median	1.82 (1.21, 2.74)	3.93E-03
		Maximum likelihood	1.39 (1.04, 1.88)	2.83E-02
		Weighted mode	2.01 (1.04, 3.91)	5.86E-02
Average total household income before tax	IVDD	IVW	0.90 (0.77, 1.04)	1.61E-01
		MR Egger	0.48 (0.24, 0.97)	5.10E-02
		Weighted median	0.90 (0.72, 1.13)	3.66E-01
		Maximum likelihood	0.90 (0.77, 1.05)	1.81E-01
		Weighted mode	0.93 (0.66, 1.33)	7.11E-01

(*Continued*)

Table 1 (Continued).

Exposure	Outcome	Method	OR (95% CI)	*P*-value
Average total household income before tax	Low back pain	IVW	0.80 (0.67, 0.94)	7.10E-03
		MR Egger	0.69 (0.31, 1.55)	3.77E-01
		Weighted median	0.80 (0.64, 1.01)	6.35E-02
		Maximum likelihood	0.80 (0.68, 0.95)	9.63E-03
		Weighted mode	0.80 (0.56, 1.15)	2.41E-01

Identifying Obesity-Related Traits Mediating the Causal Effects of SES on IVDD and Low Back Pain

Figure 3A illustrates the causal effects of five types of SES on three obesity-related traits assessed by the IVW method, while Figure 3B illustrates the causal effects of three obesity-related traits on the risk of IVDD and low back pain assessed by the IVW method. Apart from the causal inference of years of schooling on hip circumference and the average total household income before tax on hip circumference, which were significantly affected by heterogeneity ($P_{Q\_ivw} < 0.05$ and $P_{Q\_Egger} < 0.05$) and horizontal pleiotropy ($P_{PRESSO} < 0.05$), the other causal inferences were not significantly disturbed by heterogeneity and horizontal pleiotropy (Figure 3A and Supplementary Table S35-S38).

Figure 3A shows that years of schooling has a significant negative causal effect on BMI ($\beta = -0.082$, 95% CI: −0.112 - −0.053, P = 4.93E-08) and waist circumference ($\beta = -0.076$, 95% CI: −0.105 - −0.047, P = 2.29E-07). Due to the

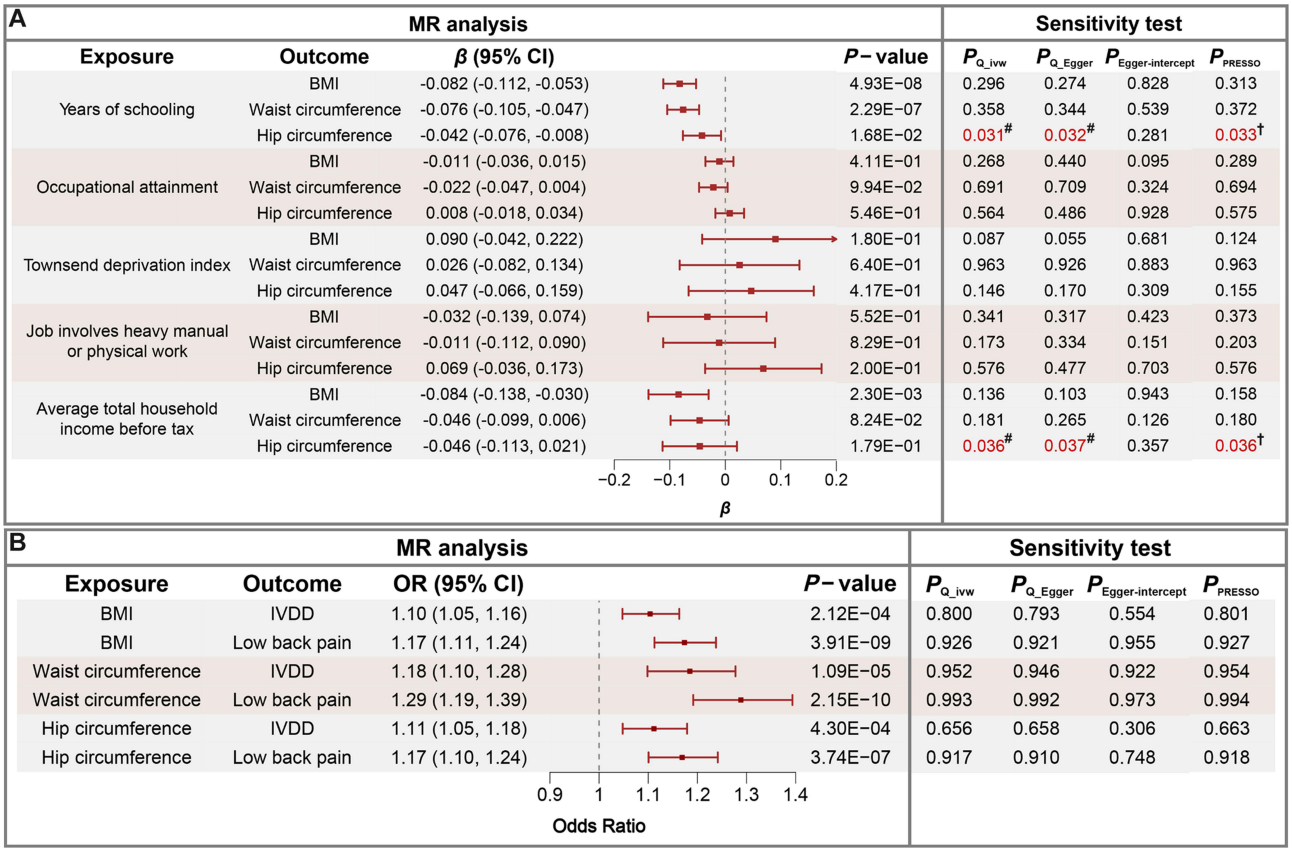

Figure 3 Identification of key obesity-related traits as mediators by two-step mediation MR analysis. (**A**) Causal effects of SES on obesity-related traits identified by IVW method. (**B**) Causal effects of obesity-related traits on risks of IVDD and low back pain identified by IVW method. # $P_{Q\_ivw}/P_{Q\_Egger} < 0.05$, indicating that this causal association may be influenced by heterogeneity, and therefore excluded from subsequent analysis. † $P_{PRESSO} < 0.05$, indicating that this causal association may be influenced by horizontal pleiotropy, and therefore excluded from subsequent analysis.

https://doi.org/10.2147/JPR.S501083

potential influence of horizontal pleiotropy on the causal effect of years of schooling on hip circumference, it is excluded from further analysis. Additionally, the average total household income before tax has a significant negative causal effect on BMI (β = −0.084, 95% CI: −0.138 - −0.030, P = 2.30E-03). Figure 3B shows that all three obesity-related traits have a positive causal association with the risk of IVDD and low back pain (OR > 1, P < 0.05). Tables 2 and 3 indicate that

Table 2 Results of MR Analysis Assessed by Five Diverse MR Methods (Evaluating the Causal Effects of Socioeconomic Status on Obesity-Related Traits)

Exposure	Outcome	Method	β (95% CI)	*P*-value
Years of schooling	BMI	IVW	−0.082 (−0.112, −0.053)	4.93E-08
		MR Egger	−0.097 (−0.232, 0.039)	1.65E-01
		Weighted median	−0.079 (−0.122, −0.035)	4.00E-04
		Maximum likelihood	−0.082 (−0.112, −0.052)	8.33E-08
		Weighted mode	−0.203 (−0.339, −0.067)	4.26E-03
Years of schooling	Waist circumference	IVW	−0.076 (−0.105, −0.047)	2.29E-07
		MR Egger	−0.117 (−0.250, 0.016)	8.82E-02
		Weighted median	−0.076 (−0.119, −0.033)	5.70E-04
		Maximum likelihood	−0.077 (−0.106, −0.048)	2.38E-07
		Weighted mode	−0.049 (−0.152, 0.054)	3.53E-01
Years of schooling	Hip circumference	IVW	−0.042 (−0.076, −0.008)	1.68E-02
		MR Egger	−0.125 (−0.278, 0.029)	1.14E-01
		Weighted median	−0.042 (−0.091, 0.006)	8.67E-02
		Maximum likelihood	−0.043 (−0.074, −0.011)	7.55E-03
		Weighted mode	−0.179 (−0.334, −0.025)	2.46E-02
Occupational attainment	BMI	IVW	−0.011 (−0.036, 0.015)	4.11E-01
		MR Egger	−0.098 (−0.195, −0.002)	7.42E-02
		Weighted median	−0.006 (−0.043, 0.031)	7.61E-01
		Maximum likelihood	−0.011 (−0.037, 0.015)	3.99E-01
		Weighted mode	−0.002 (−0.059, 0.054)	9.42E-01
Occupational attainment	Waist circumference	IVW	−0.022 (−0.047, 0.004)	9.94E-02
		MR Egger	−0.070 (−0.166, 0.025)	1.81E-01
		Weighted median	−0.027 (−0.063, 0.008)	1.28E-01
		Maximum likelihood	−0.022 (−0.048, 0.004)	9.65E-02
		Weighted mode	−0.034 (−0.088, 0.020)	2.42E-01
Occupational attainment	Hip circumference	IVW	0.008 (−0.018, 0.034)	5.46E-01
		MR Egger	0.013 (−0.090, 0.116)	8.13E-01
		Weighted median	0.029 (−0.008, 0.066)	1.21E-01
		Maximum likelihood	0.008 (−0.018, 0.034)	5.42E-01
		Weighted mode	0.040 (−0.020, 0.100)	2.12E-01
Townsend deprivation index	BMI	IVW	0.090 (−0.042, 0.222)	1.80E-01
		MR Egger	0.513 (−1.325, 2.352)	6.22E-01
		Weighted median	0.181 (0.005, 0.357)	4.39E-02
		Maximum likelihood	0.095 (−0.041, 0.232)	1.72E-01
		Weighted mode	0.207 (−0.010, 0.424)	1.35E-01
Townsend deprivation index	Waist circumference	IVW	0.026 (−0.082, 0.134)	6.40E-01
		MR Egger	0.099 (−0.837, 1.035)	8.43E-01
		Weighted median	0.048 (−0.084, 0.179)	4.77E-01
		Maximum likelihood	0.026 (−0.082, 0.134)	6.39E-01
		Weighted mode	0.062 (−0.129, 0.253)	5.46E-01

(*Continued*)

Table 2 (Continued).

Exposure	Outcome	Method	β (95% CI)	P-value
Townsend deprivation index	Hip circumference	IVW	0.047 (−0.066, 0.159)	4.17E-01
		MR Egger	0.709 (−0.483, 1.901)	2.82E-01
		Weighted median	0.086 (−0.077, 0.249)	3.01E-01
		Maximum likelihood	0.048 (−0.067, 0.164)	4.09E-01
		Weighted mode	0.200 (−0.108, 0.509)	2.39E-01
Job involves heavy manual or physical work	BMI	IVW	−0.032 (−0.139, 0.074)	5.52E-01
		MR Egger	0.173 (−0.293, 0.638)	5.07E-01
		Weighted median	−0.023 (−0.165, 0.119)	7.46E-01
		Maximum likelihood	−0.033 (−0.141, 0.075)	5.47E-01
		Weighted mode	−0.022 (−0.227, 0.183)	8.41E-01
Job involves heavy manual or physical work	Waist circumference	IVW	−0.011 (−0.112, 0.090)	8.29E-01
		MR Egger	0.359 (−0.082, 0.799)	1.72E-01
		Weighted median	−0.049 (−0.191, 0.094)	5.01E-01
		Maximum likelihood	−0.012 (−0.114, 0.091)	8.25E-01
		Weighted mode	−0.080 (−0.308, 0.148)	5.16E-01
Job involves heavy manual or physical work	Hip circumference	IVW	0.069 (−0.036, 0.173)	2.00E-01
		MR Egger	−0.020 (−0.466, 0.426)	9.33E-01
		Weighted median	0.057 (−0.083, 0.198)	4.22E-01
		Maximum likelihood	0.070 (−0.036, 0.176)	1.97E-01
		Weighted mode	0.071 (−0.150, 0.292)	5.51E-01
Average total household income before tax	BMI	IVW	−0.084 (−0.138, −0.030)	2.30E-03
		MR Egger	−0.092 (−0.327, 0.142)	4.51E-01
		Weighted median	−0.134 (−0.211, −0.058)	5.77E-04
		Maximum likelihood	−0.085 (−0.141, −0.030)	2.58E-03
		Weighted mode	−0.160 (−0.290, −0.031)	2.77E-02
Average total household income before tax	Waist circumference	IVW	−0.046 (−0.099, 0.006)	8.24E-02
		MR Egger	0.154 (−0.096, 0.405)	2.44E-01
		Weighted median	−0.083 (−0.162, −0.005)	3.68E-02
		Maximum likelihood	−0.045 (−0.098, 0.008)	9.63E-02
		Weighted mode	−0.103 (−0.270, 0.064)	2.43E-01
Average total household income before tax	Hip circumference	IVW	−0.046 (−0.113, 0.021)	1.79E-01
		MR Egger	0.076 (−0.186, 0.337)	5.77E-01
		Weighted median	−0.088 (−0.168, −0.008)	3.08E-02
		Maximum likelihood	−0.045 (−0.099, 0.010)	1.07E-01
		Weighted mode	−0.172 (−0.355, 0.011)	7.90E-02

Table 3 Results of MR Analysis Assessed by Five Diverse MR Methods (Evaluating the Causal Effects of Obesity-Related Traits on IVDD and Low Back Pain)

Exposure	Outcome	Method	OR (95% CI)	P-value
BMI	IVDD	IVW	1.10 (1.05, 1.16)	2.12E-04
		MR Egger	1.06 (0.92, 1.22)	4.24E-01
		Weighted median	1.15 (1.06, 1.25)	6.64E-04
		Maximum likelihood	1.10 (1.05, 1.16)	2.11E-04
		Weighted mode	1.29 (1.06, 1.56)	1.18E-02

(*Continued*)

https://doi.org/10.2147/JPR.S501083

Table 3 (Continued).

Exposure	Outcome	Method	OR (95% CI)	*P*-value
BMI	Low back pain	IVW	1.17 (1.11, 1.24)	3.91E-09
		MR Egger	1.18 (1.03, 1.35)	1.74E-02
		Weighted median	1.23 (1.12, 1.35)	1.17E-05
		Maximum likelihood	1.17 (1.11, 1.24)	4.01E-09
		Weighted mode	1.22 (1.04, 1.45)	1.75E-02
Waist circumference	IVDD	IVW	1.18 (1.10, 1.28)	1.09E-05
		MR Egger	1.20 (0.94, 1.52)	1.39E-01
		Weighted median	1.28 (1.15, 1.44)	1.69E-05
		Maximum likelihood	1.19 (1.10, 1.28)	1.08E-05
		Weighted mode	1.47 (1.09, 1.98)	1.19E-02
Waist circumference	Low back pain	IVW	1.29 (1.19, 1.39)	2.15E-10
		MR Egger	1.29 (1.01, 1.65)	4.04E-02
		Weighted median	1.31 (1.17, 1.48)	4.37E-06
		Maximum likelihood	1.29 (1.19, 1.40)	1.90E-10
		Weighted mode	1.66 (1.21, 2.27)	1.98E-03
Hip circumference	IVDD	IVW	1.11 (1.05, 1.18)	4.30E-04
		MR Egger	1.22 (1.01, 1.47)	3.81E-02
		Weighted median	1.17 (1.07, 1.28)	6.82E-04
		Maximum likelihood	1.11 (1.05, 1.18)	4.46E-04
		Weighted mode	1.34 (1.07, 1.68)	1.19E-02
Hip circumference	Low back pain	IVW	1.17 (1.10, 1.24)	3.74E-07
		MR Egger	1.14 (0.96, 1.35)	1.45E-01
		Weighted median	1.18 (1.08, 1.29)	4.24E-04
		Maximum likelihood	1.17 (1.10, 1.24)	3.98E-07
		Weighted mode	1.24 (0.97, 1.59)	8.15E-02

four additional MR methods yielded results consistent with the direction of the IVW method, further strengthening these causal estimates. Furthermore, the results of the leave-one-out test demonstrated that the significant causal estimates remained unaffected by any outlier IVs (Supplementary Figures S9–S17).

Combining these results, a total of five causal associations mediated by obesity-related traits were identified: (i) Years of schooling reduces the risk of IVDD through lowering BMI (mediating proportion = 2.8% [95% CI: 1–4.6%]); (ii) Years of schooling reduces the risk of low back pain through lowering BMI (mediating proportion = 3.3% [95% CI: 1.7–4.9%]); (iii) Years of schooling reduces the risk of IVDD through lowering waist circumference (mediating proportion = 4.5% [95% CI: 1.9–7.1%]); (iv) Years of schooling reduces the risk of low back pain through lowering waist circumference (mediating proportion = 4.8% [95% CI: 2.5–7.1%]); and (v) Average total household income before tax reduces the risk of low back pain through lowering BMI (mediating proportion = 5.9% [95% CI: 1.6–10.2%]). Supplementary Table 39 presents the detailed results of the mediation MR analysis.

Results of Reverse MR Analysis

Figure 4 shows the primary reverse MR results. Interestingly, genetic liability to low back pain was significantly related to reduced average total household income before tax (β = −0.047, 95% CI: −0.085 - −0.008, P = 1.82E-02). Four supplementary MR methods further revealed the parallel findings ($\beta < 0$) (Table 4). No further causal relationship was identified by the reverse MR analysis.

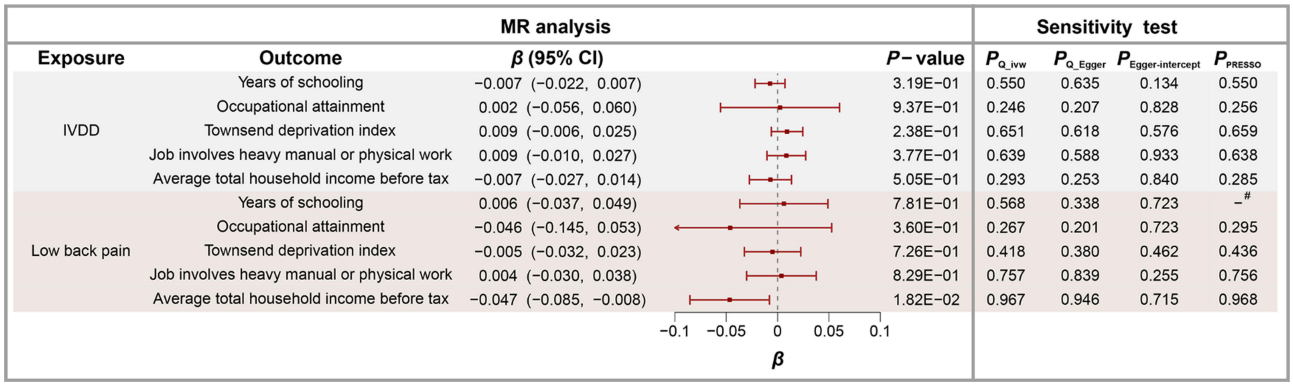

Figure 4 Causal effects of IVDD/low back pain on SES identified by IVW method. # MR-PRESSO was not applicable due to number of IVs ≤ 3.

Discussion

This study comprehensively evaluated the causal effects of SES on the risks of IVDD and low back pain a two-sample MR analysis. Additionally, through a two-step mediation MR analysis, obesity-related traits mediating these causal associations were identified.

Table 4 Results of Reverse MR Analysis Assessed by Five Diverse MR Methods (Evaluating the Causal Effects of IVDD/Low Back Pain on Socioeconomic Status)

Exposure	Outcome	Method	β (95% CI)	P-value
IVDD	Years of schooling	IVW	−0.007 (−0.022, 0.007)	3.19E-01
		MR Egger	−0.068 (−0.147, 0.010)	1.00E-01
		Weighted median	−0.006 (−0.026, 0.014)	5.33E-01
		Maximum likelihood	−0.007 (−0.022, 0.007)	3.28E-01
		Weighted mode	0.018 (−0.026, 0.061)	4.32E-01
IVDD	Occupational attainment	IVW	0.002 (−0.056, 0.060)	9.37E-01
		MR Egger	0.043 (−0.322, 0.407)	8.21E-01
		Weighted median	−0.035 (−0.121, 0.051)	4.27E-01
		Maximum likelihood	0.002 (−0.056, 0.061)	9.36E-01
		Weighted mode	−0.070 (−0.243, 0.102)	4.29E-01
IVDD	Townsend deprivation index	IVW	0.009 (−0.006, 0.025)	2.38E-01
		MR Egger	0.033 (−0.050, 0.116)	4.45E-01
		Weighted median	0.001 (−0.022, 0.024)	9.50E-01
		Maximum likelihood	0.009 (−0.006, 0.025)	2.29E-01
		Weighted mode	−0.002 (−0.045, 0.041)	9.28E-01
IVDD	Job involves heavy manual or physical work	IVW	0.009 (−0.010, 0.027)	3.77E-01
		MR Egger	0.004 (−0.095, 0.104)	9.34E-01
		Weighted median	0.007 (−0.021, 0.034)	6.30E-01
		Maximum likelihood	0.009 (−0.010, 0.028)	3.72E-01
		Weighted mode	0.011 (−0.043, 0.066)	6.81E-01
IVDD	Average total household income before tax	IVW	−0.007 (−0.027, 0.014)	5.05E-01
		MR Egger	−0.019 (−0.137, 0.099)	7.54E-01
		Weighted median	−0.010 (−0.040, 0.020)	5.19E-01
		Maximum likelihood	−0.007 (−0.028, 0.014)	5.14E-01
		Weighted mode	−0.052 (−0.121, 0.017)	1.47E-01

(*Continued*)

https://doi.org/10.2147/JPR.S501083

Table 4 (Continued).

Exposure	Outcome	Method	*β* (95% CI)	*P*-value
Low back pain	Years of schooling	IVW	0.006 (−0.037, 0.049)	7.81E-01
		MR Egger	0.221 (−0.687, 1.129)	7.17E-01
		Weighted median	−0.001 (−0.053, 0.051)	9.77E-01
		Maximum likelihood	0.006 (−0.037, 0.049)	7.80E-01
		Weighted mode	−0.007 (−0.067, 0.052)	8.29E-01
Low back pain	Occupational attainment	IVW	−0.046 (−0.145, 0.053)	3.60E-01
		MR Egger	−0.142 (−0.663, 0.379)	6.11E-01
		Weighted median	−0.101 (−0.246, 0.044)	1.71E-01
		Maximum likelihood	−0.048 (−0.148, 0.053)	3.52E-01
		Weighted mode	−0.135 (−0.350, 0.079)	2.51E-01
Low back pain	Townsend deprivation index	IVW	−0.005 (−0.032, 0.023)	7.26E-01
		MR Egger	0.044 (−0.083, 0.172)	5.17E-01
		Weighted median	−0.003 (−0.039, 0.034)	8.89E-01
		Maximum likelihood	−0.005 (−0.033, 0.023)	7.24E-01
		Weighted mode	−0.001 (−0.056, 0.055)	9.80E-01
Low back pain	Job involves heavy manual or physical work	IVW	0.004 (−0.030, 0.038)	8.29E-01
		MR Egger	−0.090 (−0.241, 0.062)	2.84E-01
		Weighted median	−0.004 (−0.046, 0.039)	8.66E-01
		Maximum likelihood	0.004 (−0.030, 0.038)	8.28E-01
		Weighted mode	−0.012 (−0.087, 0.062)	7.59E-01
Low back pain	Average total household income before tax	IVW	−0.047 (−0.085, −0.008)	1.82E-02
		MR Egger	−0.016 (−0.178, 0.146)	8.51E-01
		Weighted median	−0.036 (−0.084, 0.013)	1.49E-01
		Maximum likelihood	−0.047 (−0.086, −0.008)	1.94E-02
		Weighted mode	−0.028 (−0.098, 0.042)	4.52E-01

While previous studies have suggested a potential association between SES and risk of IVDD and low back pain,[18,37–40] the findings have been inconsistent. For instance, a cross-sectional study involving 2876 Chinese army soldiers reported no significant correlation between educational attainment and low back pain.[41] A study of 4771 Danish twins found no clear association between adolescent socioeconomic status and low back pain, though a weak protective effect against persistent pain was statistically unclear.[42] The inconsistencies in observational study conclusions may result from sample heterogeneity, differences in measurement methods, uncontrolled confounding factors, and variations in statistical analysis. This MR study aligned with the findings of many observational studies, providing a more robust level of evidence. Conducted with five different SES-related indicators, the analysis established a significant causal relationship between higher SES and lower risks of IVDD and low back pain, enhancing the validity of these observational correlations.

The causal pathways linking SES to IVDD and low back pain likely involve multiple interrelated mechanisms. Psychosocial stress from job insecurity, financial instability, and adverse living conditions in lower SES groups can heighten HPA axis activity, leading to chronic inflammation and increased pain sensitivity.[43,44] Occupational factors also play a role, as lower SES individuals are more likely to engage in physically demanding jobs that impose mechanical stress on the spine.[45] Limited access to healthcare further exacerbates risks by delaying early diagnosis and treatment.[46] Additionally, unhealthy lifestyle behaviors, such as smoking, physical inactivity, and substance use, are more prevalent in lower SES groups.[47] Smoking accelerates IVDD by impairing blood flow, reducing nutrient delivery, and inducing oxidative stress, which damages cellular structures and promotes inflammation.[48,49]

In addition to these mechanisms, obesity emerges as a particularly important mediator in the relationship between SES and IVDD or low back pain. Previous observational studies have increasingly highlighted a strong correlation

between SES and obesity,[20] which in turn is recognized as a significant risk factor for IVDD and low back pain.[23] Through mediation MR analyses, we identified BMI and waist circumference as key mediators of years of schooling, and BMI as a key mediator of average total household income before tax. Obesity could increase the risk of IVDD and low back pain by adding mechanical stress to the spine, accelerating disc wear and tear, and altering normal spinal biomechanics.[50] Additionally, the altered posture and movement patterns in obese individuals could further strain the lumbar region, increasing the risk of IVDD and low back pain.[51] Furthermore, obesity could increase the risk of IVDD and low back pain through chronic low-grade inflammation mediated by adipokines.[12]

The implications of these findings extend beyond the medical and health sciences to inform policy and community health initiatives. It underscores the influence of SES disparities on the incidence of IVDD and low back pain. There is a demonstrated need to enhance educational opportunities, increase economic stability, and improve employment conditions to mitigate the risks associated with IVDD and low back pain. Furthermore, in regions characterized by lower SES, interventions aimed at reducing obesity metrics, particularly BMI and waist circumference, could partially counteract the adverse effects associated with low SES. However, it is crucial to note that the mediators identified only account for a minor portion of SES's causal effect on IVDD and low back pain (2.8% to 5.9%, as shown in Supplementary Table S39). This indicates that improvements in obesity-related traits may slightly lessen the adverse effects of low SES. Additionally, SES may influence these conditions through other non-genetic factors like access to medical resources and work environment conditions, which are not detectable in GWAS and hence not included in this study.

This study had several strengths. Firstly, the two-sample MR analysis was based on GWAS summary statistics for exposure and outcomes derived from different cohorts, ensuring a large sample size. Secondly, various SES indicators were included to ensure the comprehensiveness of the MR estimation. Lastly, multiple MR methods and sensitivity tests were used to ensure the reliability of the MR analysis.

However, it must be acknowledged that this study had some limitations. Firstly, the GWAS summary statistics used were all derived from European populations, potentially limiting the applicability of the MR results to other ethnic groups. Future research should aim to validate these findings across diverse ethnic backgrounds to enhance the generalizability of the results. Additionally, the reliance on summary-level statistics meant that more detailed subgroup analyses, such as assessing the impact of SES on the risk of IVDD and low back pain in different genders and age groups, could not be performed. Expanding the dataset to include more extensive GWAS summary statistics and potentially individual-level data could provide deeper insights into these associations.

Conclusion

This MR study provided evidence for the causal effect of genetically determined SES on the risk of IVDD and low back pain and revealed the potential mediating effect of obesity-related traits.

Data Sharing Statement

The GWAS summary statistics used in this MR study are available in the Supplementary Table S1.

Ethics Approval and Informed Consent

This study utilized data obtained from a publicly available dataset that has been fully de-identified and anonymized, ensuring that no personal identifiable information can be traced back to individuals. According to Items 1 and 2 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (effective February 18, 2023, China), research involving anonymized and publicly available data is exempt from ethical review. Therefore, this study does not require additional ethical approval.

Acknowledgments

We are deeply thankful for the IEU OpenGWAS (https://gwas.mrcieu.ac.uk/), GWAS catalog (https://www.ebi.ac.uk/gwas/), and FinnGen (https://www.finngen.fi/en) for providing GWAS summary-level statistics.

Funding

No fundings were received in support of this work.

Disclosure

The authors have no conflict of interest to report.

References

1. Koes BW, van Tulder MW, Thomas S. Diagnosis and treatment of low back pain. *BMJ*. 2006;332(7555):1430–1434. doi:10.1136/bmj.332.7555.1430
2. Ferreira ML, de Luca K, Haile LM, GBD 2021 Stroke Risk Factor Collaborators. Global, regional, and national burden of low back pain, 1990-2020, its attributable risk factors, and projections to 2050: a systematic analysis of the global burden of disease study 2021. *Lancet Rheumatol*. 2023;5(6):e316–e329. doi:10.1016/s2665-9913(23)00098-x
3. Diwan AD, Melrose J. Intervertebral disc degeneration and how it leads to low back pain. *JOR spine*. 2023;6(1):e1231. doi:10.1002/jsp2.1231
4. Yang S, Zhang F, Ma J, Ding W. Intervertebral disc ageing and degeneration: the antiapoptotic effect of oestrogen. *Ageing Res Rev*. 2020;57:100978. doi:10.1016/j.arr.2019.100978
5. Roughley PJ. Biology of intervertebral disc aging and degeneration: involvement of the extracellular matrix. *Spine*. 2004;29(23):2691–2699. doi:10.1097/01.brs.0000146101.53784.b1
6. Raj PP. Intervertebral disc: anatomy-physiology-pathophysiology-treatment. *Pain Pract*. 2008;8(1):18–44. doi:10.1111/j.1533-2500.2007.00171.x
7. Fatoye F, Gebrye T, Ryan CG, Useh U, Mbada C. Global and regional estimates of clinical and economic burden of low back pain in high-income countries: a systematic review and meta-analysis. *Front Public Health*. 2023;11:1098100. doi:10.3389/fpubh.2023.1098100
8. Fatoye F, Gebrye T, Mbada CE, Useh U. Clinical and economic burden of low back pain in low- and middle-income countries: a systematic review. *BMJ open*. 2023;13(4):e064119. doi:10.1136/bmjopen-2022-064119
9. Pataro SM, Fernandes Rde C. Heavy physical work and low back pain: the reality in urban cleaning. *Revista brasileira de epidemiologia*. 2014;17(1):17–30. doi:10.1590/1809-4503201400010003eng
10. Lis AM, Black KM, Korn H, Nordin M. Association between sitting and occupational LBP. *Eur Spine J*. 2007;16(2):283–298. doi:10.1007/s00586-006-0143-7
11. Shiri R, Karppinen J, Leino-Arjas P, Solovieva S, Viikari-Juntura E. The association between obesity and low back pain: a meta-analysis. *Am J Epidemiol*. 2010;171(2):135–154. doi:10.1093/aje/kwp356
12. Ruiz-Fernández C, Francisco V, Pino J, et al. Molecular relationships among obesity, inflammation and intervertebral disc degeneration: are adipokines the common link? *Int J Mol Sci*. 2019;20(8):2030. doi:10.3390/ijms20082030
13. Eriksen W, Natvig B, Bruusgaard D. Smoking, heavy physical work and low back pain: a four-year prospective study. *Occup Med*. 1999;49(3):155–160. doi:10.1093/occmed/49.3.155
14. Elmasry S, Asfour S, de Rivero Vaccari JP, Travascio F. Effects of tobacco smoking on the degeneration of the intervertebral disc: a finite element study. *PLoS One*. 2015;10(8):e0136137. doi:10.1371/journal.pone.0136137
15. Pinheiro MB, Ferreira ML, Refshauge K, et al. Symptoms of depression and risk of new episodes of low back pain: a systematic review and meta-analysis. *Arthritis Care Res*. 2015;67(11):1591–1603. doi:10.1002/acr.22619
16. Harris JR, Huang Y, Hannon PA, Williams B. Low-socioeconomic status workers: their health risks and how to reach them. *J Occup Environ Med*. 2011;53(2):132–138. doi:10.1097/JOM.0b013e3182045f2c
17. Adler NE, Ostrove JM. Socioeconomic status and health: what we know and what we don't. *Ann N.Y. Acad Sci*. 1999;896:3–15. doi:10.1111/j.1749-6632.1999.tb08101.x
18. Katz JN. Lumbar disc disorders and low-back pain: socioeconomic factors and consequences. *J Bone Joint Surg Ame Volume*. 2006;88 Suppl 2:21–24. doi:10.2106/jbjs.E.01273
19. Latza U, Kohlmann T, Deck R, Raspe H. Can health care utilization explain the association between socioeconomic status and back pain? *Spine*. 2004;29(14):1561–1566. doi:10.1097/01.brs.0000131435.56714.15
20. Anekwe CV, Jarrell AR, Townsend MJ, Gaudier GI, Hiserodt JM, Stanford FC. Socioeconomics of obesity. *Current Obes Rep*. 2020;9(3):272–279. doi:10.1007/s13679-020-00398-7
21. McLaren L. Socioeconomic status and obesity. *Epidemiol Rev*. 2007;29:29–48. doi:10.1093/epirev/mxm001
22. Zhang Q, Wang Y. Trends in the association between obesity and socioeconomic status in U.S. adults: 1971 to 2000. *Obes Res*. 2004;12(10):1622–1632. doi:10.1038/oby.2004.202
23. Zhou J, Mi J, Peng Y, Han H, Liu Z. Causal associations of obesity with the intervertebral degeneration, low back pain, and sciatica: a two-sample Mendelian randomization study. *Front Endocrinol*. 2021;12:740200. doi:10.3389/fendo.2021.740200
24. da Cruz Fernandes IM, Pinto RZ, Ferreira P, Lira FS. Low back pain, obesity, and inflammatory markers: exercise as potential treatment. *J Exercise Rehab*. 2018;14(2):168–174. doi:10.12965/jer.1836070.035
25. Sanderson E, Glymour MM, Holmes MV, et al. Mendelian randomization. *Nat Rev Method Primers*. 2022;2. doi:10.1038/s43586-021-00092-5
26. Swanson SA, Tiemeier H, Ikram MA, Hernán MA. Nature as a trialist?: deconstructing the analogy between Mendelian randomization and randomized trials. *Epidemiology*. 2017;28(5):653–659. doi:10.1097/ede.0000000000000699
27. Bowden J, Holmes MV. Meta-analysis and Mendelian randomization: a review. *Res Synthesis Meth*. 2019;10(4):486–496. doi:10.1002/jrsm.1346
28. Swerdlow DI, Kuchenbaecker KB, Shah S, et al. Selecting instruments for Mendelian randomization in the wake of genome-wide association studies. *Int J Epidemiol*. 2016;45(5):1600–1616. doi:10.1093/ije/dyw088
29. Lee JJ, Wedow R, Okbay A, et al. Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. *Nat Genet*. 2018;50(8):1112–1121. doi:10.1038/s41588-018-0147-3
30. Ko H, Kim S, Kim K, et al. Genome-wide association study of occupational attainment as a proxy for cognitive reserve. *Brain*. 2022;145(4):1436–1448. doi:10.1093/brain/awab351

31. Elsworth B, Lyon M, Alexander T, et al. The MRC IEU OpenGWAS data infrastructure. *bioRxiv*. 2020:2020.08.10.244293. doi:10.1101/2020.08.10.244293.
32. Pulit SL, Stoneman C, Morris AP, et al. Meta-analysis of genome-wide association studies for body fat distribution in 694 649 individuals of European ancestry. *Hum Mol Genet*. 2019;28(1):166–174. doi:10.1093/hmg/ddy327
33. Mbatchou J, Barnard L, Backman J, et al. Computationally efficient whole-genome regression for quantitative and binary traits. *Nat Genet*. 2021;53(7):1097–1103. doi:10.1038/s41588-021-00870-7
34. Kurki MI, Karjalainen J, Palta P, et al. FinnGen provides genetic insights from a well-phenotyped isolated population. *Nature*. 2023;613(7944):508–518. doi:10.1038/s41586-022-05473-8
35. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. *Genet Epidemiol*. 2013;37(7):658–665. doi:10.1002/gepi.21758
36. Carter AR, Gill D, Davies NM, et al. Understanding the consequences of education inequality on cardiovascular disease: mendelian randomisation study. *BMJ*. 2019;365:l1855. doi:10.1136/bmj.l1855
37. Ikeda T, Sugiyama K, Aida J, et al. Socioeconomic inequalities in low back pain among older people: the JAGES cross-sectional study. *Int J Equity Health*. 2019;18(1):15. doi:10.1186/s12939-019-0918-1
38. Fliesser M, De Witt Huberts J, Wippert PM. Education, job position, income or multidimensional indices? Associations between different socioeconomic status indicators and chronic low back pain in a German sample: a longitudinal field study. *BMJ open*. 2018;8(4):e020207. doi:10.1136/bmjopen-2017-020207
39. Prego-Domínguez J, Khazaeipour Z, Mallah N, Takkouche B. Socioeconomic status and occurrence of chronic pain: a meta-analysis. *Rheumatology*. 2021;60(3):1091–1105. doi:10.1093/rheumatology/keaa758
40. Plouvier S, Leclerc A, Chastang JF, Bonenfant S, Goldberg M. Socioeconomic position and low-back pain--the role of biomechanical strains and psychosocial work factors in the GAZEL cohort. *Scand J Work Environ Health*. 2009;35(6):429–436. doi:10.5271/sjweh.1353
41. Wei G, Li H, Wang B, Wu J, Wu F, Lin Z. A retrospective cross-sectional survey of non-specific lower back pain among a cohort of Chinese army soldiers. *Int J Surg*. 2018;56:288–293. doi:10.1016/j.ijsu.2018.06.023
42. Hestbaek L, Korsholm L, Leboeuf-Yde C, Kyvik KO. Does socioeconomic status in adolescence predict low back pain in adulthood? A repeated cross-sectional study of 4771 Danish adolescents. *Eur Spine J*. 2008;17(12):1727–1734. doi:10.1007/s00586-008-0796-5
43. Businelle MS, Mills BA, Chartier KG, Kendzor DE, Reingle JM, Shuval K. Do stressful events account for the link between socioeconomic status and mental health? *J Public Health*. 2014;36(2):205–212. doi:10.1093/pubmed/fdt060
44. Klyne DM, Barbe MF, Hodges PW. Systemic inflammatory profiles and their relationships with demographic, behavioural and clinical features in acute low back pain. *Brain Behav Immun*. 2017;60:84–92. doi:10.1016/j.bbi.2016.10.003
45. Seidler A, Bolm-Audorff U, Heiskel H, et al. The role of cumulative physical work load in lumbar spine disease: risk factors for lumbar osteochondrosis and spondylosis associated with chronic complaints. *Occup Environ Med*. 2001;58(11):735–746. doi:10.1136/oem.58.11.735
46. McMaughan DJ, Oloruntoba O, Smith ML. Socioeconomic status and access to healthcare: interrelated drivers for healthy aging. *Front Public Health*. 2020;8:231. doi:10.3389/fpubh.2020.00231
47. Gautam N, Dessie G, Rahman MM, Khanam R. Socioeconomic status and health behavior in children and adolescents: a systematic literature review. *Front Public Health*. 2023;11:1228632. doi:10.3389/fpubh.2023.1228632
48. Fogelholm RR, Alho AV. Smoking and intervertebral disc degeneration. *Med Hypotheses*. 2001;56(4):537–539. doi:10.1054/mehy.2000.1253
49. Cao G, Yang S, Cao J, et al. The role of oxidative stress in intervertebral disc degeneration. *Oxid Med Cell Longev*. 2022;2022:2166817. doi:10.1155/2022/2166817
50. Cannata F, Vadalà G, Ambrosio L, et al. Intervertebral disc degeneration: a focus on obesity and type 2 diabetes. *Diabetes/Metab Res Rev*. 2020;36(1):e3224. doi:10.1002/dmrr.3224
51. Ambrosio L, Mazzuca G, Maguolo A, et al. The burden of low back pain in children and adolescents with overweight and obesity: from pathophysiology to prevention and treatment strategies. *Therap Adv Musculoskel Dis*. 2023;15:1759720x231188831. doi:10.1177/1759720x231188831