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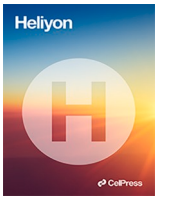

Research article

Mediating effect of metabolic syndrome in the association of educational attainment with intervertebral disc degeneration and low back pain

Xijie Tang [a,1], Qiu Li [b,**,1], Zhang-Hua Li [a,*]

[a] Department of Orthopedics, Wuhan Third Hospital, Tongren Hospital of Wuhan University, Wuhan, 430000, China
[b] Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430077, China

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ABSTRACT

The causal association of educational attainment (EA) with intervertebral disc degeneration (IVDD) or low back pain (LBP), and the mediating effect of metabolic syndrome (MetS) in this association, is not studied to date. In this study, using summary statistics of genome-wide association studies primarily conducted in the individuals of European ancestry, Mendelian randomization (MR) analyses were performed to investigate: (1) the total and direct effects of EA on IVDD and LBP, (2) bidirectional associations of EA with MetS or the components of MetS, (3) causal effects of MetS or its components on IVDD and LBP, and (4) mediating effects of MetS or its components on the causal associations of EA with IVDD and LBP. Univariable MR analysis demonstrated that genetically proxied EA was inversely associated with IVDD (ORIVW: 0.90; 95 % CI: 0.87–0.92) and LBP (ORIVW: 0.86; 95 % CI: 0.84–0.89). Consistent results were obtained after adjusting for potential confounders (cognition, economic level, smoking traits, and metabolic factors). Mediation analysis proved that the effect of EA on IVDD mediated by MetS, waist circumference, and high-density lipoprotein cholesterol was 11.38 %, 9.22 %, and 2.17 %, respectively. Besides, MetS mediated 8.42 % and waist circumference mediated 5.81 % of the EA effects on LBP, respectively. Our findings provided support for MetS mediating the causal protective effects of EA on IVDD and LBP, which provided causal evidence to the etiology and intervention targets of IVDD and LBP.

1. Introduction

Low back pain (LBP) is a significant cause of labor loss and disability globally, impacting the psychological well-being and quality of life of patients while also placing a substantial economic burden on families and society [1,2]. The etiology of LBP is complex and varied, with intervertebral disc degeneration (IVDD) being identified as a key factor [3]. IVDD is characterized by a progressive loss of proteoglycans and water content in the nucleus pulposus, marking the initial stage of spinal changes [4]. With the influence of diverse etiological factors, IVDD gradually causes prolapsing nucleus pulposus, tearing of the fibrous ring, disc narrowing, spinal canal

* Corresponding author.
** Corresponding author.
E-mail addresses: 1697017767@qq.com (Q. Li), 18971610121@qq.com (Z.-H. Li).
[1] These authors contributed equally to this work.

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stenosis, and ultimately LBP [5]. In general, the etiology of IVDD is complex and multifaceted, mainly including genetic causes, aging, and lifestyle [6,7]. Recently, growing evidence suggested that metabolic syndrome (MetS) and its components (including central obesity, hypertension, dyslipidemia, hyperglycemia, and hypertriglyceridemia) might be involved in the development of IVDD, which shifts the focus of IVDD research to metabolic risk factors [8–10].

Educational attainment (EA) is a robust predictor of cognitive ability and economic success, with broad implications for a person's lifestyle behaviors and health resource advantages [11]. Recent univariable Mendelian randomization (UVMR) studies have shown that higher EA is linked to a lower risk of IVDD or LBP, but it is unclear if this association is influenced by cognition, economic income, or lifestyle [12,13]. Additionally, other Mendelian randomization (MR) studies suggest that higher EA may also help reduce the risk of hypertension and diabetes in patients with metabolic syndrome (MetS) [14,15]. As a result, further research is needed to explore the connections between EA, MetS, IVDD, and LBP.

Mendelian randomization (MR) is a method for causal inference that offers a more robust assessment of potential causal relationships compared to traditional epidemiological studies [16]. By utilizing genetic variants strongly linked to the exposure of interest as instrumental variables (IVs), MR provides estimates of the relationship between exposure and outcome that are less susceptible to bias from confounding and reverse causality [17]. Multivariable Mendelian randomization (MVMR) is an extension of MR that enables the examination of the individual effects of related exposures on an outcome and allows for the investigation of potential mediation [18,19].

In this study, we investigated the independent causal effects of EA on IVDD and LBP with adjustment for cognition, economic income, and lifestyle (smoking traits). Furthermore, we aimed to assess whether the causal effects of EA on the risk of IVDD and LBP are mediated by Mets or its components.

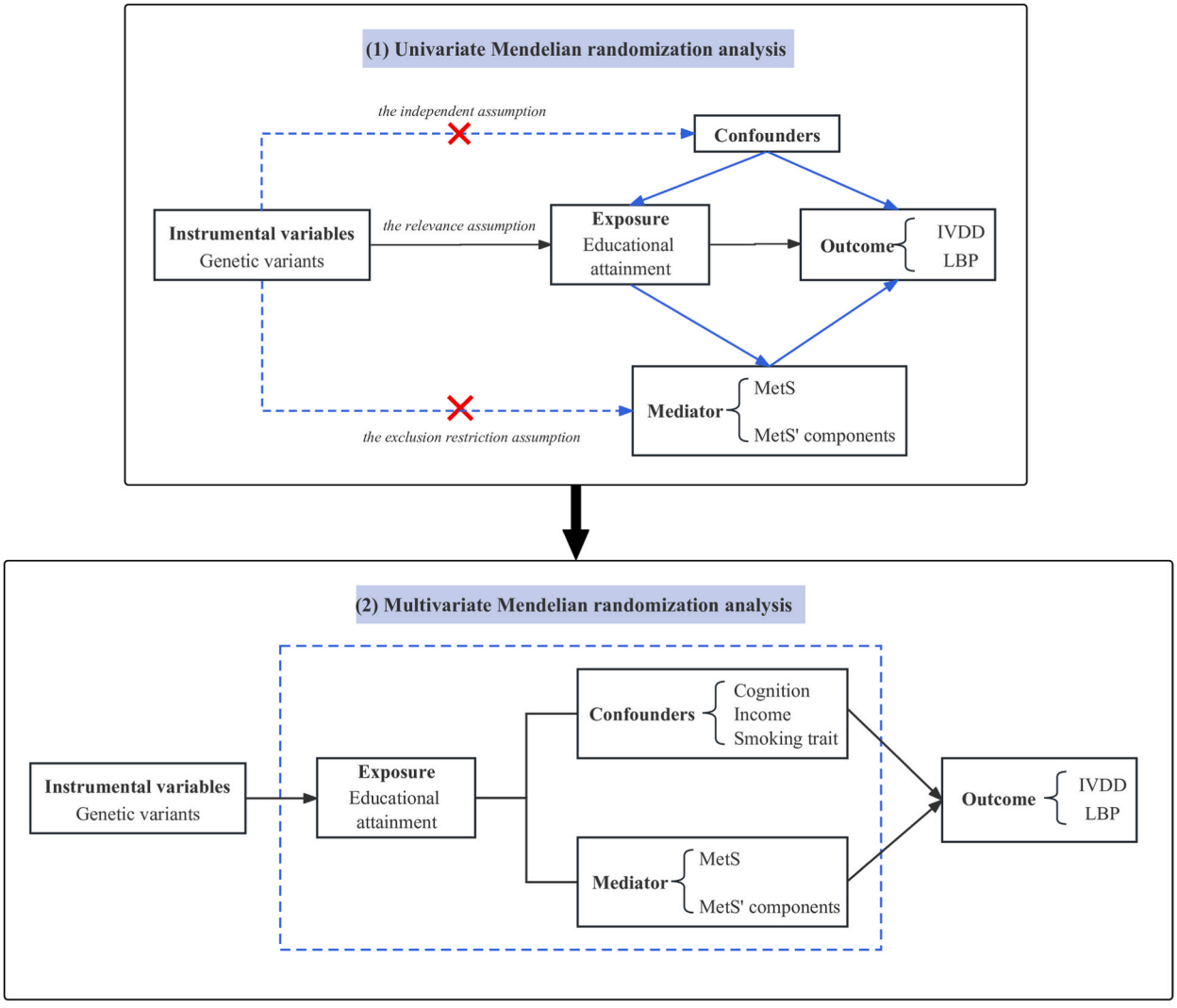


Fig. 1. Study design overview. IVDD, intervertebral disc degeneration; LBP, low back pain; MetS, metabolic syndrome.

2. Methods

2.1. Study design

MR analysis has three critical assumptions: (1) relevance assumption, in which the IVs should be strongly correlated with the exposure; (2) independence assumption, in which the IVs used should be independent of any potential confounders; and (3) exclusion–restriction assumption, in which the IVs should only affect the outcome through the exposure of interest [16]. Based on the rationale of two-sample MR, the causal relationship of EA with IVDD or LBP was identified, and mediation analyses were designed to assess whether this relationship could be mediated by MetS and MetS' components. A brief description of this MR design is given in Fig. 1.

2.2. Data sources of exposures, mediators, and outcomes

In this MR study, the data sources of exposures, mediators, and outcomes were derived from the summary-level data of genome-wide association studies (GWASs) conducted primarily in the individuals of European ancestry (Table 1). All GWASs datasets were obtained from public databases and had received ethical approval from respective institutions.

Cognition, economic income, and smoking behavior are genetically associated with EA and are potential confounders in the causal effects of EA on IVDD or LBP [21]. Genetic instruments for cognition were selected from a GWAS meta-analysis of a broadband index (g) or verbal-numerical reasoning scores in 257,841 individuals from the Cognitive Genomics Consortium and UK Biobank [22]. Regarding economic income, a categorical variable representing annual household income (less than £18,000, £18,000–30,999, £31,000–51,999, £52,000–100,000, or greater than £100,000) was obtained from the questionnaires established by the MRC-IEU (http://gwas.mrcieu.ac.uk/). Summary-level data for smoking-related phenotypes, including smoking initiation and cigarettes per day, were extracted from a recent GWAS meta-analysis [23]. Smoking initiation was defined as a binary phenotype for "current or former smoking" versus "never smoking", and cigarettes per day was a quasicontinuous variable defined as the number of cigarettes smoked per day for smokers.

MetS and its components were used as mediators in this study. Individuals who fulfilled at least 3 of the following 5 criteria were classified as having MetS: abdominal obesity, increased blood pressure, increased blood glucose, increased triglyceride levels, and decreased high-density lipoprotein cholesterol (HDL-C). The MetS data were obtained from the Complex Trait Genetics Lab (https://ctg.cncr.nl/software/summary_statistics), consisting of 461,902 valid subjects of European ancestry [24]. The GWAS summary statistics for five components of MetS (hypertension, fasting blood glucose [FBG], waist circumference [WC], triglycerides, and HDL-C) were derived from the IEU Open GWAS Project (http://gwas.mrcieu.ac.uk/).

LBP and IVDD were the outcomes of this MR study. The GWAS for IVDD (20001 cases and 164682 controls) and LBP (13178 cases and 164682 controls) were all from the FinnGen consortium (https://www.finngen.fi/en).

2.3. Selection of genetic instruments and data harmonization

For each MR analysis, all single nucleotide polymorphisms (SNPs) used as IVs were selected by the following criteria: (1) SNPs were significantly associated with the exposure of interest at a genome-wide significance ($P < 5 \times 10^{-8}$); (2) SNPs were set to near-independence using a linkage disequilibrium (LD) threshold of $r^2 < 0.001$ at a window size of 10,000 Kb [25]; (3) ambiguous and

Table 1
Summary of the GWAS Data Used in the Mendelian randomization analyses.

Phenotype	Sample size	Year of publication	Pubmed ID	GWAS ID
Exposure				
Educational attainment	461457	2018	29892013	ebi-a-GCST90029013
Confunders				
Cognition	257841	2018	30038396	NA
Income level	397751	2018	NA	ukb-b-740
Smoking initiation	249171	2019	30643251	ieu-b-4877
Cigarettes smoked per	143210	2019	30643251	ieu-b-4877
Mediators				
Metabolic syndrome	461902	2022	35983957	NA
Triglycerides	343992	2021	34594039	ebi-a-GCST90018975
HDL-cholesterol	403943	2020	32203549	ieu-b-109
Waist circumference	462166	2018	NA	ukb-b-9405
Fasting blood glucose	200622	2021	34059833	ebi-a-GCST90002232
Hypertension	484598	2021	33959723	ebi-a-GCST90038604
Outcomes				
intervertebral disc disorders	184683	2021	NA	finn-b-M13_INTERVERTEB
Low back pain	177860	2021	NA	finn-b-M13_LOWBACKPAIN

EA, defined as years of schooling quantified by the International Standard Classification of Education (ISCED) category, was used as exposure in this study. Genetic associations with EA were extracted from a GWAS of years of schooling in 461,457 individuals of European ancestry conducted by Loh PR et al. [20].

palindromic SNPs were excluded by harmonizing processes; and (4) SNPs containing pleiotropy as detected by MR-PRESSO were removed [26]. In addition, the F-statistic was calculated to quantify the strength of genetic tool for all SNPs by formula $F=R^2(N-k-1)/K(1-R^2)$, where R^2 is the proportion of explained variance, N is the sample size, and K is the number of SNPs [27]. The SNPs with an F value < 10 were considered weak IVs [28].

2.4. Univariable mendelian analysis

As recommended by Burgess et al. [29], inverse-variance weighted (IVW) analysis with random effects was employed as the primary analysis method, because it efficiently combines the Wald ratio estimates of each SNP into 1 causal estimate for each exposure and accounts for the heterogeneity of individual variants in the causal estimates [29,30]. The IVW approach provides the most precise estimates but ignores the invalid IVs and pleiotropic effects. Therefore, we used four complementary methods including MR–Egger, weighted median (WM), simple mode, and weighted mode to evaluate the robustness of effects. The MR–Egger approach based on the assumption of Instrument Strength Independent of Direct Effect (InSIDE) can identify and adjust for the directional pleiotropic effect but suffers from underpower [31]. The WM stipulates that at least 50 % of the weight in the analysis comes from valid IVs, while the weighted mode requires a plurality of variants which identify the same causal effect to be valid instruments [32]. The simple mode assumes that the most common causal effect is consistent with the true causal effect, allowing some instruments to be invalid without biasing the estimated causal effect [33]. Moreover, to avoid the possibility of reverse causation, we additionally estimated each of these causal effects in the direction opposite using bidirectional MR [34].

2.5. Multivariable Mendelian analysis

As an extension of UVMR, the MVMR can jointly estimate the causal effects of various risk factors on outcome risk by incorporating all exposures within the same model [35]. Accounting for strong genetic correlation between EA and cognition, economic income, or smoking traits [21], the MVMR was adopted to assess the direct effect of EA on IVDD or LBP that is not affected by other confounders. Significant SNPs ($P < 5 \times 10^{-8}$) were extracted from the relevant GWASs, and the IVs of all included exposures were integrated. After excluding the duplicate SNPs, the effects and corresponding standard errors were obtained for each SNP from the exposures and outcomes [36]. Both the weighted linear regression based IVW and MR-Egger approaches were applied to infer causal effects in MVMR analysis.

2.6. Mediation analysis

The formula and process of the mediation analysis are described in Fig. 2. The β value of IVW method was used for the mediation analysis. Mediation effect M was calculated using the formula: $M = \beta 1 \times \beta 4$, and the proportion of the mediating effect was calculated by the formula: $P(M) = \frac{M}{\beta 3} \times 100\%$. The corresponding 95 % CI of the mediation effect was calculated using the following formula: 95% $CI = e^{M \pm 1.96\ SE(M)}$, where SE(M) represents the standard error of the mediation effect and was calculated as: $SE(M) = M \times \sqrt{\left(\frac{SE_{\beta 1}}{\beta 1}\right)^2 + \left(\frac{SE_{\beta 4}}{\beta 4}\right)^2}$.

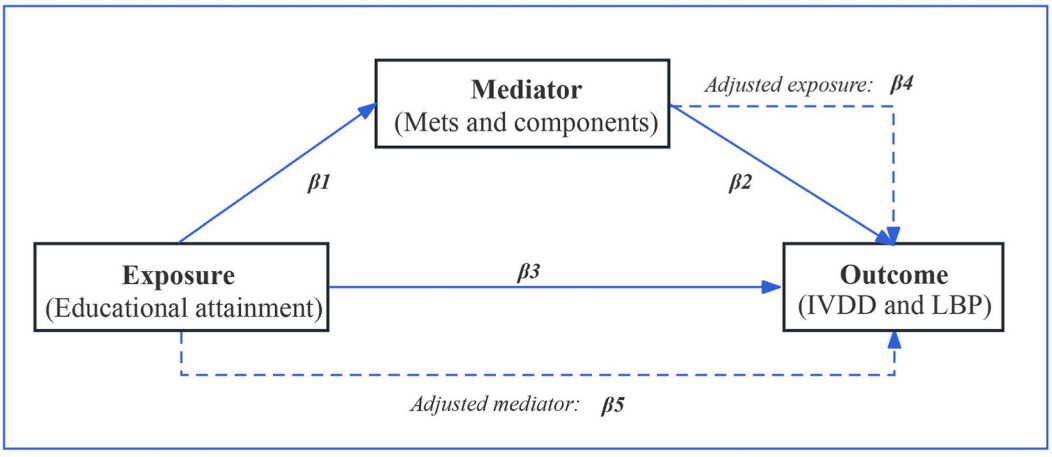


Fig. 2. Mediation analysis. β1, the causal effect of the exposure on the mediator in UVMR analysis; β2, the causal effect of the mediator on the outcome in UVMR analysis; β3, the total causal effect of the exposure on the outcome in UVMR analysis; β4, the causal effect of the mediator on the outcome after adjusted for exposure in MVMR analysis; β5, the causal effect of the exposure on the outcome after adjusted for mediator in MVMR analysis.

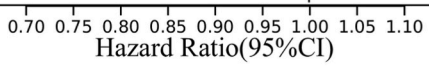
2.7. Sensitivity analysis

For sensitivity analysis, five approaches of heterogeneity test, MR-Egger test, funnel plot, MR pleiotropy residual sum and outlier (MR-PRESSO) test, and leave-one-out method were employed. Cochrane's Q-test was used to test for heterogeneity, and Q P value $<$ 0.05 was considered as indicative of heterogeneity [37]. The intercept in MR-Egger regression depicts the average pleiotropic effect

A

EA on IVDD

Method	SNPs	OR(95%CI)	P value
UVMR			
MR Egger	202	0.95 (0.85-1.08)	4.51E-01
Weighted median	202	0.89 (0.86-0.93)	2.01E-09
IVW	202	0.90 (0.87-0.92)	5.29E-15
Simple mode	202	0.82 (0.72-0.94)	3.85E-03
Weighted mode	202	0.81 (0.71-0.93)	2.85E-03
MVMR			
Adjused for Cognition	169	0.91 (0.87-0.96)	1.08E-04
Adjused for Income	198	0.90 (0.86-0.95)	1.79E-04
Adjused for Cigarettes per Day	4	0.84 (0.73-0.98)	2.80E-02
Adjused for Smoking Initiation	17	0.89 (0.83-0.95)	5.48E-04



B

EA on LBP

Method	SNPs	OR(95%CI)	P value
UVMR			
MR Egger	202	0.88 (0.77-1.01)	6.27E-02
Weighted median	202	0.87 (0.84-0.91)	2.05E-10
IVW	202	0.86 (0.84-0.89)	1.22E-21
Simple mode	202	0.87 (0.76-1.00)	4.96E-02
Weighted mode	202	0.89 (0.78-1.01)	8.37E-02
MVMR			
Adjused for Cognition	168	0.89 (0.85-0.94)	5.32E-06
Adjused for Income	198	0.85 (0.80-0.91)	2.52E-07
Adjused for Cigarettes per Day	4	0.78 (0.68-0.90)	4.81E-04
Adjused for Smoking Initiation	17	0.85 (0.80-0.91)	5.82E-06

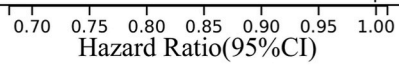


Fig. 3. UVMR and MVMR analyses for the causal associations of genetically predicted EA with IVDD and LBP. (A) EA on IVDD; (B) EA on LBP. EA, educational attainment; IVDD, intervertebral disc degeneration; LBP, low back pain; OR, odds ratio; CI, confidence interval; UVMR, univariable Mendelian randomization; MVMR, multivariable Mendelian randomization; IVW, inverse variance weighted method.

across the IVs. So that if the MR−Egger intercept term was statistically significant (P value < 0.05), there is evidence of pleiotropy [31]. By visual inference of the funnel plot, asymmetry can also be recognized as an indicator of horizontal pleiotropy [38]. MR-PRESSO test was applied to identify and correct for outliers in IVW linear regression [26]. To determine the impact of a single SNP on the causal association, "leave-one-out" analysis was used to eliminate each SNP in turn.

2.8. Statistical analysis

UVMR analysis was conducted using the package "Two Sample MR" in R (version 4.2.0). MVMR was performed using the "MendelianRandomization," "MRPRESSO," "MVMR," and "TwoSampleMR" R packages. In MR analysis, P < 0.05 indicated a significant causal relationship between exposure and outcome.

3. Results

3.1. Inverse association of genetically predicted EA with IVDD and LBP

According to the genetic instrument selection criteria, 202 SNPs were chosen as genetic instruments for EA after excluding 9 palindromic SNPs. The F-statistic values for each individual IVs were all above the threshold 10 (Tables S1–S2) (Supplementary Tables S1–S2). In UVMR analysis, the results of primary IVW method indicated that each standard deviation (SD) increase in genetically predicted EA was associated with a 10 % reduction in odds of IVDD (OR_{IVW}: 0.90, 95 % CI: 0.87–0.92, $P = 5.29E\text{-}15$). Other complementary methods also showed an inverse association between EA and IVDD in addition to the MR-Egger analysis (Fig. 3A). Meanwhile, IVW, WM, and simple mode analyses also revealed a negative causal relationship between EA and LBP (OR_{IVW}: 0.86, 95 % CI: 0.84–0.89, $P = 1.22E\text{-}21$; OR_{WM}: 0.87, 95 % CI: 0.84–0.91, $P = 2.05E\text{-}10$; $OR_{simple\ mode}$: 0.87, 95 % CI: 0.76–1.00, $P = 0.049$) (Fig. 3B). For sensitivity analysis, genetic IVs of EA showed persistent heterogeneity (Q P-value <0.05), but no outliers were detected by the MR-PRESSO test and no horizontal pleiotropy was observed using the MR−Egger test ($P_{intercept} > 0.05$) (Supplementary

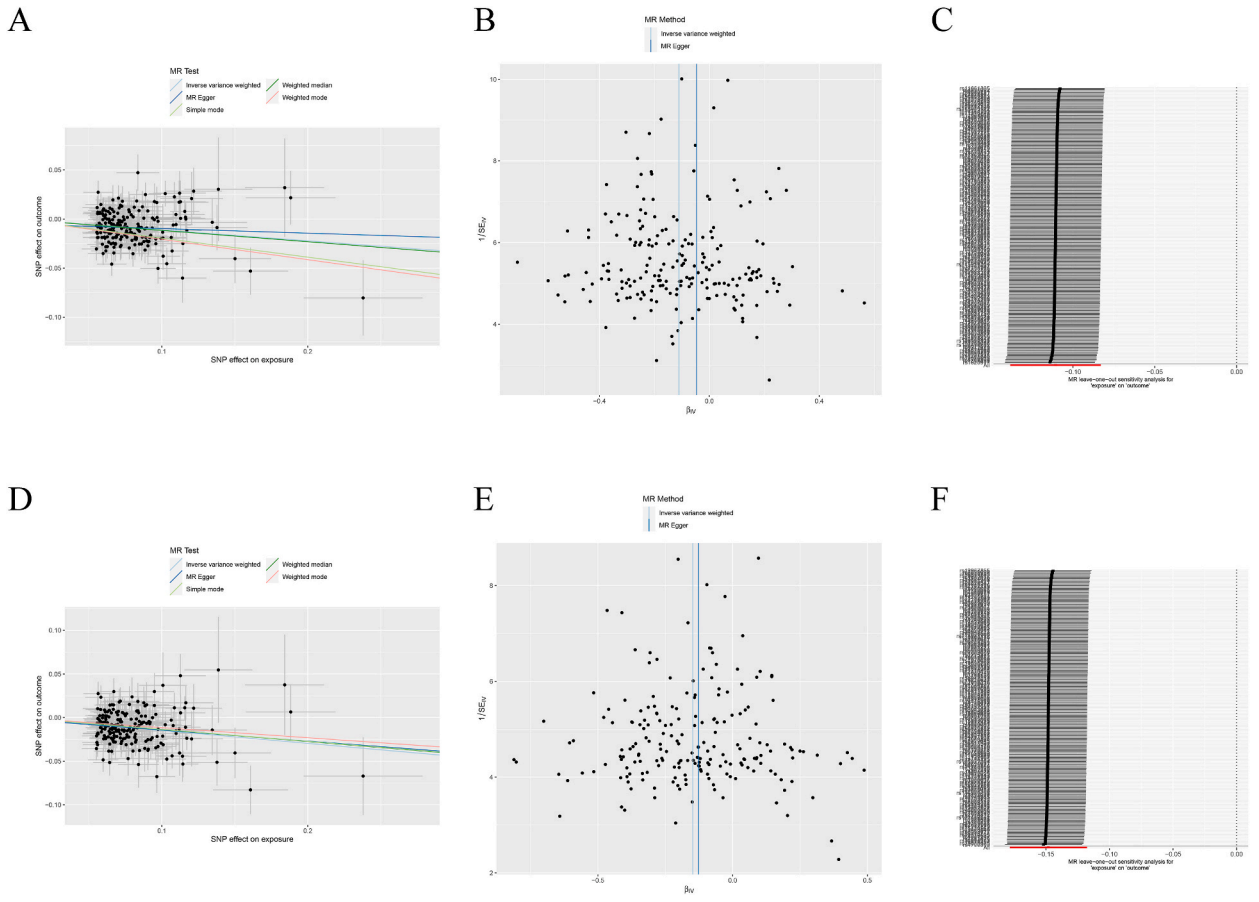


Fig. 4. Scatter plots, funnel plot, and leave-one-out plot for the associations of genetically predicted EA with IVDD and LBP in the UVMR analysis. (A, B, C) EA on IVDD; (D, E, F) EA on LBP. UVMR, univariable Mendelian randomization; EA, educational attainment; IVDD, intervertebral disc degeneration; LBP, low back pain.

Table S3). Additionally, the fitting results of five analysis methods have the same trend in scatter plot, and no asymmetry was detected in the funnel plot and no distortion was observed in the leave-one-out plot (Fig. 4A–F).

In the MVMR analyses, a causal association between EA and IVDD persisted even after adjusting for cognition (OR_{IVW}: 0.91, 95 % CI: 0.87–0.96, $P = 1.08E-04$), economic income (OR_{IVW}: 0.90, 95 % CI: 0.86–0.95, $P = 1.79E-04$), cigarettes per day (OR_{IVW}: 0.84, 95 % CI: 0.73–0.98, $P = 2.80E-02$), or smoking initiation (OR_{IVW}: 0.89, 95 % CI: 0.83–0.95, $P = 5.48E-04$) (Fig. 3A). Similarly, the causal association of EA with LBP was also statistically significant with adjustment for cognition (OR_{IVW}: 0.89, 95 % CI: 0.85–0.94, $P = 5.32E-06$), economic income (OR_{IVW}: 0.85, 95 % CI: 0.80–0.91, $P = 2.52E-07$), cigarettes per day (OR_{IVW}: 0.78, 95 % CI: 0.68–0.90, $P = 4.81E-04$), or smoking initiation (OR_{IVW}: 0.85, 95 % CI: 0.80–0.91, $P = 5.82E-06$) (Fig. 3B). Most of the statistical significance of IVW results in MVMR were consistent with those of MVMR Egger sensitivity analyses, indicating a low risk of bias attributed to horizontal pleiotropy (Supplementary Table S4).

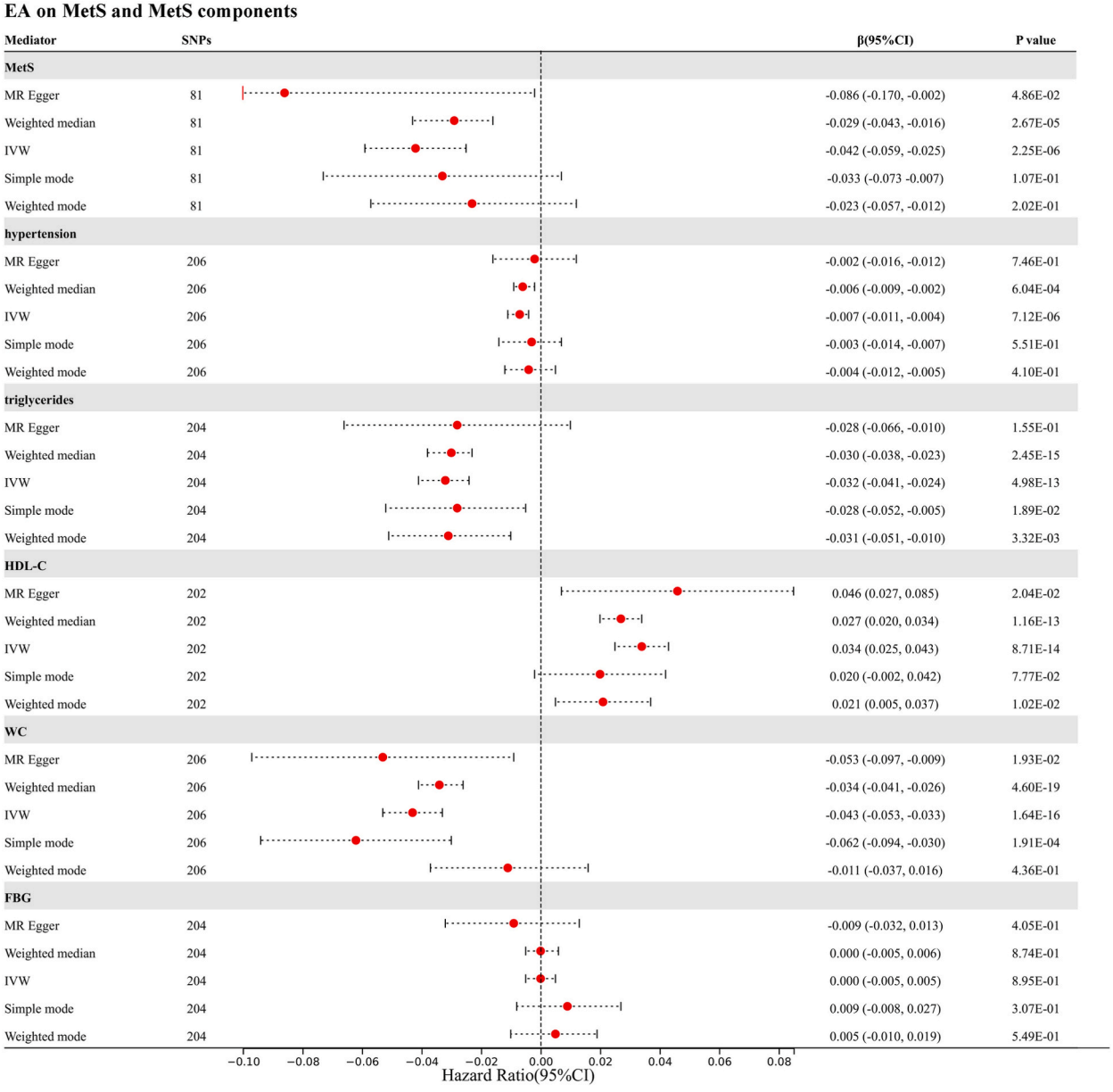


Fig. 5. UVMR assess the causal effects of EA on MetS and the component of MetS. EA, educational attainment; MetS, metabolic syndrome; HDL-C, high-density lipoprotein cholesterol; WC, waist circumference; FBG, fasting blood glucose; OR, odds ratio; CI, confidence interval.

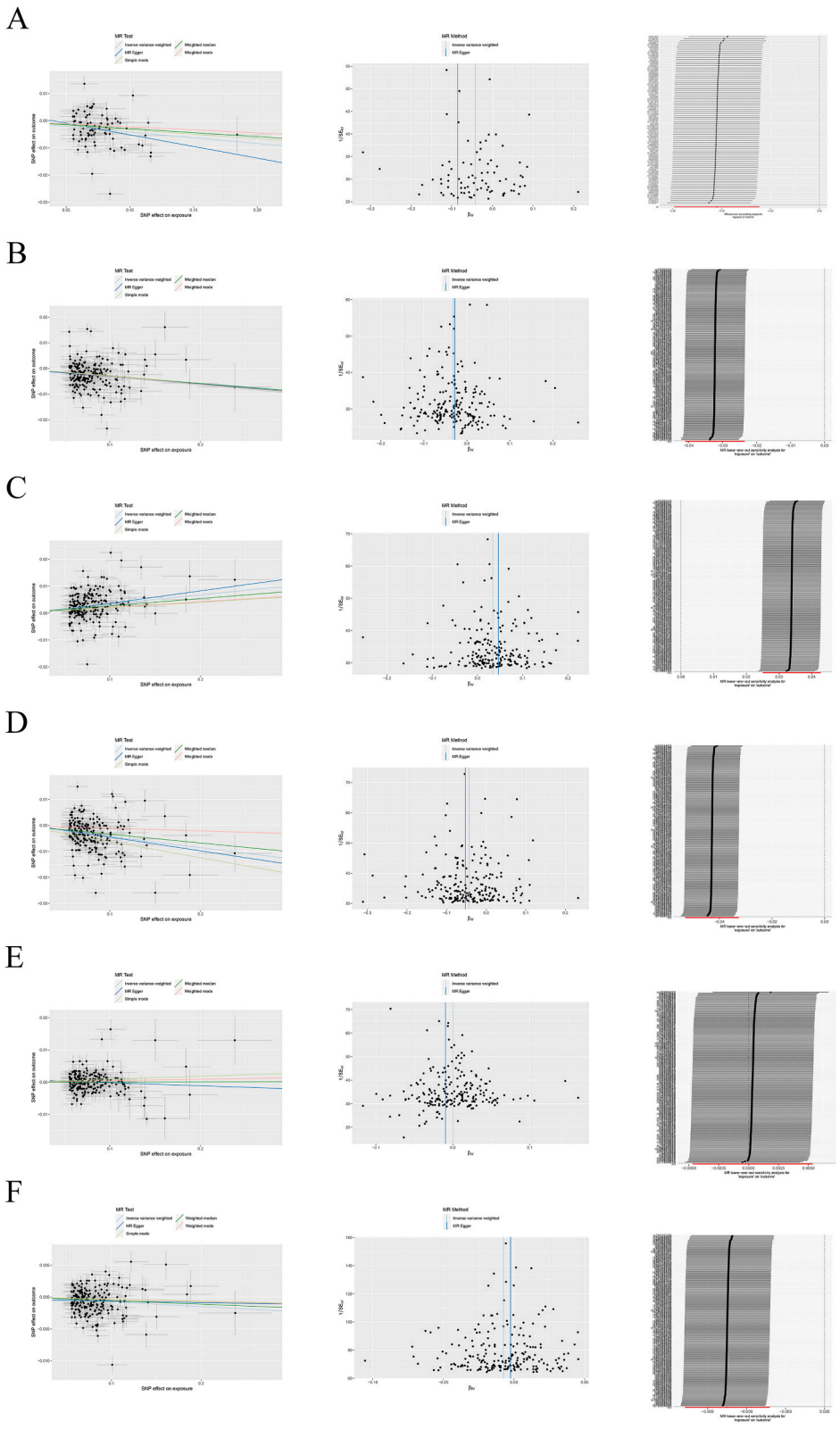


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Fig. 6. Scatter plots, funnel plot, and leave-one-out plot for the associations of genetically predicted EA with MetS and MetS′ component in the UVMR analysis. (A) EA on MetS; (B) EA on triglyceride; (C) EA on HDL-CUVMR; (D) EA on WC; (E) EA on FBG; (F) EA on hypertension. UVMR, univariable Mendelian randomization; EA, educational attainment; MetS, metabolic syndrome; HDL-C, high-density lipoprotein cholesterol; WC, waist circumference; FBG, fasting blood glucose.

3.2. Association of genetically predicted EA with MetS and MetS components

Two-sample UVMR analysis was conducted to investigate the causal effects of EA on MetS and MetS' components. In the analyses of MetS, hypertension, triglycerides, HDL-C, WC, and FBG, 81, 206, 204, 202, 206, and 204 independent SNPs were selected as IVs for EA after removing palindromic SNPs, respectively (Supplementary Table S5). All F-statistic values for individual IVs were all above the threshold 10, which suggested strong instrument variables (Supplementary Table S5). The IVW results demonstrated that genetically predicted EA was associated with a reduced risk of MetS (β_{IVW}: −0.042, 95 % CI: −0.059,-0.025, P = 2.25E-06), lower risk of hypertension (β_{IVW}: −0.007, 95 % CI: −0.011,-0.004, P = 7.12E-06), lower triglycerides (β_{IVW}: −0.032, 95 % CI: −0.014, −0.024, P = 4.98E-13), higher HDL-C (β_{IVW}: 0.034, 95 % CI: 0.025, 0.043, P = 8.71E-14), and lower WC (β_{IVW}: −0.043, 95 % CI: −0.053, −0.033, P = 1.64E-16), but no causal association between EA and FBG (P = 0.89) (Fig. 5). The consistency of these IVW estimates was confirmed

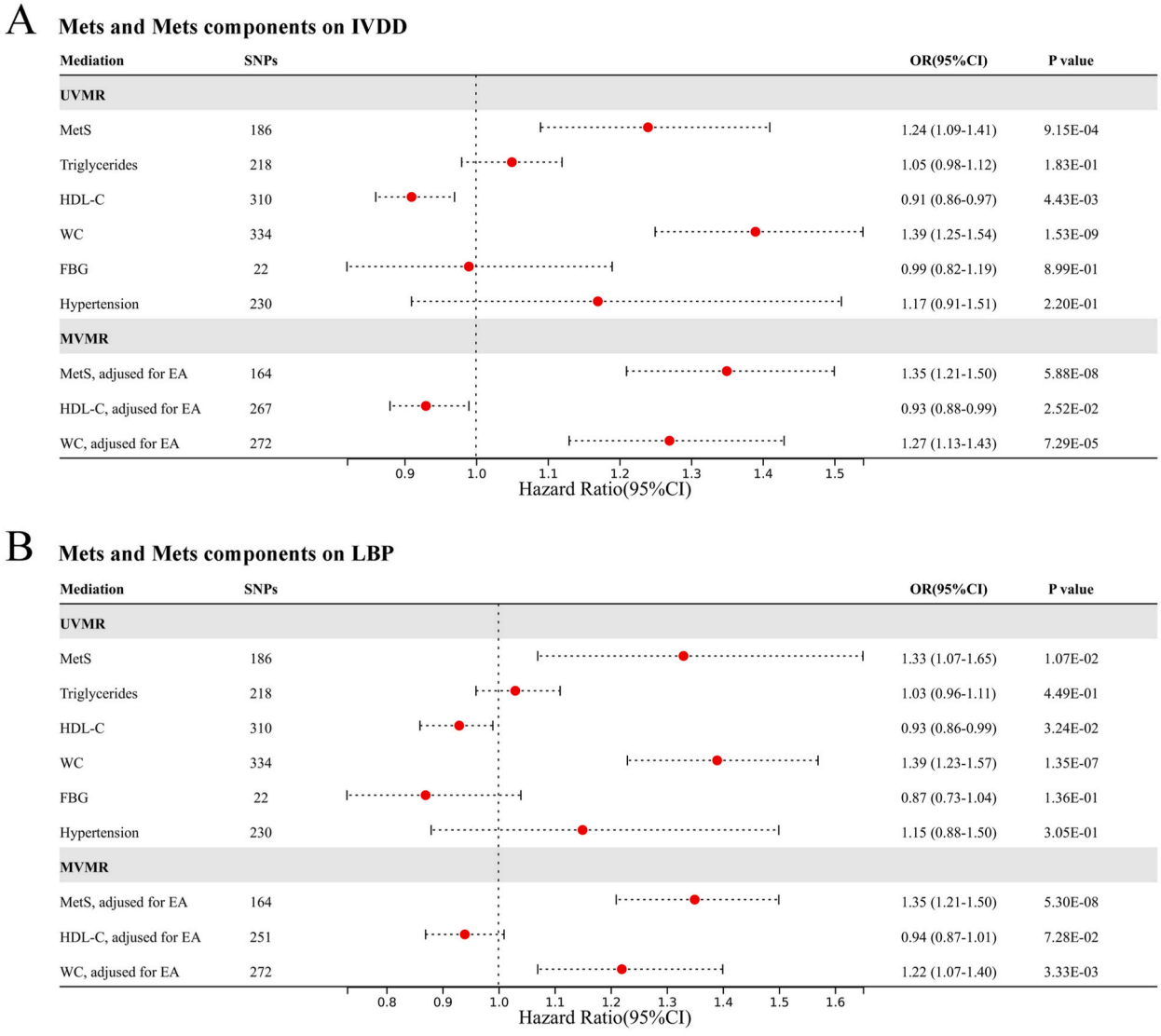

Fig. 7. UVMR and MVMR analyses for the causal associations of MetS and MetS′ components with IVDD and LBP. (A) MetS and MetS′ components on IVDD. (B) MetS and MetS′ components on LBP. UVMR, univariable Mendelian randomization; MVMR, multivariable Mendelian randomization; IVW, inverse variance weighted method; OR, odds ratio; CI, confidence interval; EA, educational attainment; IVDD, intervertebral disc degeneration; LBP, low back pain; MetS, metabolic syndrome; HDL-C, high-density lipoprotein cholesterol; WC, waist circumference; FBG, fasting blood glucose.

by at least 2 or 3 complementary methods. In bidirectional MR analyses, the causal associations of MetS or its components with EA were primarily driven by horizontal pleiotropy ($P_{intercept}$ <0.05) (Supplementary Table S7).

In the sensitivity analysis comparing EA with MetS or MetS' components, most analyses revealed significant heterogeneity in the variant-specific causal estimates (Q *P*-value <0.05), but MR-Egger intercept test did not detect any evidence of horizontal pleiotropy in any of MR analyses ($P_{intercept} > 0.05$) (Supplementary Table S6). Furthermore, the fitting results of five analysis methods have the same trend in scatter plot, symmetry was detected in the funnel plots, and none of the leave-one-out plots displayed distortion (Fig. 6A–F).

3.3. Effects of MetS and MetS components on IVDD and LBP with or without adjustment for EA

In the UVMR analysis of MetS and its components to IVDD, the detailed IVs for MetS, hypertension, FBG, WC, triglyceride, and HDL-C were shown in Supplementary Table S8. The IVW results indicated significant causal associations of MetS (OR_{IVW}: 1.24, 95 % CI: 1.09–1.41, $P = 9.15E-04$), HDL-C (OR_{IVW}: 0.91, 95 % CI: 0.86–0.97, $P = 4.43E-03$), and WC (OR_{IVW}: 1.39, 95 % CI: 1.25–1.54, $P = 1.53E-09$) with the risk of IVDD, but no causal associations were found between hypertension, FBG, and triglyceride with IVDD ($P_{IVW} > 0.05$) (Fig. 7A). Furthermore, the causal associations of MetS (OR_{IVW}: 1.35, 95 % CI: 1.21–1.50, $P = 5.88E-08$), HDL-C (OR_{IVW}: 0.93, 95 % CI: 0.88–0.99, $P = 2.52E-02$), and WC (OR_{IVW}: 1.27, 95 % CI: 1.13–1.43, $P = 7.29E-05$) with IVDD remained after adjusting for EA in MVMR analyses (Fig. 7A). The robustness of IVW results was tested by the complementary methods, and no horizontal pleiotropy was detected in sensitivity analyses (Supplementary Table S10 and Table S12).

In the UVMR analysis of MetS and MetS' components to LBP, the detailed IVs for MetS, hypertension, FBG, WC, triglyceride, and HDL-C are shown in Supplementary Table S9. The primary IVW method of UVMR analysis provided evidence that MetS (OR_{IVW}: 1.33, 95 % CI: 1.07–1.65, $P = 1.07E-02$), HDL-C (OR_{IVW}: 0.93, 95 % CI: 0.86–0.99, $P = 3.24E-02$), and WC (OR_{IVW}: 1.39, 95 % CI: 1.23–1.57, $P = 1.35E-07$) were causally associated with the risk of LBP, but no causal associations of hypertension, FBG, and triglyceride with LBP ($P_{IVW} > 0.05$) (Fig. 7B). In MVMR analysis, only MetS (OR_{IVW}: 1.35, 95 % CI: 1.21–1.50, $P = 5.30E-08$) and WC (OR_{IVW}: 1.22, 95 % CI: 1.07–1.40, $P = 3.33E-03$) had independent causal effects on LBP, while the causal association between HDL-C and LBP ($P_{IVW} = 0.07$) was no longer statistically significant after correcting for EA (Fig. 7B). Furthermore, no horizontal pleiotropy was detected in MR-Egger intercept tests for any of the MR analyses (Supplementary Table S10 and Table S12).

3.4. Mediation analysis

If MetS or MetS′ components play the mediating role in the causal effects of EA on IVDD and LBP, the following criteria should be met: (1) there were causal effects of EA on IVDD and LBP; (2) there were causal effects of EA on MetS and MetS' components, with the effects being unidirectional; and (3) the causal association consistently exists between the MetS and IVDD (or LBP) with or without adjustment for EA. The findings from the network analysis indicate that MetS, WC, and HDL-C may act as mediators in the impact of EA on IVDD, while MetS and WC may mediate the causal relationship between EA and LBP.

The results of Mediation analysis showed that the proportion of the causal effects of EA on IVDD mediated by MetS, HDL-C, and WC were 11.38 % (95 % CI: 5.12%–17.63 %), 2.17 % ((95 % CI: 0.19%–4.15 %), and 9.22 % (95 % CI: 4.17%–14.28 %), respectively (Table 2). Additionally, the mediating proportion of MetS and WC in the relationship between EA and LBP was 8.42 % (95 % CI: 3.78%–14.05 %) and 5.81 % (95 % CI: 1.69%–9.92 %), respectively (Table 2).

4. Discussion

This MR Study with mediation analyses provides new evidence for the causal associations of EA with IVDD and LBP, and assesses the mediating effects of MetS and each component of MetS in these associations. Our findings suggested that a high level of EA was associated with a reduced risk of IVDD or LBP, independent of the effects of cognition, economic income, and smoking behavior. Additionally, we found that the protective effects of EA on IVDD and LBP mediated by MetS were slight (only about 10 %). of which, HDL-C and WC respectively mediated 2.17 % and 9.22 % in the association between EA and IVDD, and WC mediated 5.81 % in the pathway from EA to LBP.

Table 2
Mediation effect of MetS and MetS' components in the association of EA with IVDD and LBP.

Exposure	Outcome	Mediator	Mediation effect (95 % CI)	Mediation proportion (95 % CI)
EA	IVDD	MetS	−0.013 (−0.006, −0.020)	11.38 % (5.12%–17.63 %)
		HDL-C	−0.002 (−0.000, −0.005)	2.17 % (0.19%–4.15 %)
		WC	−0.262 (−0.141, −0.383)	9.22 % (4.17%–14.28 %)
	LBP	MetS	−0.012 (−0.006, −0.019)	8.42 % (3.78%–14.05 %)
		WC	−0.008 (−0.002, −0.014)	5.81 % (1.69%–9.92 %)

IVDD, intervertebral disc degeneration; LBP, low back pain; EA, educational attainment; MetS, metabolic syndrome; HDL-C, high-density lipoprotein cholesterol; WC, waist circumference.

4.1. Effect of EA on the risk of IVDD and LBP

The results of our study support the protective causal effect of education on IVDD and LBP, which is consistent with previous MR studies and systematic reviews [39–41]. However, a cross-sectional study of 2,876 Chinese Army soldiers found no correlation between EA and LBP [42], while some studies suggested that the protective effect of EA on LBP may be influenced by gender [43]. The conflicting evidence in these observational studies could be attributed to differences in ethnicity or the control of confounding variables. Education level, cognition, economic income, and smoking behaviors are intricately linked and cannot be separated, supported by robust genetic evidence from previous GWAS and MR studies [21,44]. Our findings extended previous studies by adjusting for confounders including cognition, income, smoking traits, and metabolic factors, we then identified higher EA as an independent protective contributor to IVDD and LBP. By focusing on EA as the main variable of interest, we highlight its potential as a modifiable factor that significantly influences the development of healthy habits throughout an individual's lifespan [45]. Therefore, our results suggest that emphasizing educational policies and determining the duration of mandatory schooling could be effective strategies for the primary prevention of IVDD and LBP at a population level.

4.2. MetS on the risk of IVDD and LBP

A Wakayama Spine Study manifested that MetS was strongly associated with an increased risk of IVDD in the cervical, thoracic, and lumbar vertebrae, and that the accumulation of MetS' components significantly increased the risk of IVDD [10]. In line, our MR study revealed that genetically predicted MetS was causally associated with IVDD or LBP, and this causal association partially mediates the protective effect of education on IVDD and LBP. As we know, MetS may increase the risk of cardiovascular events, because the accumulation of MetS components induces the development of atherosclerosis [46,47]. This could lead to a lack of nutrient supply to disc cells, resulting in gradual disc degeneration in MetS patients [48,49]. Moreover, growing evidence suggests that MetS triggers chronic inflammation and oxidative stress throughout the body, ultimately leading to nucleus pulposus cell death, extracellular matrix degradation, fibrosis, and IVDD [50]. Notably, the mediated effect of MetS is relatively slight in the pathway from EA to IVDD and LBP, suggesting that there may be other significant factors influencing the protective effect of EA on IVDD and LBP.

In terms of a single component of MetS, traditional observational studies have consistently found a strong relationship between abdominal obesity and increased risk of IVDD and LBP [51–54]. Strong genetic evidence from this study and previous MR studies also supports an adverse association of abdominal obesity with IVDD and LBP. The causal relationship between lipid metabolism and IVDD or LBP remains unclear, although two Chinese observational studies have shown that high levels of cholesterol, LDL cholesterol, and triglycerides are independent risk factors for IVDD [55,56]. Our study is the first to discover a causal link between high HDL-C levels and a reduced risk of IVDD and LBP, but did not find a causal effect of triglycerides on IVDD or LBP.

Surprisingly, even though compelling observational studies demonstrated that diabetes is an important factor in IVDD and LBP, our findings had no causal associations of genetically determined FBG with IVDD and LBP [57,58]. It is important to note that our study defined diabetes using FBG, which only reflects short-term blood sugar levels. In contrast, fasting insulin and HbA1c can reflect pancreatic function and an average change in glucose levels over a longer time, suggesting that further studies are required to prove the causal associations of various glucose characteristics with IVDD and LBP. The current literature presents conflicting views on the impact of hypertension on IVDD or LBP, with observational studies yielding inconsistent results [59–61]. In our UVMR analyses, hypertension manifested no causal effect on IVDD or LBP, part of which is in line with the causal associations reported by an MR analysis between modifiable risk factors and IVDD [12]. This suggests that significant associations observed in observational studies may be influenced by residual confounding or reverse causation bias.

4.3. Strengths and limitations

To the best of our knowledge, this is the first MR study to elucidate the independent causal effects of EA on IVDD and LBP and to evaluate the mediating effects of MetS and each component of MetS in the pathway from EA to IVDD and LBP. This work has several strengths. First, this design is much less likely to be affected by the confounders and reverse causation than traditional observational studies because the alleles have random allocation and are static throughout the life of an individual [62,63]. Second, UVMR was used to study the linear link between exposure and outcome, as well as MVMR analysis were used to examine potential nonlinear correlations.

However, this study has some limitations. First, MR Estimates are susceptible to horizontal pleiotropy, and to control for the confounders associated with genetic variants that bias the main results, we adjusted for potential confounders to minimize the effect of horizontal pleiotropy. Second, the association of EA with IVDD or LBP may be mediated by specific genetic variation and many factors, and our study could not completely avoid these interferences. Third, the data of IVDD and LBP used in this study were from public databases; a subgroup analysis of specific factors, such as gender, age, and occupation, could not be conducted. Fourth, as the majority of GWASs used in the analyses were restricted to European populations, our results should be cautiously generalized to other populations.

5. Conclusion

Our MR study elaborated on the causal protective impact of EA on the risk of IVDD and LBP, independently of cognition, economics, and smoking behavior. MetS and its componenets (abdominal obesity and HDL-C) might be involved in the mechanism of EA reducing

the risk of IVDD and LBP. This study adds causal evidence to the etiology of IVDD and LBP, and informs prevention and intervention targets for IVDD and LBP.

Data availability

All GWAS data analyzed in this study were available in the IEU open GWAS project (https://gwas.mrcieu.ac.uk/), except for the GWAS data of metabolic syndrome that was obtained from the Complex Trait Genetics Lab (https://ctg.cncr.nl/software/summary_statistics).

CRediT authorship contribution statement

Xijie Tang: Writing – review & editing, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Qiu Li:** Writing – original draft, Validation, Methodology, Investigation, Data curation, Conceptualization. **Zhang-Hua Li:** Writing – review & editing, Validation, Supervision.

Declaration of competing interest

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

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Appendix A. Supplementary data

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