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Association between lipid-lowering agents with intervertebral disc degeneration, sciatica and low back pain: a drug-targeted mendelian randomized study and cross-sectional observation

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Abstract

Background Abnormal lipid metabolism is linked to intervertebral disc degeneration (IVDD), sciatica, and low back pain (LBP), but it remains unclear whether targeted interventions can prevent these issues. This study investigated the causal effects of lipid-lowering drug use on IVDD, sciatica, and LBP development.

Methods Single-nucleotide polymorphisms (SNPs) linked to total cholesterol (TC), low-density-lipoprotein cholesterol (LDL-C), and non-high-density-lipoprotein cholesterol (non-HDL-C) were obtained from the Global Lipids Genetics Consortium's genome-wide association study (GWAS). Genes near HMGCR, PCSK9, and NPC1L1 were selected to represent therapeutic inhibition targets. Using Mendelian randomization (MR) focusing on these drug targets, we identified causal effects of PCSK9, HMGCR, and NPC1L1 on the risk of developing IVDD, sciatica, and LBP, with coronary heart disease risk serving as a positive control. Using summary data from Mendelian randomization (SMR) analysis, we evaluated potential therapeutic targets for IVDD, sciatica, and LBP through protein quantitative trait loci (pQTL). The genetic associations with IVDD, sciatica, LBP, and coronary heart disease were derived from FinnGen (discovery) and UK Biobank (replication). Additionally, a cross-sectional observational study was performed using data from the National Health and Nutrition Examination Survey (NHANES) to further investigate the connection between LBP and statin use, with a sample size of 4343 participants. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated to assess the outcomes.

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Results The NHANES-based cross-sectional study indicated that non-statin use was associated with an increased risk of developing LBP (OR = 1.29, 95% CI [1.04, 1.59], *P* = 0.019). Moreover, Inverse-variance weighting (IVW) analysis revealed that NPC1L1-mediated reductions in TC, LDL-C, and non-HDL-C concentrations were associated with a decreased risk of developing IVDD (*P* = 9.956E-03; *P* = 3.516E-02; *P* = 1.253E-04). Similarly, PCSK9-mediated reductions in LDL-C and TC concentrations were linked to a lower risk of developing sciatica (*P* = 3.825E-02; *P* = 2.709E-02). Sensitivity analysis confirmed the stability and reliability of the MR results. MST1 (macrophage stimulating 1) levels was inversely associated with IVDD, sciatica, and LBP risks.

Conclusion The results of cross-sectional study suggested that non-use of statins was positively correlated with LBP. The results of Mendelian randomization study suggest that NPC1L1 could lower the risk of developing IVDD by reducing TC, LDL-C, and non-HDL-C levels. Additionally, PCSK9 may reduce the risk of developing sciatica by lowering LDL-C and TC levels. In contrast, HMGCR appears to have no significant effect on IVDD, sciatica, or LBP development. Nonetheless, further research is needed to verify these preliminary results. MST1 warrants further exploration as a potential therapeutic target. It is necessary to do further research to validate these findings.

Keywords Lipid-lowering drugs, Sciatica, Intervertebral disc disorders, Low back pain, Mendelian randomization, Observational study

Introduction

Intervertebral disc degeneration (IVDD) is a common degenerative condition characterized by a reduction in water and proteoglycan contents in the nucleus pulposus. This degeneration often leads to the rupture of intervertebral discs, potentially causing disc herniation or spinal stenosis [1, 2]. Clinically, IVDD is frequently associated with sciatica and low back pain (LBP), which can progress to radiculopathy and myelopathy [3, 4]. Sciatica, a common manifestation of IVDD, causes severe pain along the course of the sciatic nerve, typically affecting the thighs and buttocks. In severe cases, sciatica also includes back pain and neurological dysfunction [5, 6]. Approximately 85% of sciatica cases are related to IVDD, and statistical data indicate that one in three individuals may experience sciatica at some point in their life [7–10]. LBP is a prevalent orthopaedic condition characterized by discomfort between the hip crease and the lower ribs. While LBP is not exclusive to any specific ailment, it is closely linked to poor trunk muscle strength, coordination deficits, and proprioceptive issues. These factors can exacerbate lumbar instability, increasing the risk of developing spinal injury and undermining physical activity [11]. In severe cases, the cross-sectional area of the muscles around the vertebral body is usually reduced, further exacerbating the pain and leaving the patient vulnerable to additional injury and recurrent attacks [12]. These conditions significantly impact patients' quality of life and pose substantial financial burdens due to high disability rates [13]. Therefore, further research on the potential risk factors for IVDD, sciatica, and LBP is essential to reduce the burden of these diseases and improve patient outcomes.

Dyslipidaemia has been suggested to contribute to the development of various diseases and pathological conditions, including cancer, type 2 diabetes, and osteoarthritis [14]. An in-depth analysis of risk and lifestyle factors among patients with lumbar degenerative diseases revealed that higher levels of low-density lipoprotein cholesterol (LDL-C) (odds ratio (OR) = 1.46–2.65) and triglycerides (TGs) (OR = 2.97–8.49) are associated with an increased risk of disc herniation [15]. The connections between dyslipidaemia and the risk of developing IVDD, sciatica, and LBP are thought to stem from abnormal lipid metabolism. This abnormality may contribute to atherosclerosis, which in turn reduces the blood supply to the lumbar spine region [16, 17]. Recent animal studies have demonstrated that cholesterol, through the stimulation of mSREBP1 in IVDD, can activate endoplasmic reticulum stress, a process that subsequently induces myeloid cell pyroptosis and extracellular matrix degradation [18]. Moreover, lipid-lowering drugs such as rosuvastatin or atorvastatin can alleviate degenerative changes in patients with lumbar IVDD [19, 20]. Previous studies on the relationship between statins and spinal conditions have yielded mixed results. Some studies suggest that hyperlipidemia may increase the risk of spinal degenerative diseases, such as lumbar spine degeneration [21, 22], possibly due to factors like obesity or overweight [23]. However, gender-based analyses have found no significant association between hyperlipidemia and spinal conditions in women, although lipid-lowering treatments were linked to sciatica in women [24]. Additionally, no conclusive evidence has been found regarding the relationship between serum lipids and intervertebral disc degeneration [25]. These conflicting findings highlight the need for further research on the potential role of lipid-lowering drugs in spinal health.

Currently, the primary targets for lipid reduction in the field of metabolic disorders include three key proteins: preprotein convertase *Bacillus subtilis* protease/kexin type 9 (PCSK9), Niemann-Pick C1-Like 1 (NPC1L1), and 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA).

Innovative drugs, such as PCSK9 inhibitors, specifically alirocumab and evolocumab, have emerged as effective agents for lowering lipids by impeding the influence of PCSK9 on the LDL receptor, thereby increasing the LDL receptor clearance efficiency of LDL-C from the bloodstream [26–28]. HMG-CoA reductase inhibitors, better known as statins, are extensively utilized for both primary and secondary prevention of coronary heart disease (CHD). Statins reduce cholesterol synthesis within the liver, resulting in decreased plasma levels of total cholesterol (TC), LDL-C, very-low-density lipoprotein cholesterol (VLDL-C), TGs, and apolipoprotein-B (Apo-B). Furthermore, statins can elevate plasma concentrations of high-density lipoprotein cholesterol (HDL-C), contributing to a more beneficial lipid profile [29]. Another significant regulator of lipid metabolism is NPC1L1, a protein crucial for maintaining cholesterol homeostasis. NPC1L1 influences the absorption of cholesterol by intestinal cells and the excretion of cholesterol into bile by liver cells, playing a crucial role in overall cholesterol regulation through these vital processes [30, 31].

Despite the widespread use of lipid-lowering drugs in a variety of therapeutic areas, there is currently less research on the potential correlation between this class of drugs and the risk of developing IVDD, sciatica and LBP. However, lipid modulation is promising for the treatment of these specific disorders affecting the lumbar spine region and intervertebral discs. Presently, there is a shortage of definitive guidelines or research recommendations for the use of lipid-lowering drugs in patients with abnormal lipid metabolism who also suffer from IVDD, sciatica, and LBP. Furthermore, uncertainty exists regarding the optimal type of lipid-lowering medication for these patients.

Mendelian randomization (MR) involves the utilization of genetic variations to establish causality, thereby overcoming the limitations of observational studies and yielding more reliable results [32]. Despite its promise, MR studies specifically investigating the link between lipid-lowering agent use and the risk of developing conditions such as IVDD, sciatica, and LBP are limited. In this research, MR analysis of drug targets were employed to simulate the pharmacological inhibition of genetic variations at drug-related gene targets. The regression estimates derived from these analyses reflect the long-term effects of drug use. This methodology allows for a comprehensive evaluation of the causal relationships between lipid-lowering agent use and the conditions being studied. In this study, a proteome-wide MR analysis was conducted by integrating plasma proteomic and genomic data to systematically identify circulating protein biomarkers associated with the risk of IVDD, sciatica, and LBP. Given that standard MR approaches may not fully capture the complexity of causal pathways, summary-data-based MR (SMR) was also employed to enhance the identification of reliable protein targets. Furthermore, in this study, data from the National Health and Nutrition Examination Survey (NHANES), which evaluates the health and nutritional status of both adults and children in the United States, were utilized. NHANES data serve as an invaluable resource for examining the relationships among statin use, lipid metabolism, and LBP within a representative sample of the U.S. population [33]. By combining MR analysis with NHANES data, the aim of this study was to elucidate the causal role of statins in the onset and progression of IVDD, sciatica, and LBP. This integrated approach enhances the robustness of the findings and provides a deeper understanding of the potential therapeutic benefits of lipid-lowering agents for these conditions.

Materials and methods

Observational research design and data sources

Data from the NHANES collected from 1999 to 2004 and 2009–2010 were used for this cross-sectional research. The primary aim of the NHANES initiative is to evaluate the health and nutritional status of noninstitutionalized Americans via stratified multistage probability surveys [30]. Data for this study were accessed from the NHANES website (http://www.cdc.gov/nchs/nhanes.htm) on August 10, 2022. Data from four NHANES cycles were analysed on the basis of LBP and statin use. Initially, 41,663 participants aged 20–80 years were considered for enrolment. Pregnant women (n=2,882), participants without statin information (n=32,894), and those without LBP information (n=1,544) were excluded, resulting in a final sample of 4,343 participants for follow-up analyses. The detailed exclusion process is illustrated in Fig. 1.

Low back pain and statin usage status

LBP was categorized as a binary variable. Participants were considered to have LBP if they answered "yes" to the question "Have you experienced LBP in the past three months?" Statin usage was categorized into "taking statins" (yes) and "not taking statins" (no).

Covariables of interest

In addition to basic demographic data such as age, sex, and race, the analysis included clinical covariates related to LBP, such as body mass index (BMI), TG levels, and cholesterol levels. The racial categories in this cross-sectional study included "Mexican American," "Non-Hispanic Black," "Non-Hispanic White," "Other Hispanic," "Non-Hispanic," and "Other race - including Multi-Racial." BMI was divided into four categories: "underweight" (<18 kg/m^2), "normal weight" (18–24 kg/m^2), "overweight" (24–28 kg/m^2), and "obese" (>28 kg/

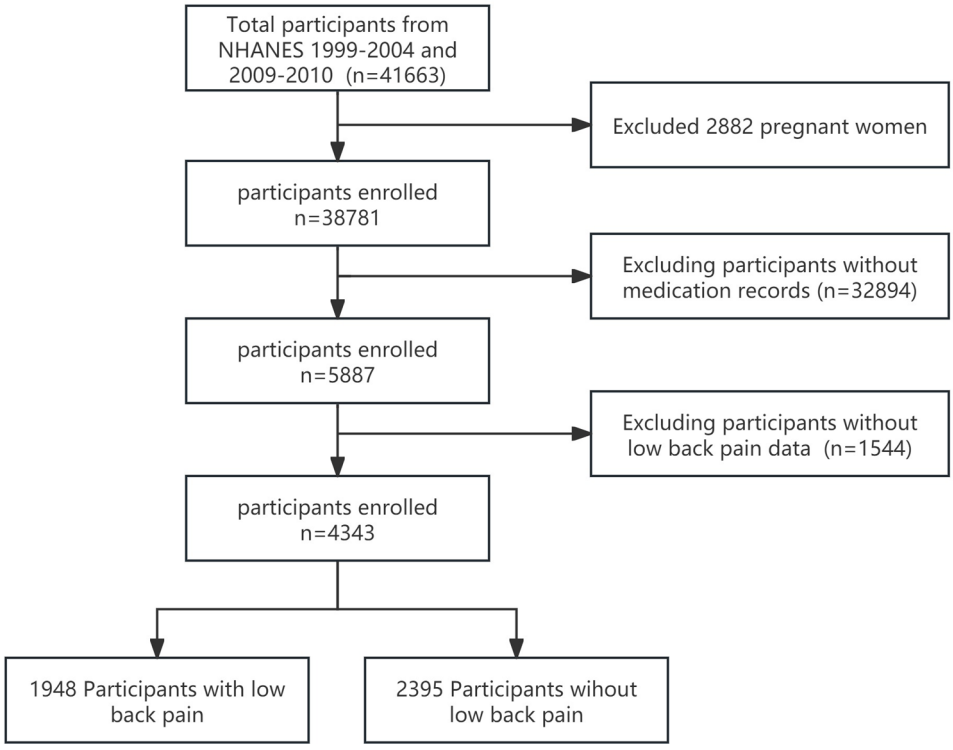

Fig. 1 NHANES 1999–2004 and 2009–2010 sample selection flowchart. Abbreviations: NHANES, National Health and Nutrition Examination Survey

m^2). Both univariate and multivariate analyses were performed to assess the impact of statin usage on the incidence of LBP. The univariate analysis offered an initial understanding of the relationship between statin use and LBP incidence. The multivariate analysis included covariates that significantly differed between individuals with and without LBP to mitigate potential biases affecting the final results.

Statistical analysis

In the NHANES study, interview weights were applied to appropriately weight the data. Categorical variables are presented as proportions (%), whereas continuous variables are summarized as the means ± standard deviations (SDs) or medians with interquartile ranges (IQRs). The Wilcoxon rank-sum test was used to compare differences among groups in the complex survey sample for continuous variables, and the chi-square test with Rao–Scott second-order correction was used for categorical variables. Logistic regression, adjusted for the complex survey design, was used to calculate ORs and 95% confidence intervals (95% CIs) to assess the associations between covariates and LBP. The univariate analysis compared the LBP and non-LBP groups via the chi-square test, with "taking statins" as the reference group. The multivariate analysis employed weighted logistic regression, adjusting for covariates to evaluate the impact of statin use on LBP risk. Model 1 was the univariate analysis model. Model 2 was adjusted for BMI and HDL-C, TC, and LDL-C concentrations. Model 3 included additional adjustments for sex and age. All data processing and analyses were performed via R version 4.2.3.

Mendelian randomization studies

Data sources

Aggregated data for TC, LDL-C, and non-HDL-C were obtained from a comprehensive genome-wide genetic meta-analysis involving approximately 1.65 million individuals, predominantly of European descent [34]. To avoid sample overlap, datasets excluding FinnGen and UK Biobank (UKBB) participants were used, with sample sizes for these cholesterol traits ranging from 525,239 to 930,637 individuals. CHD data were used as a positive control dataset. Genetic variant information for IVDD, sciatica, LBP, and CHD was sourced from the FinnGen consortium (https://www.finngen.fi) with the following accession numbers: finn-b-M13_SCIATICA, which included 9,917 European-descent patients and 134,889 control participants; finn-b-M13_INTERVERTEB, with 6,827 European-descent patients and 134,889 control participants; and finn-b-M13_LOWBACKPAIN, comprising 15,565 European-descent patients and 134,889 control participants (Supplementary Table 1). In addition to the FinnGen dataset, we validated our findings using data from the UK Biobank to ensure robustness and generalizability. The UKBB dataset includes detailed

information on medication use and diagnoses such as IVDD, sciatica, and LBP. The specific data for these conditions can be found in Supplementary Table 1. These additional cohorts enhance the robustness of our findings and provide a broader perspective on the association between lipid-lowering drugs and the risk of IVDD, sciatica, and LBP. The protein quantitative trait loci (pQTL) dataset originated from a comprehensive study involving 35,559 Icelandic participants, from which summary statistics for genetic associations were obtained for 4,907 circulating proteins [35].

Selection of instrumental variables

As depicted in Fig. 2, the robustness of the two-sample MR study was ensured by strictly adhering to three core assumptions: (1) the selected single-nucleotide polymorphisms (SNPs) must be highly correlated with the exposure; (2) the selected SNPs must not have a direct relationship with the outcome; and (3) the selected SNPs must not be correlated with other confounding factors that could affect the exposure or outcome. The selection of instrumental variables for predicting gene-mediated TC, LDL-C, and non-HDL-C was conducted meticulously using the aggregated data mentioned above, following stringent criteria. These variables were required to meet several conditions: a prevalence above 1% (minor allele frequency), a significant correlation with the respective cholesterol trait ($P<5.0\times10^{-8}$), and the exclusion of weak instrumental variables on the basis of the F statistic (F statistic>10). Additionally, these variables needed to be minimally affected by horizontal pleiotropy, as indicated by an R^2 value of less than 0.30, and located within a 100 kb proximity of the gene on the chromosome. This rigorous approach ensured the reliability and validity of the instrumental variables used in the analysis.

The expression quantitative trait loci (eQTL) summary data for the HGMCR gene were sourced from the eQTLGen Consortium, which included 31,684 individuals. In contrast, the eQTL data for the PCSK9 and NPC1L1 genes were obtained from the GTEx Portal and included 755 and 663 participants, respectively [36, 37]. Most of these participants were of European ancestry. From these datasets, suitable eQTL instrumental variables for the genes were identified on the basis of criteria including minor allele frequency exceeding 1%, genome-wide correlation significance ($P<5.0\times10^{-8}$), and an F-statistic greater than 10. Additionally, the eQTLs needed to be within 1 Mb of the respective genes to ensure robustness and validity in the analysis.

Statistical analysis

SNPs predictive of exposures were extracted from the outcome dataset, and their orientations were harmonized through allele correction. The inverse-variance weighting (IVW) method was used to determine the associations of gene-mediated cholesterol traits with the risk of developing IVDD, sciatica, and LBP. The IVW method is robust for causal inference, especially in the absence of horizontal pleiotropy [32]. Beta values, 95% CIs, and P values are provided. A P value less than 0.05 was considered to indicate nominal significance, whereas for multiple comparisons, Bonferroni correction was applied, and a P value of less than 0.004 (12 exposures and one outcome) was considered to indicate statistical significance. Several sensitivity tests were performed after the IVW analysis:

1. The primary analysis was repeated with a stricter clumping threshold ($R^2 < 0.10$) to assess linkage disequilibrium.
2. The Cochran's Q test was used to identify heterogeneity.
3. MR–Egger regression and MR–Pleiotropy RESidual Sum and Outlier (MR–PRESSO) were used to detect horizontal pleiotropy.

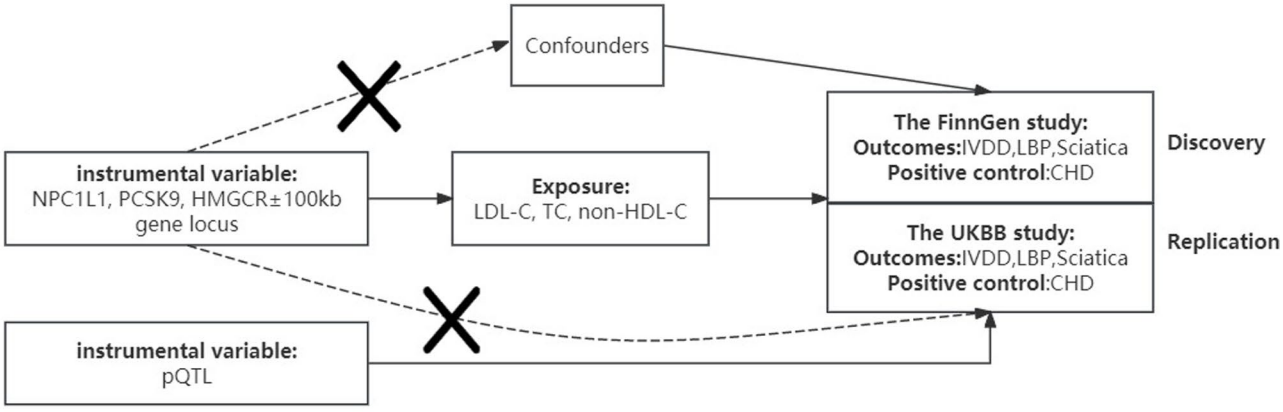

Fig. 2 Overview of the research and design of drug target MR analysis

Table 1 Baseline characteristics of enrolled LBP and non-LBP participants

Variables	Total (*n* = 4343)	LBP (*n* = 1948)	Non-LBP (*n* = 2395)	*P* val
Age, Mean ± SD	59.2 ± 15.3	58.4 ± 15.2	59.9 ± 15.4	0.001
Gender, n(%)				< 0.001
Male	2044 (47.1)	860 (43.3)	1184 (50.2)	
Female	2299 (52.9)	1124 (56.7)	1175 (49.8)	
Race, n (%)				0.032
Mexican American	784 (18.1)	343 (17.3)	441 (18.7)	
Other Hispanic	189 (4.4)	106 (5.3)	83 (3.5)	
Non-Hispanic White	2529 (58.2)	1163 (58.6)	1366 (57.9)	
Non-Hispanic Black	698 (16.1)	312 (15.7)	386 (16.4)	
Other Race	143 (3.3)	60 (3)	83 (3.5)	
Marital status, n (%)				0.234
Married	2538 (60.3)	1129 (58.9)	1409 (61.6)	
Widowed	620 (14.7)	285 (14.9)	335 (14.6)	
Divorced	472 (11.2)	236 (12.3)	236 (10.3)	
Separated	127 (3.0)	66 (3.4)	61 (2.7)	
Never married	291 (6.9)	129 (6.7)	162 (7.1)	
Living with partner	155 (3.7)	70 (3.7)	85 (3.7)	
PIR, n (%)				< 0.001
< 1.30	982 (24.9)	526 (29)	456 (21.4)	
1.30–3.49	1532 (38.9)	707 (39)	825 (38.7)	
≥3.50	1427 (36.2)	578 (31.9)	849 (39.9)	
BMI(kg/m^2)				< 0.001
Low weight	12 (0.3)	3 (0.2)	9 (0.4)	
Normal weight	649 (16.3)	247 (13.5)	402 (18.7)	
Overweight	1167 (29.3)	495 (27)	672 (31.3)	
Obses	2151 (54.1)	1086 (59.3)	1065 (49.6)	
Statin use status, n (%)				0.009
Taking statins	2395 (55.1)	1137 (57.3)	1258 (53.3)	
Not taking statins	1948 (44.9)	847 (42.7)	1101 (46.7)	
TG, dia Men (IQR)	216.0 (188.0, 245.0)	216.0 (188.0, 245.0)	215.0 (187.0, 246.0)	0.829
HDL, Median (IQR)	48.0 (40.0, 60.0)	47.0 (39.0, 59.0)	49.0 (41.0, 60.0)	0.002
TC, Median (IQR)	149.0 (105.0, 217.0)	151.0 (106.0, 220.8)	148.0 (103.0, 214.0)	0.589
LDL, Median (IQR)	129.0 (103.0, 155.0)	131.0 (105.0, 155.0)	128.0 (101.0, 156.0)	0.292

Abbreviation LBP, Low back pain; TG, triglyceride; HDL, High-density lipoprotein; TC, Total Cholesterol; LDL, low-density lipoprotein; BMI, Body mass index; PIR, Poverty-income ratio; LBP, low back pain; Non-LBP, non-low back pain

4. A positive control analysis was performed to verify the validity of the SNPs, and CHD was used as the outcome.

The IVW analysis, multivariate MR, and sensitivity analyses were conducted via the TwoSampleMR in R software (version 4.3.0).

In addition to these methods, we implemented the Summary-data-based MR (SMR) analysis to use protein quantitative trait loci (pQTLs) as instrumental variables (IVs), treating pQTLs as exposures, and IVDD, sciatica, and LBP as outcomes. The SMR approach allows us to examine the potential causal relationship between specific drug targets and disease outcomes using genetic data. We performed the heterogeneity in dependent instruments (HEIDI) test to assess whether the phenotype mediated by gene SNPs was due to linkage disequilibrium rather than a true causal effect. A P-value for the HEIDI test greater than 0.01 (P-HEIDI > 0.01) indicates that the association is not likely driven by linkage disequilibrium, suggesting a potential causal relationship [38].

Results

Observational study

This research included 4,343 participants, of whom 1,948 had LBP. A comprehensive description of the entire sample's characteristics and a comparison between individuals with and without LBP are presented in Table 1. The median age of the participants was 59.2 years, with 52.9% being female and 47.1% male. Older women were more likely to experience LBP, and HDL levels were lower in LBP patients than in those without LBP. There is a significant difference in the distribution of different races between the LBP and non-LBP groups, particularly in the proportions of Other Hispanic and Other Race (P=0.032). The proportion of individuals with a PIR less than 1.30 is 29% in the LBP group compared to 21.4% in the non-LBP group, with the difference being statistically significant (P<0.001). The proportion of obese individuals is 59.3% in the LBP group compared to 49.6% in the non-LBP group, with the difference being statistically significant (P<0.001). The median HDL is 47.0 in the LBP group compared to 49.0 in the non-LBP group, with the difference being statistically significant (P=0.002). 57.3% of the LBP group are taking statins compared to 53.3% of the non-LBP group, with the difference being statistically significant (P=0.009).

In the NHANES study, the association of each covariate with the risk of developing LBP was initially analysed via univariate logistic regression (Supplementary Table 2). The findings revealed that sex, BMI, family income, marital status, and TC, TG, HDL-C, and LDL-C concentrations were associated with the prevalence of LBP,

whereas race was not. In the multivariate analysis, several models were constructed to account for confounding variables. The univariate analysis indicated that participants not taking statins had a greater probability of having LBP [OR (95% CI): 1.17 (1.04, 1.32), $P=0.009$]. The weighted multiple logistic regression analysis further demonstrated that not using statins was linked to an increased risk of developing LBP after adjusting for other covariates [OR (95% CI): 1.22 (1.00, 1.49), $P=0.047$]. To verify the stability of the model, two covariates (age and sex) near the significance threshold were added to create another model for analysis. No significant changes were observed, confirming the robustness of the results (Table 2).

Mendelian randomization studies

Selection of genetic instruments for drug target and participant screening

Between 6 and 37 SNPs were chosen to predict gene-mediated cholesterol traits. The details of these instrumental variables, including R^2 values and F statistics, are presented in Supplementary Tables 3 to 5. Specifically, the top eQTLs rs62366588, rs11206499, and rs52815063 were selected to predict the HMGCR, PCSK9, and NPC1L1 genes, respectively. Supplementary Table 6 provides further details on these instrumental variables.

Lipid-lowering drug targets and the risk of developing IVDD, sciatica and LBP outcomes

IVW-MR analysis based on the Finn dataset revealed that NPC1L1-mediated TC, LDL-C, and non-HDL-C levels were significantly associated with a reduced risk of developing IVDD. Specifically, in the discovery dataset, the ORs per 1-mmol/L decrease were as follows: TC [OR, 0.349; 95% CI, 0.156–0.777; $P=0.009$], LDL-C [OR, 0.349; 95% CI, 0.166–0.934; $P=0.035$], and non-HDL-C [OR, 0.294; 95% CI, 0.158–0.550; $P=0.001$]. No significant associations were found for LBP. Genetically proxied inhibition of PCSK9 was significantly associated with a decreased risk of developing sciatica. The ORs per 1-mmol/L decrease were as follows: LDL-C [OR, 0.812; 95% CI, 0.667–0.988; $P=0.038$] and TC [OR, 0.783; 95% CI, 0.631–0.972; $P=0.027$] (Fig. 3). Cochran's Q test, the MR−Egger intercept, and MR−PRESSO analysis revealed no evidence of heterogeneity or horizontal pleiotropy ($P>0.05$) (Supplementary Table 7). The validation of SNPs through positive control analyses is presented in Supplementary Table 8, and elevated levels of NPC1L1-, PCSK9-, and HMGCR-mediated cholesterol traits were significantly associated with a reduced risk of developing CHD ($P<0.05$).

In further validation using the UKBB, the results were consistent with those from the discovery dataset. The IVW-MR analysis indicated that genetically proxied inhibition of PCSK9 was associated with a reduced risk of developing sciatica, with the following odds ratios per 1 mmol/L decrease: LDL-C [OR, 0.994; 95% CI, 0.988–0.999; $P=0.032$], TC [OR, 0.992; 95% CI, 0.988–0.999; $P=0.012$], and non-HDL-C [OR, 0.993; 95% CI, 0.988–0.999; $P=0.021$]. Moreover, NPC1L1-mediated lipid traits were significantly associated with a reduced risk of developing IVDD, with the following odds ratios: LDL-C [OR, 0.864; 95% CI, 0.899–0.953; $P=0.025$], non-HDL-C [OR, 0.784; 95% CI, 0.652–0.842; $P=0.026$], and TC [OR, 0.942; 95% CI, 0.423–0.665; $P=0.025$]. These results are consistent with those observed in the FinnGen cohort (Supplementary Table 9). Additionally, the Cochran's Q test, MR-Egger intercept, and MR-PRESSO analyses did not reveal any evidence of significant heterogeneity or horizontal pleiotropy, as all P-values were greater than 0.05. This comprehensive analysis further corroborates the protective role of PCSK9 inhibition on sciatica risk while highlighting the absence of significant effects of NPC1L1-mediated lipid traits on IVDD, sciatica, and LBP in the UKBB cohort (Supplementary Table 10). As shown in Supplementary Table 11, positive control analyses confirmed that elevated levels of NPC1L1-, PCSK9-, and HMGCR-mediated cholesterol traits were significantly associated with a reduced risk of developing CHD, consistent with the results from the FinnGen dataset.

Lipid traits were not associated with IVDD, sciatica or LBP risk

To explore whether the impact of lipid-lowering drug targets on the outcomes studied was mediated through their

Table 2 Association between statins use status and risk of LBP

Outcome	Exposure	Type of medication	Model 1[1]			Model 2[2]			Model 3[3]		
			OR	95%CI	*P* val	OR	95%CI	*P* val	OR	95%CI	*P* val
Low back pain	Statin use status	Taking statins	1(Ref)			1(Ref)			1(Ref)		
		Not taking statins	1.17	(1.04,1.32)	0.283	1.22	(1,1.49)	0.047*	1.29	(1.04,1.59)	0.019*

Abbreviation BMI: Body mass index; OR: Odds ratio; CI: Confidence interval; TG, triglyceride; HDL, High-density lipoprotein; TC, Total Cholesterol; LDL, low-density lipoprotein

*$P<0.05$

[1]Model 1: Univariate analysis model;

[2]Model 2: Multivariate analysis model adjusted for TG BMI HDL TC LDL;

[3]Model 3: further adjusted for gender and age

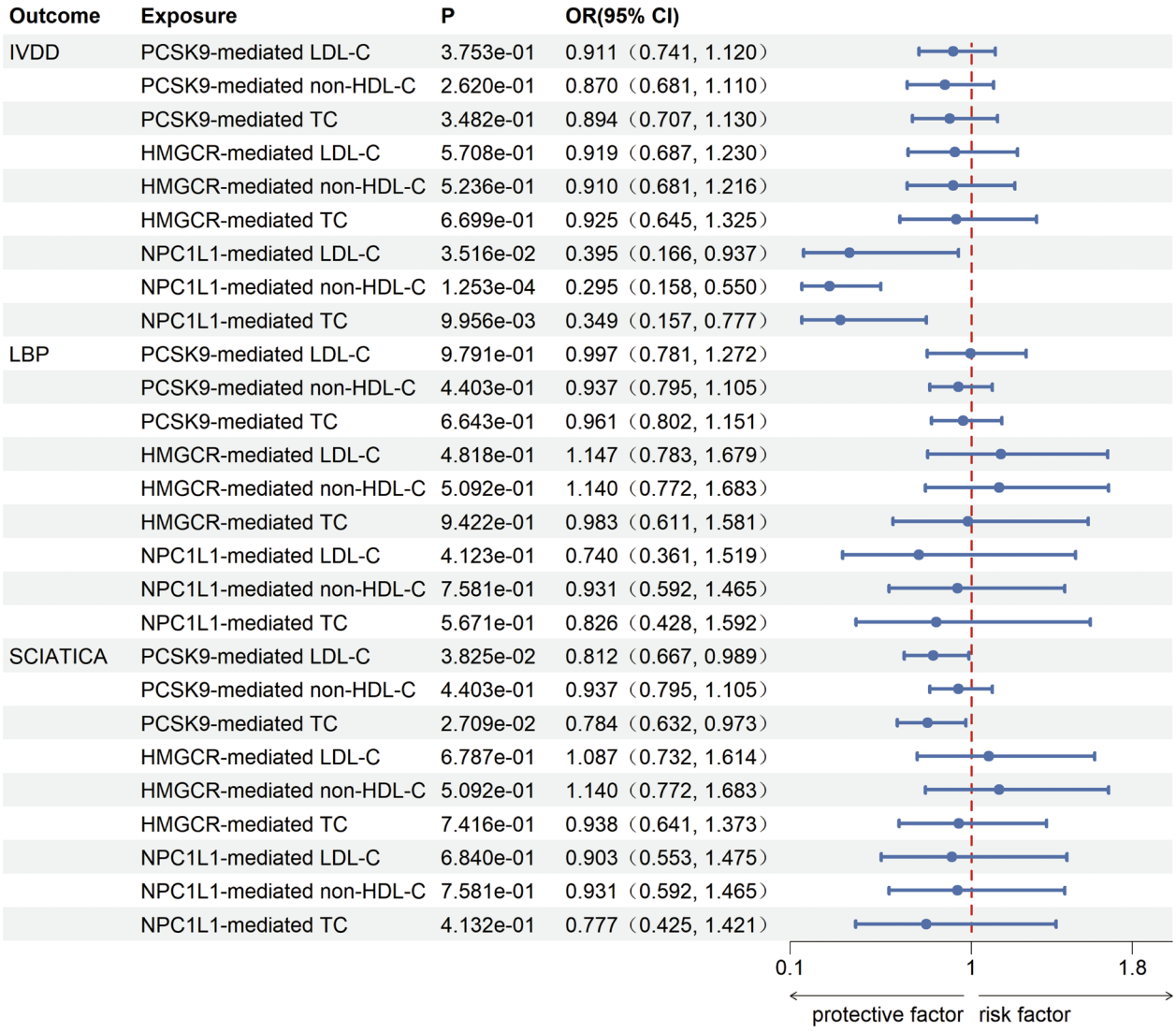

Fig. 3 IVW-MR associations of the cholesterol traits mediated by the three target genes with the risk of developing IVDD, LBP and sciatica

lipid-lowering effects, additional IVW-MR analyses were performed. These analyses evaluated the relationships between lipid traits and the risk of developing IVDD, sciatica, and LBP. The results from the IVW-MR analyses did not reveal any causal effect of genetically predicted TC, LDL-C, or non-HDL-C concentrations on the risk of developing any of these conditions (Supplementary Table 12). These findings indicate that lipid traits do not play a significant role in the development of IVDD, sciatica, or LBP. To evaluate whether lipid traits themselves play a role in the development of IVDD, sciatica, and LBP, additional analyses were performed using UKBB data. The results revealed no significant causal associations between genetically predicted TC, LDL-C, or non-HDL-C concentrations and the risk of these conditions, suggesting that lipid traits alone may not contribute to IVDD, sciatica, or LBP risk. These findings indicate that the protective effects observed from lipid-lowering drugs, such as NPC1L1 and PCSK9 inhibitors, may result from mechanisms beyond lipid reduction(Supplementary Table 13).

Protein and IVDD, sciatica or LBP risk

A total of 196 proteins were initially found to be associated with the risk of IVDD at a nominal significance level of $P<0.05$ (Supplementary Table 14). After adjusting for multiple comparisons, five proteins remained significantly associated with IVDD risk at a false discovery rate (FDR) of $P<0.05$. Among these, MST1 (OR=0.964, 95% CI: 0.950–0.978), PTHLH (OR=0.962, 95% CI: 0.946–0.978), and DLK1 (OR=0.967, 95% CI: 0.953–0.981) were found to be negatively correlated with the risk of IVDD.

In contrast, TFRC (OR=1.033, 95% CI: 1.017–1.049) showed a positive association with IVDD risk. Similarly, 143 proteins were associated with the risk of sciatica at $P<0.05$ (Supplementary Table 15). After FDR adjustment, two proteins were significantly associated with sciatica risk at the $P_{(FDR)}<0.05$ level. MST1 (OR=0.958, 95% CI: 0.939–0.973) and MAPK3 (OR=0.954, 95% CI: 0.936–0.973) were both negatively correlated with the risk of sciatica. For LBP, 139 proteins were initially identified as being associated with LBP risk at $P<0.05$. After multiple testing correction, five proteins remained significantly associated with LBP risk at the $P_{(FDR)}<0.05$ threshold (Supplementary Table 16). MST1 (OR=0.970, 95% CI: 0.955–0.985) was observed to be negatively correlated with the risk of LBP, while PROK2 (OR=1.039, 95% CI: 1.020–1.059), NT5E (OR=1.052, 95% CI: 1.026–1.078), ASL (OR=1.035, 95% CI: 1.018–1.053), and SPOCK2 (OR=1.031, 95% CI: 1.015–1.047) were positively associated with LBP risk (Fig. 4). In the UK Biobank validation cohort, only the association of MST1 with IVDD risk was successfully replicated (Supplementary Tables 17–19).

Discussion

IVDD, sciatica and LBP are common public health concerns that significantly contribute to productivity loss and disability [4]. Numerous studies have examined the connection between abnormal blood lipid metabolism and LBP, particularly in Asian populations. For example, a Chinese cross-sectional study investigating the impact of dyslipidaemia on disc degeneration and vertebral endplate morphology revealed that high serum cholesterol levels might play a crucial role in disc degeneration [25]. Additionally, a cross-sectional study of middle-aged Japanese adults revealed that low HDL-C concentrations and a high LDL-C/HDL-C ratio were significantly correlated with the risk of developing LBP [39]. To explore the possibility that modulation of lipid levels could be a new approach for the treatment of these conditions, then we evaluated the feasibility of this idea using a large, open database in this study.

This comprehensive study, which consists of two distinct parts, revealed through our initial observational phase that statin usage is significantly associated with a decreased risk of developing LBP, precisely highlighting that the absence of statin use increases vulnerability to LBP. These findings remained consistent across various model adjustments. However, since observational studies can be used to establish only correlation and not causality, we conducted a drug-target MR study in the second part of the analysis. The MR study results demonstrated that NPC1L1-mediated reductions in TC, LDL-C, and non-HDL-C were associated with a decreased risk of developing IVDD. Additionally, PCSK9-mediated reductions in TC and LDL-C concentrations were linked to a lower risk of developing sciatica. Currently, there are no large, representative studies exploring the relationships between lipid-lowering medication use and the risk of developing conditions such as IVDD, sciatica and LBP. Cross-sectional studies have suggested that dyslipidaemia is associated with the severity of lumbar disc degenerative changes and altered vertebral models. Previous NHANES studies have revealed a greater risk of developing LBP in patients with obesity [40]. In this study, we found that not taking statins was associated with an increased risk of developing LBP. Notably, there was a significant difference in HDL levels between participants with LBP and those without LBP, but no significant differences were observed for TG, TC, or LDL concentrations. In Table 2, the effects of lipid markers were also excluded to compare the potential impact of LBP occurrence in participants not taking statins versus those in the non-LBP group. SMR analysis suggested that MST1 may be a potential therapeutic target for IVDD, sciatica, and LBP. MST1, a member of the class II germinal center kinases, mediates intracellular signaling in response to various stimuli and has been identified as a negative

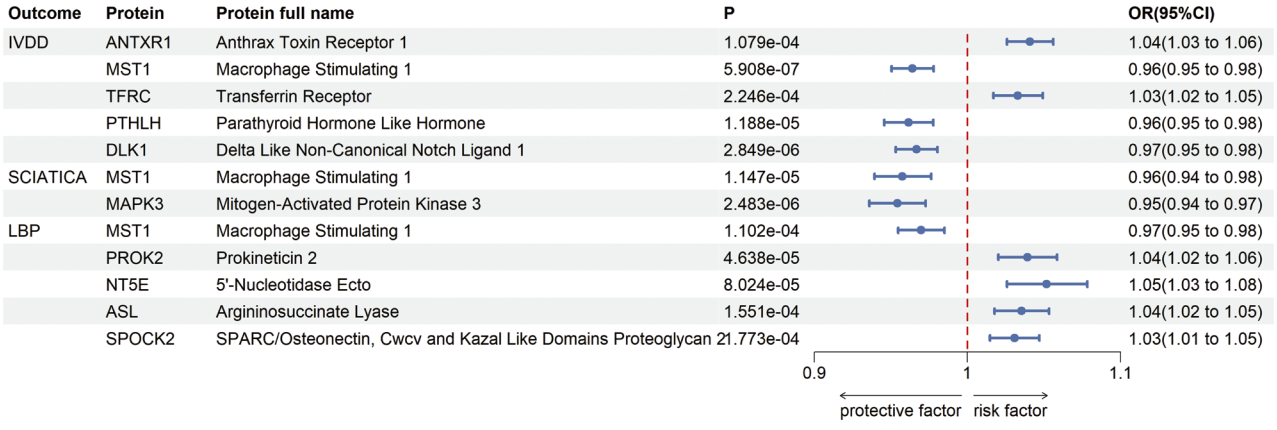

Fig. 4 Forest plot of associations between protein with IVDD, sciatica or LBP risk. OR, odds ratio; CI, confidence interval

regulator of TNF-induced inflammatory signaling [41]. Since TNF is known to induce inflammation and ferroptosis of nucleus pulposus cells, contributing to IVDD pathogenesis, the potential role of MST1 in these conditions warrants further investigation. However, while our SMR analysis indicated an association between MST1 and reduced risk of IVDD, sciatica, and LBP, existing literature presents conflicting evidence. Some studies have linked MST1 upregulation to nucleus pulposus cell degeneration and the progression of intervertebral disc degeneration. For instance, MST1 has been shown to activate the Hippo/YAP signaling pathway, promoting apoptosis in nucleus pulposus cells and accelerating disc degeneration, which appears to contradict our SMR findings [42, 43]. This discrepancy may arise from MST1's dual role in different tissues or pathological conditions. MST1 may exert protective effects by promoteing autophagy or inhibiting apoptosis, thereby reducing the risk of IVDD, sciatica, and LBP. Conversely, in stress or inflammatory microenvironments, the overactivation of MST1 overactivation could enhance Hippo/YAP signaling, leading to increased apoptosis and exacerbating disc degeneration. Thus, MST1's role is likely dynamic and context-dependent, varying with the pathological environment. While our SMR findings suggested a protective role for MST1 in IVDD progression, conflicting evidence from the literature underscores the need for further research. Future studies should focus on elucidating MST1's dual role under varying pathological conditions to better understand its potential as a molecular target for treating IVDD and related disorders.

This study is the first to explore the causal relationships between lipid-lowering drug use and the risk of developing IVDD, sciatica and LBP from a genetic perspective. By performing a large-scale MR analysis, we effectively eliminated the potential confounding biases inherent in previous observational epidemiological studies. In conducting this MR analysis, we strictly adhered to the three core assumptions, minimizing confounding factors and enhancing the reliability of our results. The study found that modulating NPC1L1 and PCSK9 genes can lower the risk of intervertebral disc degeneration (IVDD) and sciatica, but there's no direct link between lipid traits and these conditions. This may be because lipid-lowering drugs and lipid traits influence these diseases through different mechanisms. While PCSK9 and NPC1L1 lower cholesterol, they may also have anti-inflammatory and antioxidant effects that protect against these conditions. These protective effects might be due to specific drug actions rather than general changes in lipid levels. For instance, PCSK9 and NPC1L1 inhibitors might reduce disease risk by improving inflammation or vascular health in the spine, independent of their impact on lipids. Through the inhibition of NPC1L1 receptors, Ezetimibe treatment effectively hinders the absorption of dietary and bile cholesterol in the intestine without affecting the absorption of lipid-soluble nutrients. This drug primarily acts on the intestine, potentially leading to the accumulation of TG or cholesterol in the gastrointestinal tract. Numerous studies have shown that gut microbes play a significant role in the metabolism of many drugs, influencing their effectiveness and side effects [44, 45]. Researchers have discovered that ezetimibe influences the gut flora of overweight and obese patients with dyslipidaemia. After 12 weeks of treatment, the abundances of *Clostridium XVIII* and *Lachnospiraceae* incertae sedis were negatively correlated with TC and LDL-C concentrations. This finding suggested that the impact of ezetimibe on the gut microbiota could play a role in its lipid-lowering effects [46]. In animal studies, ezetimibe was found to reduce the relative abundance of certain low-abundance bacteria in the gut of high-fat diet-induced obese mice. Specifically, the abundance of Desulfovibrio was negatively correlated with TG and HDL-C levels following ezetimibe intervention. These findings suggest that the effects of ezetimibe on the gut microbiota may influence lipid metabolism and contribute to its therapeutic benefits [47]. An MR study investigating the causal relationship between the gut microbiota and the risk of developing conditions such as disc degeneration, LBP, and sciatica revealed that faecalis has a protective effect against IVDD. This protective mechanism may be linked to cholesterol metabolism, as the faecalis group can degrade cholesterol and convert it into faecal coprostanol [48]. Elevated cholesterol levels in vivo can activate mSREBP1, increase endoplasmic reticulum ER stress, induce pyroptosis, degrade the extracellular matrix, and lead to IVDD [18]. These studies suggest that ezetimibe exerts a protective effect against IVDD through the modulation of the intestinal flora.

The primary cause of sciatica is mechanical compression due to lumbar disc herniation, accompanied by local inflammation [49, 50]. The exact immune-mediated mechanisms of disc herniation are not fully understood, but many inflammatory factors, such as IL-6, IL-10, and TNF-α, are expressed in herniated disc tissues [51]. A systematic review revealed that high levels of IL-6, IL-8, and TNF-α in patients with lumbar disc herniation were associated with higher visual analogue scale (VAS) scores, indicating that these cytokines may exacerbate pain symptoms [52]. IL-6, a mediator of the acute phase response, promotes the differentiation of monocytes into macrophages and activates lymphocyte maturation [53]. Resveratrol and alpha-ketoglutaric acid have been shown to protect nucleus pulposus cells from degeneration by blocking the IL-6/JAK2/STAT3 pathway [54, 55]. TNF-α, another crucial inflammatory mediator, can irritate and damage nerve roots and is involved in inducing

ferroptosis in nucleus pulposus cells [56]. Currently, the clinical efficacy of TNF-α and IL-6 inhibitors in treating sciatica is being evaluated [57, 58]. Pharmacological studies have suggested that anti-PCSK9 monoclonal antibodies may improve the lumbar blood supply by modulating the TLR/NF-κB pathway, thereby reducing serum inflammation and plaque accumulation in the aortas of mice. These findings indicate a potential therapeutic role for lipid-lowering agents in managing sciatica and related conditions [59]. Statins, which are commonly prescribed for hyperlipidaemia, also exhibit significant anti-inflammatory effects. Recent studies have shown that rosuvastatin suppresses matrix anabolism while preventing catabolism. Specifically, the regulation of the HMGB1 gene by rosuvastatin reduces TNF-α-induced extracellular matrix degradation, senescence, and apoptosis in the medulla. Similarly, rosuvastatin mitigates TNF-α-induced matrix degradation by specifically targeting the HMGB1-NF-κB pathway and further suppresses cellular senescence and pyroptosis, ultimately assisting in the protection of intervertebral discs from degeneration, highlighting its potential therapeutic role in the treatment of IVDD [19]. Atorvastatin inhibited TNF-α-induced matrix degradation in rat NP cells. Moreover, atorvastatin decreases NLRP3 inflammatory vesicle activity and induces autophagy, and NLRP3 inhibition increases autophagic flux [20]. Despite these promising results, most research has concentrated on statins, with limited investigations into other lipid-lowering agents, such as PCSK9 inhibitors and NPC1L1 inhibitors, for the treatment of IVDD. Future studies should focus on evaluating the clinical efficacy and underlying mechanisms of these alternative drugs in managing IVDD, sciatica and LBP.

Strengths and limitations of this study

This study has several advantages. First, the use of the NHANES database revealed that not taking statins increases the risk of developing LBP, suggesting an association between lipid-lowering drug use and LBP risk, although observational studies cannot be used for causal inference. Second, by using genetic variants in drug target regions to simulate the effects of commonly used lipid-lowering drugs, we identified causal relationships between NPC1L1 and the risk of developing IVDD and between PCSK9 and the risk of developing sciatica. The MR analysis approach effectively avoids confounding and reverse causation biases. Notably, this is the first study, as reported in the literature, to examine the effects of lipid-lowering drugs on the risk of developing IVDD, sciatica and LBP. However, there are limitations to this study. The sample primarily consisted of individuals of American and European ancestry, which may affect the generalizability of the results to other ethnic groups. Future research should prioritize conducting subgroup analyses across more ethnically diverse populations to ensure broader generalizability and to validate these results in other genetic contexts. There is also a notable difference between the findings of the cross-sectional and MR studies. Specifically, the cross-sectional study suggests that non-use of statins is associated with an increased risk of LBP, while the MR study does not show significant effects of statins or other lipid-lowering drugs on IVDD or sciatica. This discrepancy might arise from the inherent differences in study design. Cross-sectional studies are more susceptible to confounding factors, whereas MR studies reduce these confounding influences by using genetic instruments, allowing a better assessment of causal relationships. Additionally, LBP might be a multifactorial condition with complex pathophysiology, which may not be fully influenced by lipid metabolism. Future studies are needed to combine larger datasets and experimental approaches to further investigate these initial findings and explore potential mechanistic differences. Furthermore, the NHANES database records only statin use and excludes other lipid-lowering drugs, which limits the ability to fully evaluate the potential effects of other lipid-lowering agents on IVDD, sciatica, and LBP. This restricted scope may affect our understanding of the broader role that other drugs could play in these conditions. Furthermore, the NHANES data defines LBP based solely on self-reported responses to whether participants experienced back pain in the past three months, without any clinical validation. This lack of objective confirmation introduces potential vagueness, which may lead to misclassification and impact the accuracy of the associations identified in this study. Additionally, this broad definition may overlook specific cases related to IVDD, thereby introducing bias and further reducing the precision of our findings. Moreover, MR analysis inherently assumes that genetic effects are present from birth and persist throughout an individual's life, while drug treatments are typically administered during specific life stages or disease courses. As a result, the effects observed in MR studies, which rely on lifelong genetic influences, may not fully align with the temporal patterns of actual drug usage. This discrepancy between the lifelong action of genetic instruments and the limited duration of drug exposure suggests that MR results may more accurately reflect the long-term effects of specific biological pathways rather than the short-term impacts of drugs. To address this limitation, future research should incorporate randomized controlled trials or real-world data analyses to complement MR findings. These approaches would provide a more comprehensive evaluation of the short-term and long-term effects of lipid-lowering medications, offering a clearer understanding of their clinical relevance. Future studies should explore the application

of various lipid-lowering drugs in patients with IVDD, sciatica and LBP, particularly those with concurrent lipid metabolism disorders, to further investigate the role of these medications in alleviating symptoms. Furthermore, examining the sensitivity of patients to different lipid-lowering drugs could provide valuable insights.

Finally, this study is primarily theoretical, necessitating more animal trials and cohort studies to validate the findings for better clinical application. Such research will enhance our understanding of the efficacy of lipid-lowering drugs in patients with complex diseases, providing a stronger basis for clinical practice.

Conclusion

In this study, the relationship between lipid-lowering drug use and the risk of developing LBP was validated through a cross-sectional analysis of NHANES data. Additionally, meticulous MR analysis of drug targets was conducted to explore the roles of NPC1L1-mediated TC, LDL-C, and non-HDL-C and PCSK9-mediated LDL-C and TC in reducing the risk of developing IVDD and sciatica, respectively. Further analysis using pQTL-based SMR showed that MST1 levels were inversely associated with the risks of IVDD, sciatica, and LBP, highlighting its potential as a therapeutic target. These findings confirm a causal relationship between the use of lipid-lowering medications and a significant reduction in the risk of developing IVDD, sciatica and LBP. However, further basic and clinical studies are needed to explore the mechanisms and effects of these medications on the risk of developing IVDD, sciatica and LBP to ensure the accuracy and validity of these results.

Abbreviations

Apo-B	Apolipoprotein-B
BMI	Body Mass Index
CHD	Coronary Heart Disease
95%CI	95%Confidence Interval
eQTL	Expression Quantitative Trait Locus
ECM	Extracellular Matrix
GWAS	Genome-Wide Association Study
HDL	High-density lipoprotein
HDL-C	High-Density-Lipoprotein Cholesterol
HMGCR-CoA	3-hydroxy-3-methylglutaryl-CoA reductase
IQR	Interquartile range
IVDD	Intervertebral Disc Degeneration
IVW	Inverse-Variance Weighted
LBP	Low Back Pain
LDL	Low-density lipoprotein
LDL-C	Low-Density Lipoprotein Cholesterol
MR	Mendelian Randomization
MST1	Macrophage stimulating 1
NHANES	National Health and Nutrition Examination Survey
non-HDL-C	Non-High-Density-Lipoprotein Cholesterol
NPC1L1	Niemann-Pick C1-Like 1
NP	Nucleus Pulposus
OR	Odds Ratio
PCSK9	Proprotein Convertase Subtilisin/Kexin Type 9
pQTL	Protein Quantitative Trait Loci
SD	Standard deviation
SMR	Summary-data-based Mendelian Randomization
SNP	Single Nucleotide Polymorphism
TC	Total Cholesterol
TG	Triglyceride
TNF	Tumor necrosis factor
VLDL-C	Very-Low-Density Lipoprotein Cholesterol. VAS: Visual Analog Scale

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-024-02311-w.

Supplementary Material 1

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Author contributions

CXL conducted an investigation, wrote the original draft, and participated in reviewing and editing the work. XQC performed formal analysis and contributed to reviewing and editing the work. YNB conducted formal analysis and assisted in reviewing and editing the work. QBJ was responsible for data curation and collaborated in reviewing and editing the work. YFZ and YG both conducted formal analysis and participated in reviewing and editing the work. JZM and SF developed the methodology and contributed to reviewing and editing the work. YXZ provided supervision and assisted in reviewing and editing the work.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

All GWASs, eQTL, and pQTL studies that provided the summary data were conducted in accordance with the ethical requirements of the World Medical Association Declaration of Helsinki. The cross-sectional observational received approval from the Ethics Review Board of the National Center for Health Statistics (NCHS), and documented consent was obtained from participants (Protocol #98 – 12, Continuation of Protocol #2005-06).

Competing interests

The authors declare no competing interests.

Informed consent

Not applicable.

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