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RESEARCH ARTICLE

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Evaluating the causal effect of atherosclerosis on the risk of intervertebral disc degeneration

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Abstract

Background: Intervertebral disc degeneration (IDD) and atherosclerosis are two common age-related conditions that can cause significant morbidity. While previous studies have suggested an association between the two conditions, the nature of this association remains unclear.

Methods: We used Mendelian randomization (MR) to investigate the causal relationship between IDD and atherosclerosis. We identified genetic variants associated with IDD using summary statistics from a large genome-wide association study (GWAS). These variants were then used as instrumental variables to infer causal relationships with atherosclerosis in summary statistics from a separate GWAS.

Results: Our MR analysis provided evidence for a causal relationship between IDD and atherosclerosis. We found that the genetic predisposition to atherosclerosis was associated with a higher risk of IDD (odds ratio [OR] = 3.55, 95% confidence interval [CI]: 1.07–11.74, $p = 0.04$). The IVW estimates were consistent with the observational findings and other robust MR methods. Sensitivity analyses suggested that our findings were robust to potential sources of bias.

Conclusions: Our study provides evidence for a causal link between IDD and atherosclerosis, suggesting that interventions targeting atherosclerosis could have potential benefits for reducing the risk of IDD. Further research is needed to explore the underlying mechanisms that link these two conditions and to investigate potential therapeutic interventions.

KEYWORDS

atherosclerosis, genome-wide association studies, intervertebral disc degeneration, Mendelian randomization

1 | BACKGROUND

Cardiovascular disease has become the leading cause of death worldwide, and atherosclerosis is the main contributing factor of

Abbreviations: CI, confidence interval; GWAS, genome-wide association study; IDD, intervertebral disc degeneration; IVW, inverse-variance weighted; MR, Mendelian randomization; OR, odds ratio; SE, standard error.

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cardiovascular disease.[1,2] Atherosclerosis is a chronic inflammatory disease of the arterial wall that can lead to the formation of plaque and subsequent cardiovascular disease.[3–5] Intervertebral disc degeneration (IDD) is a common condition that affects millions of people worldwide, and its prevalence increases with age.[6] IDD is a complex, multifactorial process involving genetic, environmental, and lifestyle factors, and is characterized by a dysfunctional intervertebral disc. The progression of IDD involves progressive structural changes and metabolic imbalances.[6] The condition causes chronic pain, reduced mobility, and disability, which require high healthcare costs to manage and treat. While the risk factors for these conditions are well-established, the underlying mechanisms that associate IDD with atherosclerosis remain undiscovered.

Previous studies have suggested that there may be mutual risk factors that contribute to the development of both conditions, such as inflammation and oxidative stress.[6–8] Additionally, some studies have identified calcification and lipid accumulation in the intervertebral disc among atherosclerotic individuals.[9,10] However, these are just observational studies,[11,12] and a causal investigation is required to better understand the association between the two conditions.

Mendelian randomization (MR) is a powerful tool that can help to infer causality by using genetic variants as instrumental variables. Genetic variants of atherosclerosis are used as proxies for exposure to establish whether the exposure is causally related to IDD. This approach can help overcome some of the limitations of observational studies, such as confounding and reverse causality, to provide valuable insights into the underlying mechanisms of IDD and atherosclerosis. This study aimed to facilitate the development of new therapeutic interventions for these conditions.

2 | METHODS

2.1 | Study design and data sources

We conducted an MR study to investigate the causal relationship between atherosclerosis and IDD. We used summary statistics from two large-scale genome-wide association studies (GWAS) as our primary data sources. The first GWAS provided summary statistics for genetic variants associated with atherosclerosis (UK Biobank, http://www.ukbiobank.ac.uk/, March 23, 2023, the GWAS ID of atherosclerosis is ukb-d-I9_CORATHER), while the second GWAS provided summary statistics for genetic variants associated with IDD (FinnGen, https://www.r8.finngen.fi/en, March 23, 2023, the GWAS ID of IDD is finn-b-M13_INTERVERTEB). The GWAS data of atherosclerosis were from 13 586 589 genetic variants in 14 334 coronary atherosclerosis cases and 346 860 controls of European ancestry. Genetic instruments for atherosclerosis were identified using results from the largest and newest available GWAS (UK Biobank) in individuals of European ancestry. Atherosclerosis was assessed using a combination of imaging techniques and clinical assessments. Imaging modalities such as coronary angiography, carotid ultrasound, and computed tomography angiography were employed to visualize and quantify atherosclerotic lesions in the arterial walls. The presence and progression of atherosclerosis had been extensively studied in relation to various pathologies, such as plaque rupture, arterial stenosis, and impaired blood flow. GWAS data for IDD were available from the FinnGen consortium, including 20 001 cases and 164 682 controls from 16 380 337 European-descent participants. IDD was measured using standardized clinical assessments, radiographic imaging, and patient-reported outcomes. Radiographic imaging, such as MRI and CT scans, was used to assess the severity of disc degeneration, including disc height loss, disc signal intensity changes, and the presence of disc herniation. Clinical assessments included physical examinations and patient-reported outcomes to evaluate pain, disability, and functional impairment associated with IDD.

2.2 | Instrumental variable selection

We used a two-sample MR approach, which involved selecting genetic variants associated with the exposure (atherosclerosis) in one sample and testing their association with the outcome (IDD) in a separate sample. We used IEU (https://gwas.mrcieu.ac.uk/, March 23, 2023) to identify genetic variants associated with atherosclerosis. The variants had the following criteria: (1) independent of each other (linkage disequilibrium $R^2 < 0.001$), (2) genome-wide significance ($p < 5 \times 10^{-8}$), (3) not associated with known confounders of the IDD-atherosclerosis relationship, and (4) available in the second GWAS dataset. We extracted summary statistics for the selected variants from the first GWAS dataset (UK Biobank).

2.3 | Statistical analysis

All analyses were conducted using the R statistical software (version 4.1.2). We used the MR-Egger regression, weighted median, and inverse-variance weighted (IVW) methods to estimate the causal effect of atherosclerosis on IDD. These analyses were performed using the MendelianRandomization package in R.[13] For genetic instruments of three or lesser, a fixed-effect model was used. For more than three genetic instruments, a multiplicative random-effects model was employed.[14] The Cochran's Q test was used for sensitivity analysis to assess the robustness of the MR assumptions. The MR Egger method was used to assess the presence of directional pleiotropy, which is considered a violation of the MR assumption that all genetic variants only influence the outcome through exposure. Leave-one-out sensitivity analyses were performed using the TwoSampleMR package in R to assess the influence of individual genetic variants on the overall effect estimate.[15]

2.4 | Ethics statement

The analytical studies received ethical approval from their respective local institutional review boards, and all participants provided written

informed consent.[14] The study was a secondary analysis of publicly available summary statistics and did not involve human subjects or personal information. As such, ethical approval was not required.

3 | RESULTS

We identified 31 genetic variants associated with atherosclerosis from the first GWAS dataset (Table S1) that met the inclusion criteria. These variants were used as instrumental variables to estimate the causal effect of atherosclerosis on IDD in the second GWAS dataset (Table S2). The sample size of the IDD analysis was 16 380 337 individuals of European ancestry.

Our MR analysis provided evidence for a causal relationship between atherosclerosis and IDD. The causal estimate from IVW was OR = 3.55 (95% confidence interval [CI]: 1.07–11.74, $p = 0.04$), indicating that each standard deviation increase in genetic predisposition to atherosclerosis was associated with a 0.61% increase in the odds of IDD. The complete MR results are provided in Table 1. The MR-Egger intercept was not statistically significant ($p = 0.69$) (Figure 1), suggesting that the results were not biased by directional pleiotropy.

Sensitivity analyses (i.e., leave-one-out analysis and alternative sets of instrumental variables) reported consistent results with the main analysis, suggesting the robustness of our findings (Table 2; Figures 2 and 3).

Overall, the results provided evidence for a causal link between IDD and atherosclerosis, suggesting that interventions targeting atherosclerosis could have potential benefits for reducing the risk of IDD. Further research is required to understand the underlying mechanisms that link these two conditions and to develop potential therapeutic interventions.

4 | DISCUSSION

This study highlighted the strong causal association between atherosclerosis and IDD. Specifically, we found that genetic variants

TABLE 1 The results of MR analysis of atherosclerosis on intervertebral disc degeneration.

Method	Nsnp	*b*	SE	*pval*	OR	95% confidence interval (CI)
Inverse-variance weighted	29	1.27	0.61	0.04	3.55	1.07–11.74
MR Egger	29	1.80	1.44	0.22	6.04	0.36–102.71
Weighted median	29	1.22	0.90	0.22	3.38	0.61–18.71

Abbreviations: CI, confidence interval; IDD, intervertebral disc degeneration; IVW, inverse-variance weighted; OR, odds ratio; SE, standard error.

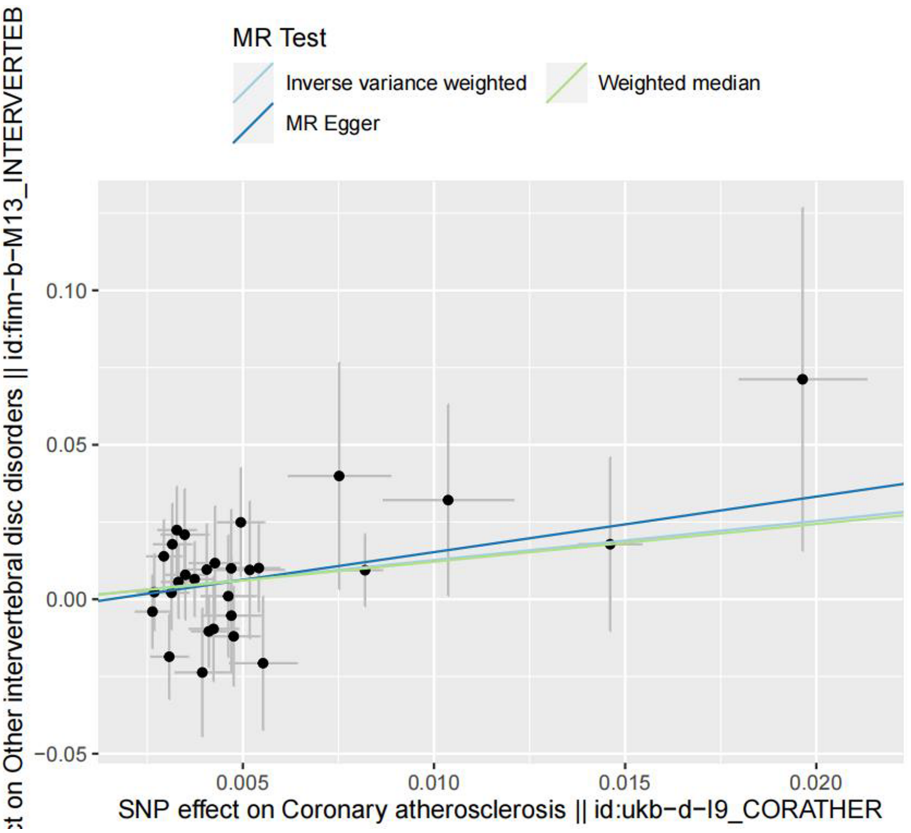

FIGURE 1 Scatter plot of the relationship between atherosclerosis and intervertebral disc degeneration using inverse-variance weighted, MR-Egger, and weighted median. Single-nucleotide polymorphism; ukb-d-I9_CORATHER, the GWAS ID of atherosclerosis; finn-b-M13_INTERVERTEB, the GWAS ID of IDD.

TABLE 2 Results of Cochran's Q test and MR-Egger intercept.

Exposure	id.exposure	Outcome	id.outcome	Method	Q	Q_df	Q_pval
Atherosclerosis	ukb-d-I9_CORATHER	IDD	finn-b-M13_INTERVERTEB	MR Egger	18.84	27	0.88
Atherosclerosis	ukb-d-I9_CORATHER	IDD	finn-b-M13_INTERVERTEB	IVW	19.00	28	0.90

Abbreviations: IDD, intervertebral disc degeneration; IVW, inverse-variance weighted.

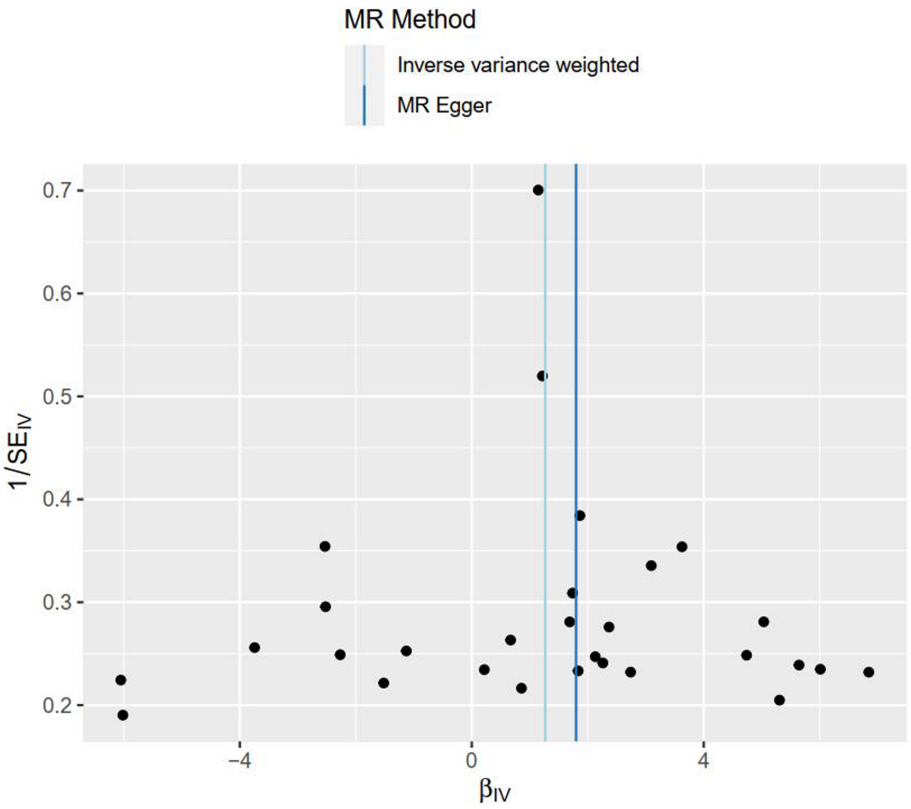

FIGURE 2 Funnel plot MR analysis of atherosclerosis on intervertebral disc degeneration.

associated with atherosclerosis were also associated with an increased risk of IDD, indicating that interventions targeting atherosclerosis could have potential benefits for reducing the risk of IDD. Our findings were consistent with prior observational studies of the two conditions.[9,16–20] However, this study provided causal evidence using a robust and unbiased approach.

The association between atherosclerosis and IDD has several clinical implications. First, it suggests that interventions targeting atherosclerosis, such as lifestyle modifications and pharmacological treatments, may also be beneficial for the prevention or management of IDD. Second, our results highlight the importance of the vascular component in the etiology of IDD, which could facilitate the development of novel therapeutic strategies targeting the shared pathophysiological mechanisms between the two conditions.

The mechanisms of the association between atherosclerosis and IDD are not well understood, but several potential pathways have been proposed. It is suggested that inflammation and oxidative stress are both involved in the pathogenesis of IDD and atherosclerosis and may be the causal link between the two conditions.[11,12] It is also suggested that atherosclerosis may contribute to IDD by reducing blood flow to the intervertebral discs, leading to decreased nutrient supply and increased oxidative stress.[18] Alternatively, atherosclerosis and IDD are both characterized by chronic inflammation, where inflammatory cytokines and chemokines produced in atherosclerotic plaques or IDD tissues may contribute to the progression of both conditions.[21] It is well known that dyslipidemia is a risk factor for atherosclerosis. Hence, alterations in lipid metabolism, abnormal cholesterol accumulation, and changes in lipid composition can promote degeneration in arteries and discs.[16,20,22–23] Recent research has demonstrated the involvement of microRNAs in the regulation of ferroptosis, a form of cell death via iron-dependent lipid peroxidation. The microRNAs involved in this pathway have been implicated in spinal disc degeneration and atherosclerosis.[24] Besides, the deposition of calcium phosphate crystals contributes to atherosclerosis and osteoarthritis. Similar pathological calcification may also occur in intervertebral discs, especially in aging and degeneration.[25] Furthermore, the loss of tensile forces in the arteries and compressive forces on discs leads to degenerative changes. Therefore, atherosclerosis and IDD may result from alterations in mechanical load sensing and signal transduction.[19] Lastly, atherosclerosis and IDD could also be linked via genetic risk

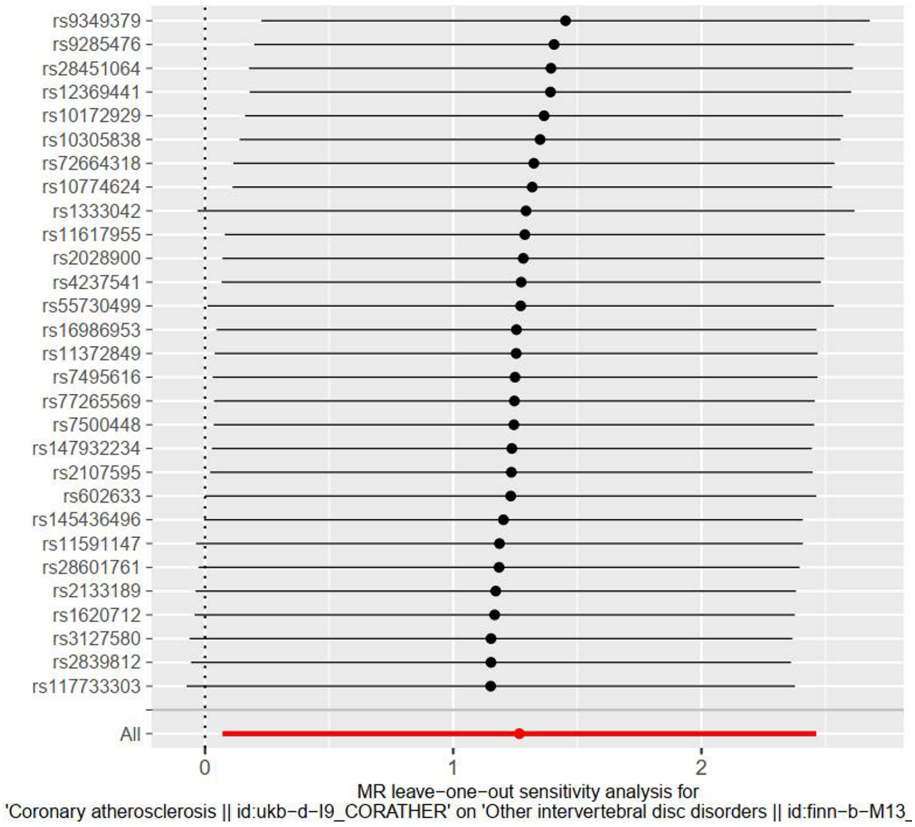

FIGURE 3 MR leave-one-out sensitivity analysis of atherosclerosis on intervertebral disc degeneration.

factors and immunometabolism.[6,26] For example, variants in the *COL9A2* and *COL9A3* genes, involved in ECM remodeling, have been associated with both conditions.[27] Some genetic variants increase susceptibility to both atherosclerosis and IDD. For example, mutations in the genes involved in collagen structure,[28] vitamin D metabolism,[16] and lipid metabolism can promote degenerative changes in arteries and discs.[28]

It is worth noting that while atherosclerosis is a well-known risk factor for cardiovascular diseases, little is known about the effects of atherosclerosis on other parts of the body. In this regard, this study complements atherosclerosis research beyond the cardiovascular system. Our study focused specifically on the potential role of atherosclerosis in IDD, using genetic variants associated with atherosclerosis as instrumental variables to estimate the causal effect of atherosclerosis on IDD. With this approach, we were able to control the confounding factors and reduce the potential for reverse causation, both of which are obstacles in observational studies.

IDD is a complex spinal condition with multifaceted clinical implications. While IDD has long been recognized as a potential source of pain and disability, its clinical relevance extends beyond its role as a pain generator. The pathogenesis of IDD involves intricate interactions between genetic, environmental, and biomechanical factors, resulting in structural and functional alterations of the intervertebral discs. These degenerative changes can manifest as disc height loss, disc herniation, and the development of spinal instability. Furthermore, IDD has been associated with a spectrum of clinical presentations, including radiculopathy, spinal stenosis, and spinal deformities. Understanding the clinical relevance of IDD is crucial for optimizing patient care, tailoring treatment strategies, and developing targeted interventions. By evaluating the causal effect of atherosclerosis on the risk of IDD using a Mendelian randomization approach, our study contributes to the broader understanding of the etiology and clinical implications of IDD, facilitating the identification of potential therapeutic targets and preventive measures.

Our findings suggested that atherosclerosis may be an important modifiable risk factor for IDD, and strategies aimed at preventing or treating atherosclerosis may have benefits beyond cardiovascular health. Further research is needed to confirm these findings and explore potential interventions to reduce the risk of IDD in individuals with atherosclerosis. Several potential interventions may help to reduce the risk of IDD, such as maintaining a healthy weight, quitting smoking, staying active, and managing underlying health conditions (e.g., diabetes and high blood pressure).

This study had several strengths, including the use of summary statistics from large-scale GWAS datasets, the use of multiple MR methods to assess the robustness of our findings, and the inclusion of sensitivity analyses to evaluate biases. Overall, this study highlighted the potential value of MR to investigate the causal relationships between exposures and outcomes, particularly in cases where randomized controlled trials may not be feasible or ethical. However, some limitations to our study should be considered. First, our analysis was restricted to individuals of European ancestry, and further research is needed to investigate other populations. Second, the change in a biomarker cannot be directly correlated with genetic

variation because the latter is indicative of the cumulative effect of lifetime exposure to the biomarker on the outcome.[29] Third, our study only investigated the potential causal association between atherosclerosis and IDD. Apart from atherosclerosis, there is a possibility that other factors can contribute to the development of IDD. Fourth, while our study utilized a large-scale population-based cohort, we recognize that the statistical power may vary for different genetic variants and outcomes. Fifth, we still have incomplete understanding of the biological mechanisms, and limited knowledge about the biological pathways connecting the genetic variant to the exposure and the outcome may affect the interpretation of the results. However, based on an array of statistical methods for quality control, the pleiotropic bias is less likely in our study.

5 | CONCLUSION

In summary, our MR study provided evidence for a causal association between atherosclerosis and IDD. These findings highlighted the importance of the vascular component in the pathophysiology of IDD and suggested that interventions targeting atherosclerosis may also have a beneficial effect on IDD. Our findings could essentially assist with disease prevention and management, and the study also highlighted the potential value of MR to investigate causal relationships between exposures and outcomes. Further research is needed to elucidate the underlying mechanisms of both atherosclerosis and IDD, as well as to explore the potential therapeutic implications of our findings.

AUTHOR CONTRIBUTIONS

S.C.Z., C.J.L., and Q.L. conceptualized and designed the study. X.X.Z., R.Z.H., and L.M. performed data analysis. Y.T.C. wrote the manuscript. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of repository/repositories and accession number(s) can be found in the article/Supporting Information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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