

## ORIGINAL RESEARCH ARTICLE

# Intervertebral disc degeneration and generalized anxiety disorder: A bidirectional two-sample Mendelian randomization study

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## Abstract

**Introduction:** The co-occurrence of chronic musculoskeletal conditions and psychiatric disorders is clinically significant; however, the causal direction between intervertebral disc degeneration (IVDD) and generalized anxiety disorder (GAD) remains poorly defined.

**Objective:** To evaluate the bidirectional causal association between IVDD and GAD using Mendelian randomization (MR).

**Methods:** Leveraging aggregate statistics from extensive genome-wide association study (GWAS) datasets, we performed a two-sample bidirectional MR investigation. Genetic proxies serving as instrumental variables (IVs) were identified using stringent filtering criteria, including a significance threshold of  $p < 5 \times 10^{-8}$ , and the exclusion of linkage disequilibrium ( $r^2 < 0.001$ , distance  $> 10,000$  kb). The primary causal effect was quantified using inverse variance-weighted (IVW) regression, while robustness of the estimates was cross-validated using MR-Egger, weighted median, and model-based estimators. To ensure the integrity of the inference, we performed sensitivity diagnostics, including Cochran's Q test for heterogeneity, the MR-Egger intercept for directional pleiotropy, and leave-one-out analysis for individual single-nucleotide polymorphism stability.

**Results:** In the forward-direction analysis, a genetic predisposition to IVDD was correlated with an increased risk of GAD, as confirmed by both the IVW model (odds ratio [OR] = 1.198, 95% confidence interval [CI]: 1.069–1.343,  $p = 0.002$ ) and the weighted median method (OR = 1.193, 95% CI: 1.024–1.389,  $p = 0.023$ ). In contrast, no statistically significant causal influence of GAD on the risk of IVDD was observed ( $p > 0.05$ ). Comprehensive sensitivity analyses confirmed that the selected IVs satisfied the core MR assumptions. Furthermore, diagnostic tests revealed no evidence of substantial heterogeneity (Q  $p$ -value = 0.098) or significant bias stemming from horizontal pleiotropy (Egger intercept  $p$ -value = 0.568).

**Conclusion:** Bidirectional MR analysis supports a unidirectional causal relationship from IVDD to GAD, underscoring the importance of routine anxiety screening and targeted psychological interventions in patients with spinal degeneration to mitigate subsequent psychiatric deterioration.

**Keywords:** Intervertebral disc degeneration; Generalized anxiety disorder; Mendelian randomization; Causality

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## 1. Introduction

Anxiety disorders constitute a formidable global health exigency, with an annual prevalence affecting approximately one-fifth of the adult population. Beyond their high incidence, these conditions are characterized by a profound clinical burden, often leading to severe disruptions to daily functioning and marked deterioration in health-related quality of life.<sup>1,2</sup> Generalized anxiety disorder (GAD), a core subtype within the anxiety spectrum, is clinically defined by persistent ( $\geq 6$  months), pervasive (involving  $\geq 2$  life domains), and uncontrollable anxiety. GAD is frequently accompanied by autonomic hyperarousal (e.g., palpitations, diaphoresis) and cognitive-motor symptoms (e.g., impaired concentration, muscle tension).<sup>3–6</sup> Epidemiological data indicate a considerable disease burden associated with GAD: its 12-month prevalence ranges from 0.9% to 2.9%, while lifetime prevalence ranges from 3.7% to 6.2%, with evidence of an increasing population burden.<sup>3,7</sup> Notably, GAD exhibits high rates of disability and comorbidity (e.g., other psychiatric disorders), and has been associated with increased mortality risk, severely impacting social functioning and augmenting all-cause mortality.<sup>8</sup> The pathogenesis of GAD is multifactorial, involving contributions from genetic factors, sex-based differences, and comorbid psychiatric conditions.<sup>9</sup> Existing evidence<sup>10,11</sup> suggests a close pathophysiological link between pain symptoms and GAD.

Low back pain (LBP), a ubiquitous clinical condition, transcends demographic boundaries and imposes a pervasive burden across the entire age spectrum. Current global surveillance estimates suggest that nearly 540 million individuals are affected annually. For several decades, LBP has remained a paramount contributor to global disability, fundamentally compromising functional independence and representing a major source of non-fatal health loss worldwide.<sup>12, 13</sup> Importantly, chronic LBP is significantly associated with psychological and psychiatric disorders. A multicenter cohort study conducted in China demonstrated that the prevalence of anxiety symptoms among individuals with chronic LBP was significantly higher than observed in the general population.<sup>14</sup> This finding is corroborated by a cross-sectional survey in India, which revealed varying degrees of psychological comorbidity, including GAD, among patients with chronic LBP.<sup>15</sup> Furthermore, the bidirectional pathological interaction between chronic LBP and GAD may substantially exacerbate pain sensitization, prolong functional impairment, and increase the risk of adverse clinical outcomes.<sup>16</sup> Intervertebral disc degeneration (IVDD), as the most prevalent form of degenerative spinal pathology, is widely recognized as a critical pathological substrate underlying the development

of LBP.<sup>17</sup> Investigations into the psychological status of patients with IVDD have found that individuals with chronic discogenic LBP are particularly vulnerable to psychological disorders, including anxiety and depression.<sup>18,19</sup> However, existing studies examining the association between IVDD and GAD are largely observational and therefore susceptible to methodological limitations, including residual confounding, reverse causation, and selection bias. Consequently, there is a compelling need to adopt causal inference approaches—specifically Mendelian randomization (MR)—to decipher the reciprocal relationship between IVDD and GAD. Such an approach can provide robust, high-level evidence essential for the development of precision-oriented biopsychosocial therapeutic strategies.

Mendelian randomization is a powerful framework for causal inference that leverages genetic polymorphisms as instrumental variables (IVs) to proxy modifiable exposures. This technique capitalizes on the stochastic distribution of alleles during gametogenesis, thereby effectively mimicking the design of randomized controlled trials to evaluate the impact of an exposure on clinical outcomes.<sup>20,21</sup> Because genotypes are assigned randomly at conception, the associations derived from MR are inherently shielded from the extraneous variables and residual confounding that often plague traditional observational studies. Consequently, this methodological advantage minimizes confounding bias, facilitating a more rigorous and dependable estimation of causal effects.<sup>22</sup> Moreover, since the germline DNA sequence remains invariant and precedes the onset of disease, the MR approach successfully bypasses the pitfalls of reverse causality.<sup>21</sup> In the present study, we implemented a bidirectional two-sample MR analysis using summary statistics from large-scale genome-wide association studies (GWAS). Our primary objective was to elucidate the reciprocal causal architecture between IVDD and GAD, aiming to provide a theoretical basis for optimizing clinical management strategies and mitigating psychiatric comorbidities in patients with spinal conditions.

## 2. Methods

### 2.1. Study design

Leveraging summary statistics from GWAS, this research adopted a bidirectional two-sample MR framework to systematically deconstruct the genetic-level causal relationship between IVDD and GAD. To ensure the validity and robustness of the causal estimates, the analytical design meticulously satisfied the three cardinal MR postulates, as illustrated in the conceptual framework presented in [Figure 1](#). These postulates include: (i)

relevance postulate: it is imperative that the selected IVs exhibit a robust and significant correlation with the target exposures (IVDD or GAD). This potent association serves as the fundamental pillar underpinning the validity of the entire causal inference process; (ii) independence postulate: the chosen genetic proxies must remain orthogonal to potential confounding factors that might otherwise distort the exposure-outcome association. As indicated by the “X” markers in Figure 1, we implemented a stringent filtration protocol to ensure that the selected loci are not associated with known confounders, effectively shielding the results from external bias; (iii) exclusion restriction postulate: this requirement mandates that the IVs operate on the clinical outcome exclusively via the exposure pathway, with no direct alternative routes—a condition essential for mitigating the impact of horizontal pleiotropy. In Figure 1, the “X” symbol along the direct IV-to-outcome path indicates that exhaustive pleiotropy diagnostics were conducted to eliminate direct genetic effects, thereby safeguarding the specificity and precision of the final causal effect estimates.

## 2.2. Data sources

Genetic summary statistics for IVDD were retrieved from the FinnGen consortium’s 12th data release (<https://r12.finnngen.fi/>), ensuring high-quality genomic data.<sup>23</sup> Case ascertainment strictly adhered to the International Classification of Diseases (ICD) diagnostic criteria, using the following third-level diagnostic codes: ICD-10: M51, ICD-9: 722, and ICD-8: 725. This dataset comprised 51,683 cases and 353,224 controls. Notably, genetic data for GAD were derived from the same source, using the diagnostic criteria ICD-10: F411 and ICD-9: 3000C to construct a genetic database comprising 7,148 individuals with GAD and 444,414 controls. Both study cohorts underwent rigorous quality control procedures to ensure accurate phenotype definition and reliable genotype data.

## 2.3. Instrumental variables selection

This study strictly adhered to the three core assumptions of MR and employed the TwoSampleMR package in R (version 4.4.2) to meticulously select IVs. First, to satisfy the relevance assumption, we extracted single-nucleotide polymorphisms (SNPs) that were significantly associated with the exposure factor from the GWAS summary data, using a genome-wide significance threshold of  $p < 5 \times 10^{-8}$ . A subsequent clumping procedure (with parameters set to  $r^2 < 0.001$  and distance  $> 10,000$  kb) was performed to eliminate redundant loci within linkage disequilibrium regions, thereby ensuring the independence of the IVs.<sup>24</sup> Second, to mitigate weak instrument bias, we evaluated the strength of the IVs by calculating the  $F$ -statistic ( $F = \beta^2/$

$SE^2$ ) and included only IVs with an  $F$ -statistic greater than 10, signifying sufficiently strong instruments.<sup>25</sup> Finally, to uphold the independence and exclusion restriction assumptions, we utilized the Phenoscanner V2 database to perform phenotypic annotation of the initially selected SNPs, systematically removing pleiotropic loci that are directly associated with known confounders and outcome variables. During the harmonization phase, we rigorously compared the exposure and outcome datasets, eliminating SNPs with palindromic structure that could introduce allele frequency discrepancies. This thorough process ultimately resulted in the construction of a high-quality set of genetic IVs.<sup>26</sup>

## 2.4. Mendelian randomization analysis

This study establishes a multi-model analytical framework centered on the inverse variance-weighted (IVW) method to evaluate the causal relationship between IVDD and GAD across multiple dimensions. For core causal assessment, the IVW method under a random-effects model was employed as the primary method for estimating causal effects. Assuming that all IVs are free of horizontal pleiotropy, this method aggregates the Wald ratios of each SNP, weighted by their inverse variance, to yield the most statistically powerful causal effect estimate.<sup>27</sup> To ensure the robustness of the findings, model consistency verification was performed using supplementary analyses, including the weighted median method, MR-Egger regression, the weighted mode method, and the simple mode method. Notably, the weighted median method provides consistent estimates even when up to 50% of the IVs are invalid, whereas MR-Egger regression assesses whether there is any genetic effect bias violating MR assumptions. For sensitivity analysis and bias detection, the research team employed a three-pronged strategy to assess the robustness of the inferred causal relationship: (i) Cochran’s  $Q$  statistic was used to quantitatively evaluate the level of heterogeneity between the IVs; (ii) the intercept term from MR-Egger regression was examined to detect significant horizontal pleiotropic bias; and (iii) a leave-one-out sensitivity analysis was implemented, systematically removing one SNP at a time and recalculating the effect size to identify any isolated genetic loci that might disproportionately influence the overall results.<sup>28</sup> This multi-layered validation framework not only effectively controls for potential biases associated with genetic IVs but also provides comprehensive, multidimensional evidence supporting the directionality and strength of the causal association.

## 2.5. Statistical analysis

Data analysis for this study was conducted using the R statistical computing platform (version 4.4.2), with a

statistical significance threshold set at  $p < 0.05$ . Effect sizes are reported as odds ratios (ORs) along with their 95% confidence intervals (CIs). The biological interpretation of the OR values is as follows: an  $OR > 1$  with  $p < 0.05$  indicates a positive correlation between the exposure factor and the outcome event, while an  $OR < 1$  with  $p < 0.05$  suggests a negative correlation. These statistical criteria were employed to assess the strength and significance of associations between variables.

### 3. Results

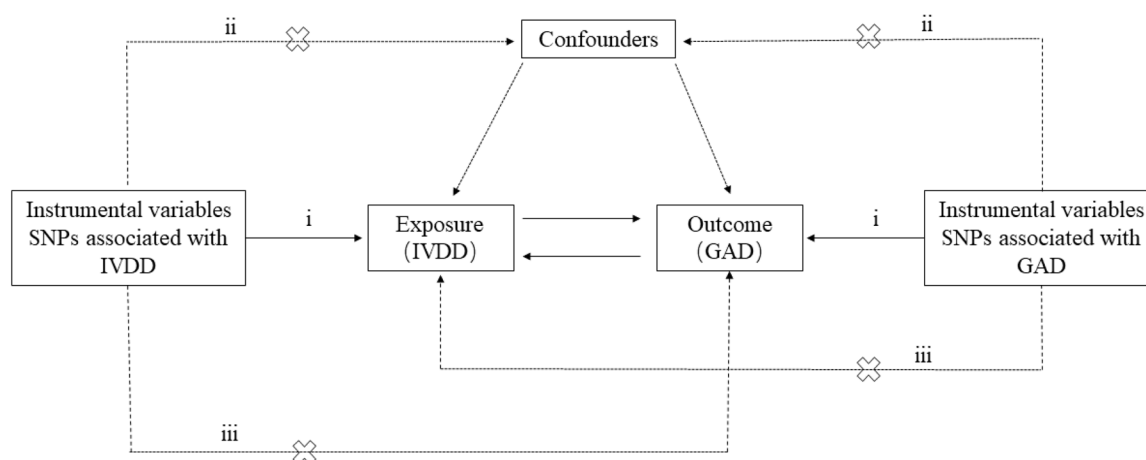
#### 3.1. Instrumental variables selection

This study constructed genetic association analysis models for IVDD and GAD via a rigorous instrumental

variable selection process. Specifically, in the analytical framework with IVDD as the exposure, 55 SNPs were identified that were significantly associated with the phenotype and met the independence criteria. All genetic instruments exhibited robust association characteristics ( $F$  statistic  $> 10$ ). In the GAD exposure model, applying the same stringent quality control criteria identified 14 valid SNPs, with instrumental-variable strength exceeding the recommended threshold ( $F$  statistic  $> 10$ ).

#### 3.2. MR analysis

We leveraged bidirectional MR to interrogate the genetic causal link between IVDD and GAD. Using random-effects IVW regression as the primary analytical approach, we found that IVDD significantly increased the risk of



**Figure 1.** Schematic diagram of the core assumptions guiding the MR study design. (i) Relevance: genetic instruments (SNPs) are associated with the exposure; (ii) Independence: SNPs are independent of confounders; (iii) Exclusion restriction: SNPs affect the outcome only through the exposure (no direct pathway/pleiotropy).

Abbreviations: GAD: Generalized anxiety disorder; IVDD: Intervertebral disc degeneration; MR: Mendelian randomization; SNPs: Single-nucleotide polymorphisms.

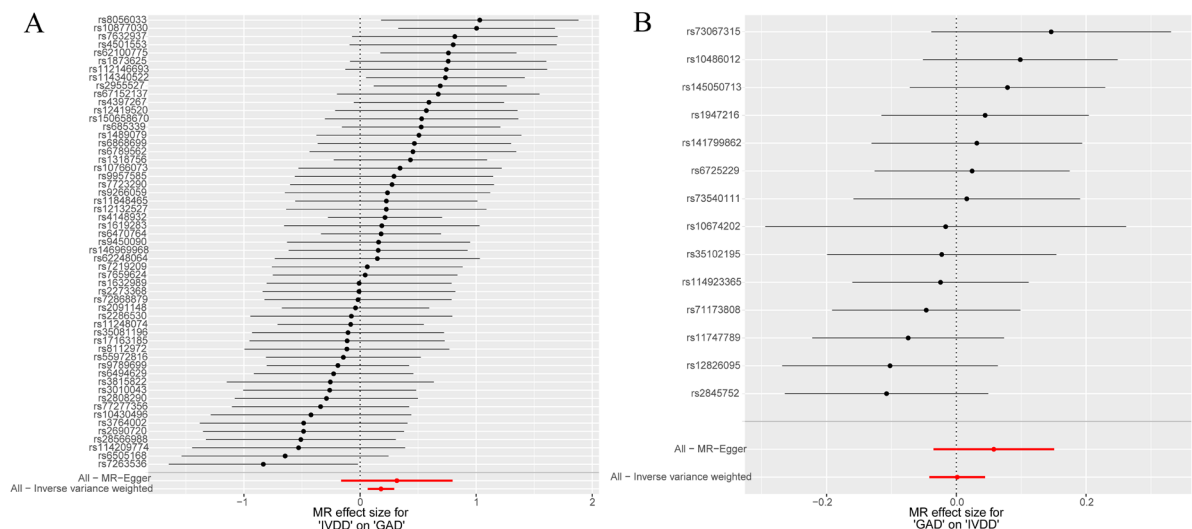
GAD ( $OR = 1.198$ , 95% CI: 1.069–1.343,  $p = 0.002$ ), a statistically robust positive association (Figure 2A). Consistent directional estimates were also obtained from complementary methods, including weighted median, simple mode, and weighted mode estimators. These results are graphically summarized in Figure 3A and detailed in Table 1. To enhance interpretability, we also constructed a forest plot integrating all five MR methods (Figure 4A).

Conversely, reverse MR analysis—again centered on IVW—did not support a causal effect of GAD on IVDD susceptibility ( $OR = 1.001$ , 95% CI: 0.959–1.045,  $p = 0.949$ ; Figure 2B). This null finding was consistently corroborated by MR-Egger, weighted median, simple mode, and weighted mode approaches. The integrated output of these analyses is displayed in Figure 3B and tabulated in Table 1,

with a corresponding forest plot for intuitive visualization (Figure 4B).

#### 3.3. Sensitivity analyses

We assessed the stability of the genetic causal link between IVDD and GAD through multidimensional sensitivity analyses. In the forward causal analysis of IVDD on GAD, neither MR-Egger regression (Cochran's  $Q = 66.696$ ,  $p = 0.098$ ) nor IVW analysis (Cochran's  $Q = 67.112$ ,  $p = 0.108$ ) indicated meaningful heterogeneity. Funnel plot symmetry further supported the absence of bias (Figure 5A). The robustness of this association remained unaffected by horizontal pleiotropy, as confirmed by the MR-Egger intercept test ( $p = 0.568$ ), as detailed in Table 2. Additionally, leave-one-out analysis demonstrated



**Figure 2.** MR forest plots for assessing bidirectional causality between IVDD and GAD. (A) Effect of IVDD on GAD. (B) Effect of GAD on IVDD. Abbreviations: GAD: Generalized anxiety disorder; IVDD: Intervertebral disc degeneration; MR: Mendelian randomization.

**Table 1. Bidirectional MR Results for IVDD and GAD**

| Exposure | Outcome | Method          | nSNP | $\beta$ | SE    | OR (95% CI)          | p-value |
|----------|---------|-----------------|------|---------|-------|----------------------|---------|
| IVDD     | GAD     | MR-Egger        | 55   | 0.317   | 0.244 | 1.373 (0.851, 2.217) | 0.200   |
|          |         | Weighted median | 55   | 0.176   | 0.078 | 1.193 (1.024, 1.389) | 0.023   |
|          |         | IVW             | 55   | 0.181   | 0.058 | 1.198 (1.069, 1.343) | 0.002   |
|          |         | Simple mode     | 55   | 0.056   | 0.213 | 1.058 (0.697, 1.605) | 0.793   |
|          |         | Weighted mode   | 55   | 0.062   | 0.185 | 1.064 (0.741, 1.528) | 0.739   |
| GAD      | IVDD    | MR-Egger        | 14   | 0.058   | 0.047 | 1.059 (0.965, 1.163) | 0.247   |
|          |         | Weighted median | 14   | -0.006  | 0.030 | 0.994 (0.938, 1.054) | 0.849   |
|          |         | IVW             | 14   | 0.001   | 0.022 | 1.001 (0.959, 1.045) | 0.949   |
|          |         | Simple mode     | 14   | 0.001   | 0.056 | 1.001 (0.897, 1.116) | 0.992   |
|          |         | Weighted mode   | 14   | 0.002   | 0.050 | 1.002 (0.909, 1.105) | 0.962   |

Abbreviations: CI: Confidence interval; GAD: Generalized anxiety disorder; IVDD: Intervertebral disc degeneration; IVW: Inverse-variance weighted; MR: Mendelian randomization; OR: Odds ratio; nSNP: Number of single-nucleotide polymorphisms; SE: Standard error.

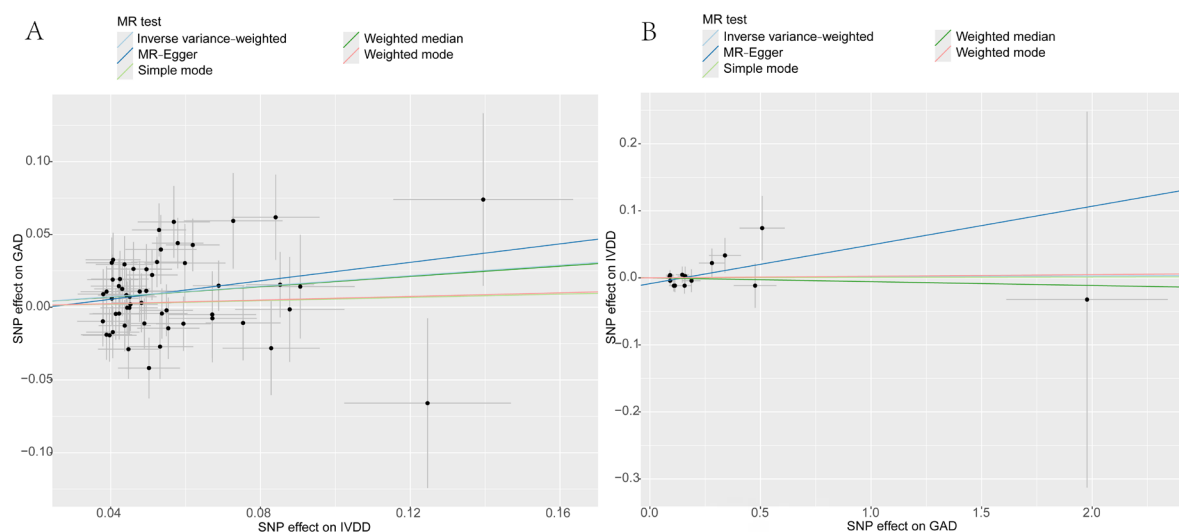
consistent findings, with no single SNP disproportionately influencing the trajectory of the MR results (Figure 6A), thus providing strength and consistency to the study findings.

In the reverse causal relationship validation framework, the genetic effect analysis of GAD on IVDD similarly exhibited a high degree of methodological consistency. Neither the MR-Egger regression model (Cochran's  $Q = 8.713$ ,  $p = 0.727$ ) nor the core results of IVW analysis (Cochran's  $Q = 10.505$ ,  $p = 0.652$ ) detected significant heterogeneity. Symmetric SNP distribution in the funnel plot (Figure 5B) corroborated the robustness of the results.

The MR-Egger intercept test ( $p = 0.205$ ) excluded horizontal pleiotropy as a confounder (Table 2). Leave-one-out analysis demonstrated that omitting any single locus did not alter the direction of the causal estimate (Figure 6B), providing additional assurance of the reliability and reproducibility of our conclusions.

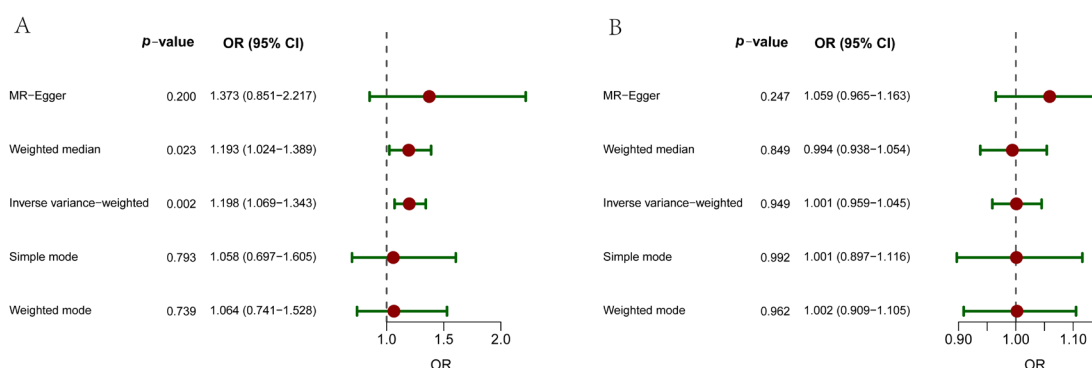
#### 4. Discussion

Using publicly available GWAS summary statistics and a two-sample bidirectional MR design, this study examined potential causal links between IVDD and GAD. The analysis indicated a significant causal effect of IVDD on elevated GAD risk. In contrast, genetic predisposition



**Figure 3.** Scatter plots of genetic associations were used to estimate causal effects between IVDD and GAD. The slope of each fitted line represents the causal estimate obtained from one of five MR methods: inverse variance-weighted, weighted median, MR-Egger, simple mode, and weighted mode. (A) Effect of IVDD on GAD. (B) Effect of GAD on IVDD.

Abbreviations: GAD: Generalized anxiety disorder; IVDD: Intervertebral disc degeneration; MR: Mendelian randomization; SNP: Single-nucleotide polymorphism.



**Figure 4.** Bidirectional MR forest plots for evaluating the causal association between IVDD and GAD. (A) Effect of IVDD on GAD. (B) Effect of GAD on IVDD.

Abbreviations: GAD: Generalized anxiety disorder; IVDD: Intervertebral disc degeneration; MR: Mendelian randomization; OR: Odds ratio.

to GAD was not found to meaningfully increase the likelihood of IVDD.

The association between IVDD and GAD has garnered increasing attention in the academic community. Relevant data from evidence-based medicine indicate a significant bidirectional relationship between chronic low back pain (CLBP) and GAD. This interaction not only intensifies patients' pain perception and functional impairment but may also lead to compounded risks of poor clinical prognosis and inadequate treatment. Notably, although pain intensity is often positively correlated with anxiety levels, this association does not always align proportionally with the severity of structural spinal pathology, suggesting

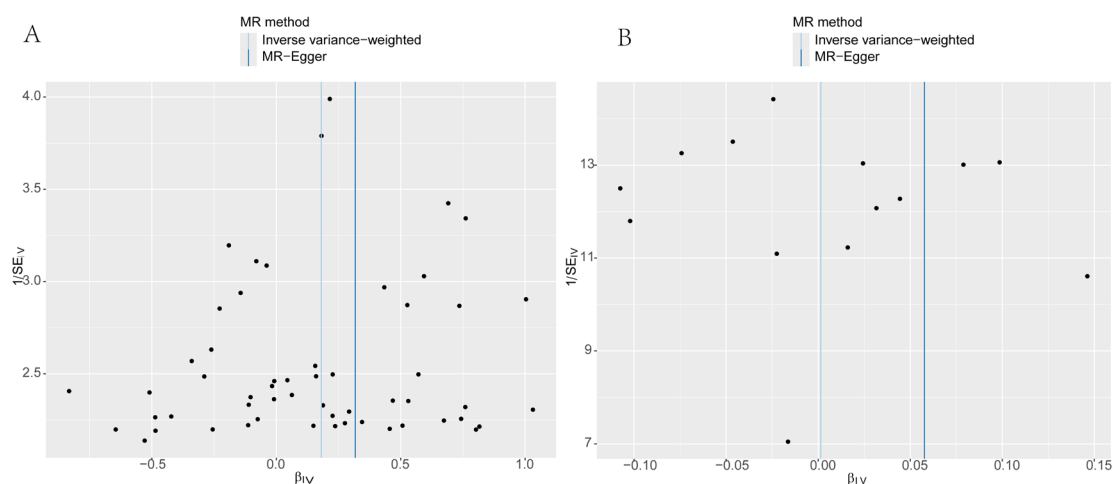
that psychological factors play an independent and pivotal role in the disease's progression.<sup>16</sup> Clinical research has further illuminated the multifaceted psychological disorder characteristics in CLBP patients. A large-scale cross-sectional study ( $n = 1,172$ ) demonstrated that the prevalence of anxiety symptoms in this population reached 23.89%, a figure substantially higher than the baseline rate of 10.4% in the general population.<sup>14</sup> Even amidst the heightened psychological stress during the COVID-19 pandemic, CLBP patients exhibited an increased susceptibility to anxiety, highlighting the unique psychological vulnerability of this group. Further analyses have shown that the degree of functional impairment in

these patients is closely linked to anxiety, depression, and sleep disturbances, though the deeper connections between pain intensity, anxiety, and emotional disorders remain to be elucidated.<sup>15</sup> As a core etiology of CLBP, the comorbid mechanisms between IVDD and GAD have become a focal point of research. Numerous studies have confirmed that the incidence of psychological disorders is significantly elevated in patients with discogenic LBP, and a clear dose-response relationship exists between the degree of IVDD degeneration and the level of anxiety.<sup>18, 19, 29</sup>

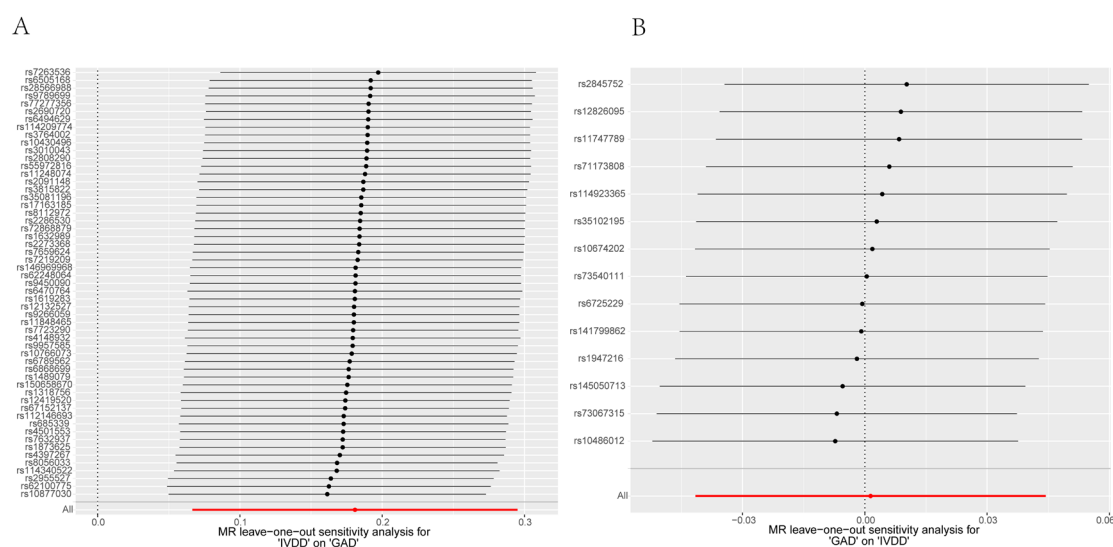
The relationship between IVDD and GAD is characterized by a complex biological interplay. At the core of this interaction are neuroplasticity and alterations in the functional mapping of the limbic system. Chronic discogenic pain, mediated by IVDD, not only sensitizes peripheral nerves but also triggers structural and functional reorganization of the central nervous system. Functional magnetic resonance imaging studies have substantiated, at the molecular level, that patients with chronic spinal pain exhibit marked morphological atrophy and functional connectivity reorganization in key brain regions responsible for emotional regulation, such as the prefrontal cortex, amygdala, and anterior cingulate cortex. These regions are central hubs for pain perception and the processing of negative emotions. When pathological signals from degenerated discs persist, the prefrontal cortex's inhibitory control over the lower limbic system is weakened, leading to heightened sensitivity to external threat signals and the emergence of GAD symptoms in the context of genetic predisposition. Furthermore, this neuroplasticity process is often accompanied by an imbalance in complex neurotransmitter systems. For instance, inhibitory pathways in central gamma-aminobutyric acid (GABAergic) neurons are diminished, while glutamatergic activity is heightened. This molecular imbalance provides the biological foundation for the transition of IVDD to anxiety symptoms, suggesting that interventions targeting these neurotransmitter pathways could offer dual benefits for both physical and psychological health.<sup>10,30,31</sup> Moreover, the “peripheral-central” inflammatory interaction plays an indispensable “messenger” role in the causal chain between IVDD and GAD. Modern spinal pathology has clarified that IVDD is not merely a mechanical degeneration but an inflammatory process driven by a cascade of pro-inflammatory mediators. During disc degeneration, damaged disc tissue releases a variety of pro-inflammatory cytokines, including interleukin-1 beta, interleukin-6, and tumor necrosis factor-alpha. We hypothesize that these inflammatory mediators in peripheral circulation may disrupt the blood-brain barrier or utilize the vagus nerve pathway to mediate “peripheral-central” inflammatory crosstalk, thereby triggering

widespread neuroinflammation. Central nervous system inflammation, through the activation of microglial cells, disrupts the homeostatic regulation of the hypothalamic–pituitary–adrenal (HPA) axis. The overactivation of the HPA axis, coupled with impaired negative feedback mechanisms, is one of the most recognized biological markers in the pathogenesis of GAD. Thus, inflammatory signals generated by IVDD may serve as a long-term biochemical stressor, continuously depleting the brain's capacity for stress regulation, thereby transforming localized disc pathology into a systemic psychiatric process. This “systemic inflammation-mediated mechanism” also plausibly explains why certain IVDD patients, even during periods of pain relief, continue to suffer from elevated levels of anxiety.<sup>32–34</sup> Furthermore, dysregulation of the autonomic nervous system (ANS) represents a critical pathway linking the physiological damage of IVDD with the emotional disturbances characteristic of GAD. The functional impairments and chronic discomfort caused by IVDD act as sustained physiological stressors, leading to disruptions in ANS regulation over the course of the disease. Clinical physiological monitoring has shown that spinal disease patients with anxiety traits commonly exhibit heightened sympathetic nervous system activity and a significant reduction in parasympathetic tone. This imbalance in homeostasis not only exacerbates disc degeneration through muscle tension and localized blood flow disturbances but also induces a range of somatic symptoms, such as palpitations, chest tightness, muscle tremors, and gastrointestinal dysfunction. These bodily sensations are often misperceived by patients as signs of severe cardiovascular or respiratory diseases, thereby reinforcing the severity of their anxiety. This physiological “feedback loop” transforms what was initially a localized structural disorder of the spine into a diffuse, multisystem suffering, significantly deepening the pathological progression of GAD.<sup>31,35,36</sup> In conclusion, IVDD not only manifests as a localized organic lesion but may also trigger or amplify psychological disorders through neurobiological pathways. However, current evidence remains insufficient to determine whether psychological disturbances are a primary causal factor of IVDD or merely a secondary manifestation. The precise dissection of this causal chain will be a crucial direction for future research.

It should be noted that prior investigations into this association have largely relied on cross-sectional designs, which are inherently limited in their ability to establish causality because they lack longitudinal evidence. Key methodological constraints in earlier observational work include frequently underpowered sample sizes and an inability to adequately address reverse causation or residual confounding—factors that may systematically bias



**Figure 5.** Funnel plots illustrating the causal effects between GAD and IVDD. The absence of marked asymmetry in the plots suggests homogeneous associations. (A) Effect of GAD on IVDD. (B) Effect of IVDD on GAD. Abbreviations: GAD: Generalized anxiety disorder; IVDD: Intervertebral disc degeneration; MR: Mendelian randomization.



**Figure 6.** Leave-one-out sensitivity analysis evaluating the influence of individual SNPs on the genetic association between IVDD and GAD. The stability of the association is supported by the consistency of the causal estimates when each SNP is sequentially excluded from the analysis. (A) Effect of GAD on IVDD. (B) Effect of IVDD on GAD. Abbreviations: GAD: Generalized anxiety disorder; IVDD: Intervertebral disc degeneration; MR: Mendelian randomization.

**Table 2. Results of Cochran's Q Test and MR-Egger intercept analysis**

| Exposure | Outcome | Method   | Heterogeneity |         | Pleiotropy |       |         |
|----------|---------|----------|---------------|---------|------------|-------|---------|
|          |         |          | Cochran's Q   | p-value | Intercept  | SE    | p-value |
| IVDD     | GAD     | MR-Egger | 66.696        | 0.098   | <0.001     | 0.013 | 0.568   |
|          |         | IVW      | 67.112        | 0.108   |            |       |         |
| GAD      | IVDD    | MR-Egger | 8.713         | 0.727   | <0.001     | 0.006 | 0.205   |
|          |         | IVW      | 10.505        | 0.652   |            |       |         |

Abbreviations: GAD: Generalized anxiety disorder; IVDD: Intervertebral disc degeneration; SE: Standard error.

results. In contrast, the present study applied an innovative bidirectional two-sample MR framework, using genetic instruments to emulate a naturally randomized trial. This approach not only mitigates the limitations inherent to observational designs but also permits explicit testing of causal directionality, yielding more robust evidence regarding the potential causal relationship between these traits.

The bidirectional two-sample MR analysis employed in this study offers significant methodological innovation, with its advantages particularly evident in the following three dimensions. First, in selecting IVs, stringent GWAS criteria ( $F$  statistic  $> 10$ ) were applied to identify genetic variants with strong associations to the exposure, thereby approximating the random allocation principle of randomized clinical trials. Although randomized trials represent the gold standard for clinical evidence, their use in practice is often limited by rigorous ethical oversight, substantial costs, and extended timelines.<sup>37</sup> In contrast, the MR framework employed in this study leverages a natural randomization process, effectively mitigating reverse causation and confounding factors while substantially improving study feasibility. Second, for data quality control, we carefully curated summary-level data from genome-wide association studies and restricted the analysis to individuals of European ancestry. This approach minimized heterogeneity due to population stratification and enhanced the comparability of genetic backgrounds across the study sample. This strategy not only minimized the potential for confounding effects arising from population stratification but also significantly improved the accuracy of causal effect estimates by excluding cross-ethnic genetic heterogeneity. It is particularly important to emphasize that the clinical translational value identified in this study carries a dual significance: on the one hand, establishing a causal association between IVDD and GAD provides novel molecular epidemiological evidence for investigating the comorbid mechanisms of the two diseases; on the other hand, quantifying the magnitude of this effect can guide the search for early predictive biomarkers and support the design of targeted preventive strategies.

Moreover, this study is not without methodological limitations that warrant further exploration in future research. First, due to the stringent requirements of MR analysis regarding population genetic homogeneity, the study sample was confined to individuals of European descent. Given the significant genetic, environmental, and phenotypic differences across ethnic groups, the global generalizability of the findings remains to be validated. Consequently, future studies must prioritize trans-ethnic MR research by integrating diverse GWAS data from

populations in East Asia, Africa, and Latin America. Such an approach would enable a comprehensive assessment of the robustness of the causal relationship between IVDD and GAD across different genetic backgrounds. Second, while MR is a powerful tool for elucidating the causal effects of lifelong genetic susceptibility, as a statistical inference method, it cannot fully capture the complexities of clinical dynamic processes. To translate the current genetic findings into actionable clinical intervention pathways, large-scale, multicenter, prospective cohort studies are essential. These studies would not only validate the genetic inferences made in this study in real-world clinical settings but also facilitate the dynamic tracking of confounding variables such as age, sex, and body mass index. This would provide deeper insights into the modifying effects of these factors on the “pain-anxiety” causal chain, thereby offering the strongest evidence to inform the development of precise, interdisciplinary clinical intervention strategies.

The findings of this study carry multiple implications for future clinical practice, calling not only for a shift in physicians’ diagnostic and therapeutic approaches but also for new demands in nursing practice. In orthopedic diagnosis and treatment, clinicians should recognize the potential psychological risks faced by patients with IVDD and incorporate psychological screening into routine follow-up care. From the nursing perspective, intervention strategies for IVDD patients should transition from a solely physical care approach to an integrated, causally driven model of “mind-body nursing.” In response to the high incidence of anxiety in IVDD patients, nurses should develop a scientifically grounded, comprehensive psychosocial care plan that spans the entire care continuum. First, an early-warning and precise-assessment mechanism must be established. Nurses should routinely administer professional psychological assessment tools such as the GAD-7 during the early stages of patient admission, particularly for IVDD patients with long disease durations or severe pain feedback. These individuals should be identified as high-risk for anxiety and prioritized for close monitoring. In terms of pain management, the approach should evolve from a simplistic, demand-based analgesic model to a dual-regulatory “neurobiological-psychological” framework. Nurses should actively promote multimodal analgesia, incorporating non-pharmacological interventions such as hot/cold compresses and positional optimization in combination with cognitive restructuring, to reduce the continuous impact of pathological pain signals on the central nervous system, thus alleviating anxiety mediated by pain. Furthermore, rehabilitation nursing should integrate psychological support more deeply. When guiding patients through functional exercises, nurses should educate patients to understand the

causal relationship between pain and anxiety, helping to modify their catastrophic interpretations of the disease.<sup>38</sup> By introducing mindfulness-based stress reduction techniques or progressive muscle relaxation exercises, nurses can help patients improve autonomic nervous system regulation, reduce sympathetic overactivity, and alleviate somatic symptoms.<sup>39</sup> The implementation of a collaborative care model is equally vital. Nurses, serving as communication bridges, should lead the establishment of a collaborative network involving orthopedic nurses, psychiatric care specialists, and family members. In post-discharge continuity of care, mobile health platforms should be utilized for targeted psychological follow-up, guiding family members to create a stable emotional support environment for patients and prevent negative familial emotions from inducing secondary stress.<sup>40,41</sup> Through this multidimensional nursing intervention, it is possible to effectively disrupt the “pain-anxiety” causal chain driven by genetic susceptibility, thereby enhancing the patient’s overall quality of life.

Looking ahead, the elucidation of causal relationships represents only the starting point of this research. The next phase should focus on the clinical validation and translational application of molecular mechanisms. We recommend conducting multicenter, large-sample longitudinal cohort studies to dynamically monitor serum inflammatory markers, neuroimaging indices, and psychological scale scores, thereby validating the causal hypotheses proposed by MR research in real-world settings. Simultaneously, exploring whether interventions targeting inflammatory pathways—whether pharmacological or non-pharmacological—can concurrently alleviate the physical symptoms of IVDD and the psychological phenotypes of GAD represents a promising and high-potential area of study. Moreover, the development of predictive models based on genetic risk scores to identify high-risk populations that are particularly sensitive to IVDD-related anxiety will provide scientific support for the implementation of an integrated “spine–psychology–rehabilitation” medical model.

## 5. Conclusion

In conclusion, this study, through rigorous bidirectional two-sample MR analysis, has revealed a significant positive genetic causal effect of IVDD on GAD. This finding not only deepens our understanding of the comorbid mechanisms underlying chronic diseases but also provides robust theoretical support for the development of interdisciplinary precision diagnostics and integrated care. Moving forward, we remain committed to unraveling the molecular intricacies behind this complex causal chain, with the ultimate goal of developing more

scientifically grounded, patient-centered, and effective integrated management strategies for the millions of individuals worldwide suffering from spinal disorders and psychological conditions.

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## Conflict of interest

The authors have no conflicts of interest to disclose.

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## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Availability of data

The GWAS data were obtained from the 12th release of the Genome-Wide Association Study Database of the Finnish Genomic Research Consortium (website: <https://r12.finnngen.fi/>)

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