Observational Study

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Body mass index and risk of lumbar spondylolisthesis

An observational study based on two-sample Mendelian randomization analysis

Zhan Wang, MM[a], Ping-Bo Chen, MM[a,*]

Abstract

This study aims to investigate the potential causal relationship between body mass index (BMI) and lumbar spondylolisthesis through the application of Mendelian randomization (MR) analysis. We utilized comprehensive data derived from large-scale genome-wide association studies to examine the association between BMI and lumbar spondylolisthesis in populations of European ancestry. Independent genetic variants with significant correlations to BMI and lumbar spondylolisthesis were selected as instrumental variables to ensure methodological rigor. To evaluate the causal impact of BMI on the risk of developing lumbar spondylolisthesis, 3 distinct MR approaches were employed: MR-Egger regression, Weighted Median analysis, and inverse variance weighted estimation. Robustness and consistency of the findings were assessed through heterogeneity testing, multiplicity analysis, and a leave-one-out sensitivity evaluation to confirm the stability of the results. The inverse variance weighted analysis revealed a significant positive association between BMI and lumbar spondylolisthesis risk, with an odds ratio of 1.66 and a 95% confidence interval of 1.20 to 2.29 (P = .002). This finding indicates that individuals with higher BMI are more predisposed to developing lumbar spondylolisthesis. Complementary results from heterogeneity and multiplicity assessments demonstrated no evidence of significant heterogeneity or horizontal pleiotropy, reinforcing the reliability of the findings. Furthermore, the leave-one-out sensitivity analysis confirmed the stability and robustness of the results, providing additional validation of the causal relationship. This investigation offers valuable insights by leveraging two-sample Mendelian randomization analysis to explore the causal link between BMI and lumbar spondylolisthesis. The evidence strongly suggests that elevated BMI contributes significantly to the risk of lumbar spine slippage. These findings highlight the importance of weight management as a preventive strategy for lumbar spine disorders. Promoting healthy BMI levels may serve as a critical intervention to mitigate the risk of lumbar spondylolisthesis, emphasizing the necessity for targeted public health initiatives focused on weight control to enhance spinal health and overall well-being.

Abbreviations: BMI = body mass index, CI = confidence interval, GWAS = genome-wide association study, IV = instrumental variable, IVW = inverse variance weighting, MR = Mendelian randomization, MR-PRESSO = Mendelian randomization pleiotropy residual sum and outlier, OR = odds ratio, SNP = single nucleotide polymorphism.

Keywords: BMI, lumbar spondylolisthesis, Mendelian randomization

1. Introduction

Lumbar spondylolisthesis is a spinal disorder characterized by the forward (anterior) or backward (posterior) displacement of a superior vertebra relative to its inferior counterpart, ultimately resulting in vertebral subluxation and spinal instability.[1] This pathological condition most commonly affects the L4–L5 and L5–S1 segments of the lumbar spine, regions that bear significant mechanical stress during movement and weight-bearing activities. The severity of lumbar spondylolisthesis typically increases with advancing age, making it a progressive degenerative condition that disproportionately affects older adults. Notably, epidemiological studies have reported a higher prevalence among women, possibly due to differences in bone density, hormonal influences, and biomechanical factors.[2]

The global prevalence of lumbar spondylolisthesis is estimated to be approximately 5% to 10% in the general population, with a higher incidence observed in middle-aged and elderly individuals.[3] This condition often presents with low back pain, which tends to worsen with physical activity,

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The datasets generated during and/or analyzed during the current study are publicly available.

Due to the nonexperimental nature of the research, the study protocol did not need to be submitted for consideration and approval to an ethical review committee.

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prolonged standing, or repetitive movements. In some patients, nerve root compression may lead to sciatica, characterized by pain radiating from the lower back to the buttocks, thighs, and lower extremities. Moreover, vertebral slippage can result in lumbar spine mobility limitations, significantly impairing daily activities. In severe cases, neurological deficits may occur, such as muscle weakness, numbness, and even loss of sphincter control, further compromising the patient's quality of life.[4]

With the rapid advancement of modern society and the continuous transformation of lifestyle habits, the global prevalence of obesity has risen sharply, posing a wide range of adverse health effects on multiple physiological systems.[5,6] Excess body weight exerts substantial mechanical stress on the musculoskeletal system, significantly increasing the risk of skeletal and joint disorders. Among these conditions, osteoarthritis and intervertebral disc herniation are commonly observed, particularly in weight-bearing joints such as the knees and the lumbar spine.[7,8] In recent years, mounting evidence has suggested that lumbar spondylolisthesis may also be closely associated with elevated body mass index (BMI), as individuals with obesity appear to be at a greater risk compared to those with normal body weight. However, the relationship between BMI and lumbar spondylolisthesis remains inconsistent across observational studies, likely due to the influence of confounding factors and potential reverse causality.[9,10]

The relationship between BMI and lumbar spondylolisthesis in traditional observational studies is often complicated by confounding variables and reverse causality.[11] These limitations make it challenging to determine whether obesity directly contributes to the development of lumbar spondylolisthesis or if the association is influenced by other underlying factors. Mendelian randomization (MR) has emerged as a powerful genetic epidemiological approach to overcome these issues by leveraging genetic variants as instrumental variables (IVs) to infer causal relationships between exposure factors and health outcomes.[12] This method can provide more reliable evidence by minimizing bias from confounders and addressing reverse causality.

In MR studies, genetic variants such as single nucleotide polymorphisms (SNPs), which are associated with specific traits like BMI, serve as instrumental variables to evaluate the causal effect of obesity on lumbar spondylolisthesis.[13] These genetic variants are randomly allocated during gamete formation based on Mendelian inheritance laws, making their distribution independent of environmental or behavioral confounders.[14] Moreover, since an individual's genotype remains constant throughout life, MR analysis is less likely to be influenced by changes in disease status over time, thereby reducing the risk of reverse causation.[15]

The application of MR has demonstrated significant advantages in various fields of medical research. It has been widely used to explore causal relationships in chronic diseases, including the association between BMI and cardiovascular disease, where traditional observational studies often produced inconsistent results.[16] In addition to metabolic disorders, MR has also been instrumental in uncovering causal links in more complex conditions, such as the relationship between gut microbiota and spinal stenosis, as well as the association between aspirin use and erectile dysfunction.[17,18]

Therefore, this study aimed to investigate the causal effect of BMI on the risk of lumbar spondylolisthesis using a two-sample MR approach. We hypothesized that higher BMI is causally associated with an increased risk of lumbar spondylolisthesis.

2. Data and methods

2.1. Data sources

The data for this study on body mass index (BMI) and lumbar spondylolisthesis were sourced from the IEU OpenGWAS project, available on the official website (https://mr.cieu.ac.uk), with access granted on September 26, 2024. All datasets used were derived from populations of European descent, ensuring consistency across the data. Furthermore, the datasets were gender-neutral, offering an inclusive perspective on the genetic associations.

The genome-wide association study (GWAS) dataset for BMI (identified as ieu-a-974) comprised a total of 2,494,613 SNPs, with a substantial sample size of 171,977 individuals. This large cohort provides robust data for assessing the genetic underpinnings of BMI. On the other hand, the dataset related to lumbar spondylolisthesis (denoted as finn-b-M13_SPONDYLOLISTHESIS) included a significantly larger SNP pool of 16,380,280 SNPs, with the study population consisting of 2669 individuals in the trial group and 164,682 individuals in the control group. This expansive dataset ensures comprehensive analysis and improves the precision of the causal relationship being explored.

As the study utilized preexisting publicly available data from the aforementioned GWAS, it did not require additional ethical approval. The high quality and comprehensive nature of the datasets provide a solid foundation for conducting this analysis, ensuring the reliability and validity of the findings. The inclusion of such extensive genetic data enhances the credibility of this study in investigating the causal links between BMI and lumbar spondylolisthesis, offering a rigorous methodological approach to exploring these relationships.

2.2. Key assumptions of MR

MR analysis is based on 3 fundamental assumptions that must be satisfied to ensure the validity of causal inference[19,20]:

Relevance assumption: The genetic variants used as instrumental variables must be strongly associated with the exposure of interest (in this study, BMI). Weak instrument bias can occur if this assumption is violated, leading to unreliable estimates.

Independence assumption: The selected genetic variants must not be associated with any confounding factors that influence both the exposure and the outcome (lumbar spondylolisthesis). If this assumption is not met, the causal estimate may be biased due to residual confounding.

Exclusion restriction assumption: The genetic variants must affect the outcome only through the exposure of interest (BMI) and not via alternative biological pathways. Horizontal pleiotropy (where a genetic variant affects the outcome through other pathways) violates this assumption, potentially leading to biased causal estimates.

2.3. Conditioning of SNP as an instrumental variable

For instrumental variables to be valid in MR studies, they must exhibit a strong correlation with the exposure variable. A commonly used criterion to assess this is an F-statistic > 10, which indicates that the instrumental variable is strongly correlated with the exposure and minimizes the risk of weak instrument bias.[21] Additionally, an instrumental variable should influence the outcome solely through the exposure variable and should not be directly linked to the outcome itself. This ensures that genetic pleiotropy does not confound the relationship being assessed. In the context of this study, the presence of pleiotropy was evaluated by examining the intercept term in the MR-Egger regression model, with a significant result being when the intercept was close to 0 ($P < .05$).[22,23] This approach helps in confirming that the instrumental variables do not exhibit directional pleiotropic effects that could introduce bias.

Moreover, to ensure that the instrumental variables are not affected by any unmeasured confounders, it is essential that they remain independent of such confounding

factors. To address this, Phenoscanner V2, a comprehensive database of human genotype–phenotype associations, was utilized to investigate whether the selected SNPs are associated with any other phenotypes at a genome-wide significant level. This step was undertaken to ensure that the SNPs used as instrumental variables are not correlated with other potential risk factors that could confound the results.[24] By conducting this additional search, we ensured that the instrumental variables were appropriately validated and not linked to extraneous factors that could undermine the robustness of our causal inference.

2.4. SNP screening

In this study, significant SNPs related to BMI were identified from the GWAS pooled data by applying a stringent threshold of P value $<5 \times 10^{-8}$, a standard in genetic association studies to ensure robust results.[25] To minimize the risk of correlated SNPs that could distort the causal inference, the r^2 value, which measures the correlation between SNPs, was set to 0.001. Additionally, the chain imbalance region was limited to 10,000 kb to ensure SNP independence and avoid unnecessary inclusion of highly correlated variants.[26]

From the BMI-specific SNPs, only those with a confirmed association were retained. Subsequently, SNPs directly linked to the outcome variable—lumbar spondylolisthesis—were removed by using the same rigorous P value threshold of $<5 \times 10^{-8}$. After these steps, F-values were calculated for each SNP to assess the strength of the instrumental variables. SNPs with an F-value of <10 were considered weak instrumental variables and were therefore excluded from further analysis to prevent weak instrument bias, which could compromise the validity of the findings.[27]

To minimize potential pleiotropic bias and ensure that the selected IVs were not associated with potential confounders, each SNP was further examined using the PhenoScanner database (https://www.phenoscanner.medschl.cam.ac.uk/).[28] SNPs that showed genome-wide significant associations ($P < 5 \times 10^{-8}$) with known confounding factors for lumbar spondylolisthesis (e.g., smoking, physical activity, diabetes, and socioeconomic status) were excluded.

2.5. Methods of causality validation

The causal relationship between exposure (BMI) and outcome (lumbar spondylolisthesis) was verified mainly using inverse variance weighted (IVW) as, supplemented by 3 MR analysis methods, namely MR-Egger and weighted median, with SNPs as instrumental variables.

2.5.1. IVW method. The IVW method combines the Wald ratios of individual SNPs using a meta-analysis approach, offering the most precise estimates when horizontal pleiotropy is absent. IVW assumes that all genetic variants are valid IVs and that there is no pleiotropic effect. However, if horizontal pleiotropy exists, the IVW method may yield biased estimates.

2.5.2. MR-Egger regression. MR-Egger regression is a sensitivity analysis that accounts for horizontal pleiotropy by estimating both an intercept (indicating the presence of pleiotropy) and a slope (representing the causal effect). A nonzero intercept suggests horizontal pleiotropy, while a significant slope indicates a causal relationship. MR-Egger provides greater flexibility but suffers from low statistical power and wider confidence intervals, especially when the number of SNPs is limited.

2.5.3. Weighted median estimator. The weighted median estimator method provides a consistent causal estimate if at least 50% of the weight comes from valid IVs. This method is more robust to outliers and horizontal pleiotropy than IVW or MR-Egger but is less efficient when all IVs are valid. It is particularly useful when some IVs violate key assumptions.

2.6. Sensitivity analysis

To assess the robustness of the findings in this study, several sensitivity analyses were conducted, employing various techniques to ensure the reliability of the results. Initially, heterogeneity among the SNP estimates was examined using the Cochran Q test. This statistical test helps determine whether there is substantial variation or inconsistency in the SNP effect estimates. A significant result from this test would indicate the presence of heterogeneity, warranting further investigation into the source of variation.

In addition to the Cochran Q test, the Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) method was applied to further validate the IVW model results. The MR-PRESSO method is particularly useful for identifying and addressing the influence of potential outliers that could distort the findings. If any outliers were identified, they were excluded from the analysis, and the model was reanalyzed to verify the consistency of the results.

To assess the possibility of horizontal pleiotropy, the study employed the MR-Egger intercept test. This test evaluates whether the genetic instruments (SNPs) have effects on the outcome that are independent of the exposure variable. If the intercept term in the MR-Egger regression model shows statistical significance, it suggests the presence of horizontal pleiotropy, which could indicate that the instrumental variables are influencing the outcome through pathways other than the exposure of interest.

Further, a "leave-one-out" sensitivity analysis was performed to explore the impact of individual SNPs on the relationship between BMI and lumbar spondylolisthesis. In this approach, 1 SNP was removed at a time, and the analysis was repeated to determine if any single SNP had an outsized influence on the overall results. This technique helps identify whether a particular SNP disproportionately affects the outcome and whether the findings remain consistent when any 1 SNP is excluded.

Lastly, funnel plots and forest plots were generated to visually represent the results of these sensitivity analyses. These plots are helpful tools for visually assessing the consistency of the findings and detecting any potential biases in the data.

For all statistical analyses, P-values <.05 were considered indicative of statistical significance, suggesting that the observed associations were likely causal in nature. All analyses were conducted using the "TwoSampleMR" package in R software version 4.3.0, ensuring that the methodology was robust and appropriate for the investigation.

3. Results

3.1. Instrumental variables

In this study, a total of 37 SNPs that exhibited a significant association with BMI ($P < 5 \times 10^{-8}$) were selected. These SNPs were screened to ensure they did not exhibit linkage disequilibrium ($r^2 < 0.001$, kb = 10,000), ensuring their independence from one another and eliminating any potential biases from related genetic variations. After this initial selection, the SNPs were cross-referenced with the SNP set of the lumbar spondylolisthesis GWAS pooled data. This step ensured that SNPs that were directly associated with the outcome variables (lumbar spondylolisthesis) were removed from the list to avoid confounding influences.

As a result, 37 SNPs were retained for further analysis. The strength of these instrumental variables was verified through *F*-value calculations, where all selected SNPs had *F*-values >10, signifying the absence of weak instrumental variables, which could potentially lead to unreliable or biased results. This is important for maintaining the robustness of the causal inference in the study (Table 1).

Additionally, a thorough screening of the Human Genotype–Phenotype Association Database was conducted to identify any other potential risk factors associated with the SNPs. This step ensured that the selected SNPs were not linked to any other confounding health-related traits that could introduce additional biases. No SNPs with potential associations to other risk factors were found in the database, confirming the specificity of the selected SNPs for the BMI–lumbar spondylolisthesis relationship.

3.2. Causal relationship between BMI and lumbar spondylolisthesis

In this study, IVW served as the primary MR analysis due to its higher statistical efficiency under ideal conditions. The IVW method revealed a significant causal relationship between elevated BMI and an increased risk of lumbar spondylolisthesis (odds ratio [OR] = 1.66, 95% confidence interval [CI] = 1.20–2.29, $P = .002$). MR-Egger regression also demonstrated a significant association (OR = 2.46, 95% CI = 1.03–5.86, $P = .049$) but presented a wider confidence interval, likely due to its sensitivity to outliers. In contrast, the weighted median estimator method showed no statistically significant difference ($P > .05$), suggesting that the results may be affected by the proportion of invalid IVs or outlier SNPs (Table 2). We can see from both the scatter plot (Fig. 1) and the forest plot (Fig. 2) that the greater

Table 1

Information on the final screening of BMI SNPs from GWAS data (n = 37).

ID	SNP	Effect_Allele	Other_Allele	β	SE	*P*	*F*
1	rs1016287	C	T	-0.0254	0.0323	5.87E-09	33
2	rs10182181	G	A	0.0366	0.0288	3.91E-21	88
3	rs10733682	G	A	-0.0229	0.0286	1.66E-08	31
4	rs10767664	A	T	0.0456	0.0378	1.88E-17	71
5	rs10938397	G	A	0.0404	0.0283	2.98E-23	97
6	rs10968576	G	A	0.0289	0.0292	1.03E-11	45
7	rs11165643	T	C	0.023	0.0289	5.76E-09	33
8	rs1121980	A	G	0.0774	0.0286	4.87E-86	393
9	rs11663558	A	G	-0.027	0.0284	4.37E-09	34
10	rs12446632	A	G	-0.0432	0.043	1.45E-13	55
11	rs12529728	G	A	0.0462	0.0354	1.76E-19	82
12	rs13098327	A	G	0.0333	0.0377	1.12E-11	46
13	rs1516725	C	T	0.0466	0.0474	1.91E-15	62
14	rs16851483	T	G	0.0524	0.0662	4.81E-08	29
15	rs17024393	C	T	0.0713	0.061	3.53E-10	39
16	rs17381664	C	T	0.0239	0.0292	5.31E-09	33
17	rs1928295	C	T	-0.0258	0.0284	3.42E-11	43
18	rs2060604	C	T	-0.0232	0.029	4.06E-09	33
19	rs2112347	G	T	-0.0298	0.0287	3.15E-13	52
20	rs2303108	C	T	0.0278	0.0297	8.53E-11	41
21	rs3127553	A	G	-0.0259	0.0293	4.58E-10	38
22	rs3817334	T	C	0.0265	0.0298	2.47E-11	43
23	rs4929923	C	T	0.0235	0.0297	9.05E-09	32
24	rs4981693	A	G	0.0336	0.0301	4.90E-10	38
25	rs543874	G	A	0.0603	0.0373	9.61E-34	145
26	rs6091540	T	C	-0.0297	0.0338	2.15E-11	45
27	rs6465468	T	G	0.0245	0.0334	4.98E-08	29
28	rs6548237	C	A	0.0687	0.0387	3.55E-40	174
29	rs663129	A	G	0.0567	0.0368	3.49E-34	151
30	rs7138803	A	G	0.0348	0.0293	1.80E-17	72
31	rs7141420	T	C	0.0262	0.0288	1.45E-11	45
32	rs7239883	A	G	-0.0231	0.0286	1.51E-08	31
33	rs745213	G	T	0.0343	0.0427	1.31E-10	41
34	rs7531118	C	T	0.0341	0.0289	3.90E-17	69
35	rs8097783	A	G	-0.0512	0.0717	2.19E-11	45
36	rs9462027	A	G	0.0273	0.0321	4.60E-10	38
37	rs9931989	C	G	-0.0258	0.0289	9.47E-10	37

BMI = body mass index, GWAS = genome-wide association study, SNP = single nucleotide polymorphism.

Table 2

MR regression results of the 3 methods.

Method	β	SE	OR (95% CI)	*P*
IVW	0.508	0.164	1.66 (1.20–2.29)	.002
WME	0.292	0.236	1.34 (0.84–2.12)	.216
MR-Egger	0.901	0.443	2.46 (1.03–5.86)	.049

CI = confidence interval, IVW = inverse variance weighting, MR = Mendelian randomization, OR = odds ratio, WME = weighted median estimator.

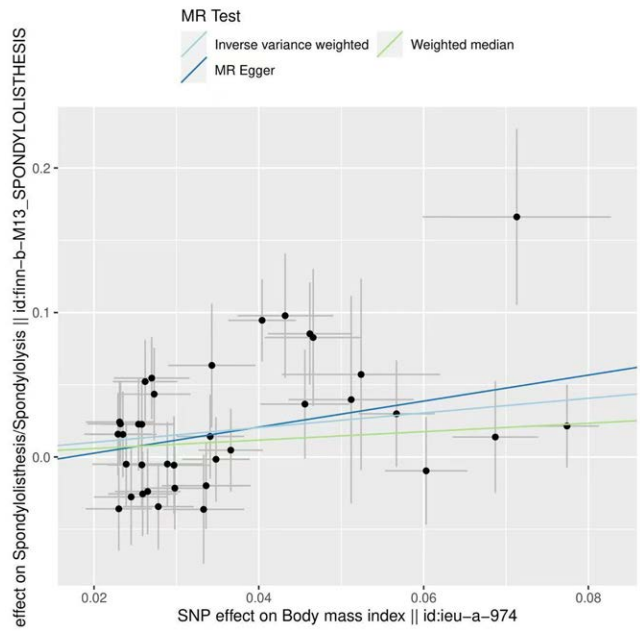

Figure 1. Scatter plot of BMI and lumbar spondylolisthesis. BMI = body mass index.

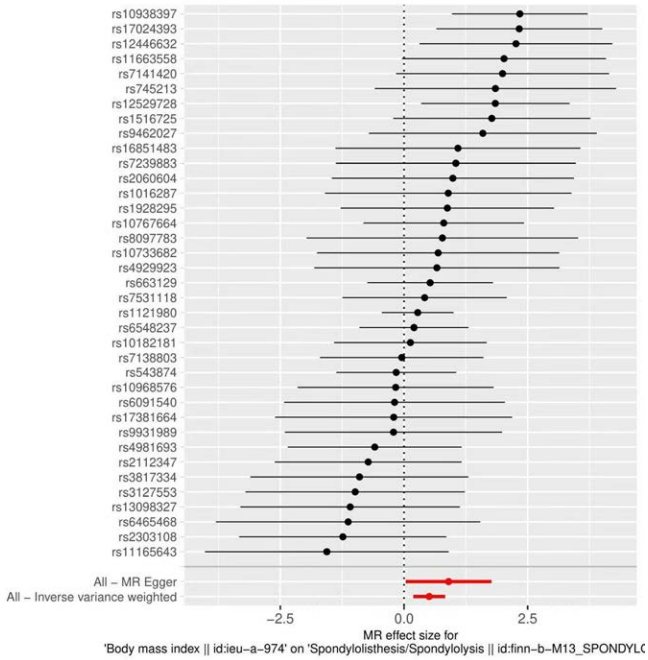

Figure 2. Forest plot of BMI and lumbar spondylolisthesis. BMI = body mass index.

the BMI, the greater the probability of suffering from lumbar spondylolisthesis.

3.3. Sensitivity analysis

The heterogeneity of the results was assessed using the Cochran *Q* test within the IVW method, which yielded a *P*-value of .157. This indicates that there was no significant heterogeneity detected in the analysis. To further illustrate these findings, a funnel plot was constructed (Fig. 3), visually depicting the absence of any notable heterogeneity in the study results.

In addition, the MR-PRESSO method was employed to identify potential SNPs that might be contributing to any heterogeneity. The analysis revealed that no SNPs exhibited significant heterogeneity, reaffirming the reliability of the data. The Global test performed as part of the MR-PRESSO method yielded a *P*-value of .264, suggesting that there was no evidence of pleiotropy in the study, meaning the instrumental variables used were not associated with any other traits that could confound the results.

Further validation of the results was conducted through the "leave-one-out" sensitivity analysis, which aimed to determine whether any individual SNP might disproportionately influence the overall findings. In this analysis, the IVW method was used by default to assess the impact of excluding each SNP one by one. The results, depicted in Figure 4, demonstrated that no single SNP had a significant effect on the overall outcomes, providing additional support for the robustness and reliability of the study's conclusions. These findings further validate the consistency and strength of the observed relationship between BMI and lumbar spondylolisthesis.

4. Discussion

It is widely recognized that a high BMI may serve as an observational risk factor for lumbar spondylolisthesis, but the exact causal relationship between the 2 remains uncertain. To address this gap, our MR study aimed to explore whether there is a true causal link between BMI and the development of lumbar spondylolisthesis. The findings from our two-sample MR analysis strongly suggest a causal association, with an OR of 1.66 (95% CI: 1.20–2.29) and a *P*-value of .002. This indicates that individuals with higher BMI levels are at a significantly greater risk of developing lumbar spondylolisthesis when compared to individuals with a normal BMI. The results support the hypothesis that BMI is not just an observational risk factor, but may directly contribute to the occurrence of lumbar spondylolisthesis, thereby providing important insights into the relationship between these 2 factors.

In a study conducted by Zhong et al,[9] it was observed that individuals with higher BMI had an increased likelihood of developing lumbar spondylolisthesis, and they also faced a greater probability of requiring reoperation following surgery. This suggested a clear association between higher BMI and both the onset of the condition and the need for subsequent surgical interventions. On the other hand, a different study by Zammar et al[10] contradicted these findings, revealing through a retrospective analysis that BMI did not have a significant impact on the development of lumbar spondylolisthesis. Furthermore, at the 5-year follow-up, patients with a BMI ≥ 35 had comparable rates of reoperation as those with lower BMI, indicating that, over time, BMI may not influence the need for additional surgical procedures. This discrepancy highlights the need for further research to clarify the relationship between BMI and both the occurrence and long-term outcomes of lumbar spondylolisthesis.

The current study provides strong evidence supporting a causal relationship between BMI and lumbar spondylolisthesis, using a genetic perspective. The findings are consistent with those of Zhong et al, who identified a higher BMI as a significant risk factor for the development of lumbar spondylolisthesis. In contrast, the retrospective study conducted by Zammar et al found no significant association between BMI and the incidence of lumbar spondylolisthesis. This discrepancy may be attributed to the inherent limitations of retrospective studies, which are often vulnerable to confounding factors and reverse causality. As a result, the causal implications of such studies are relatively constrained. In contrast, MR analysis, an emerging method in epidemiology, offers a more robust approach for drawing causal conclusions by utilizing genetic variation

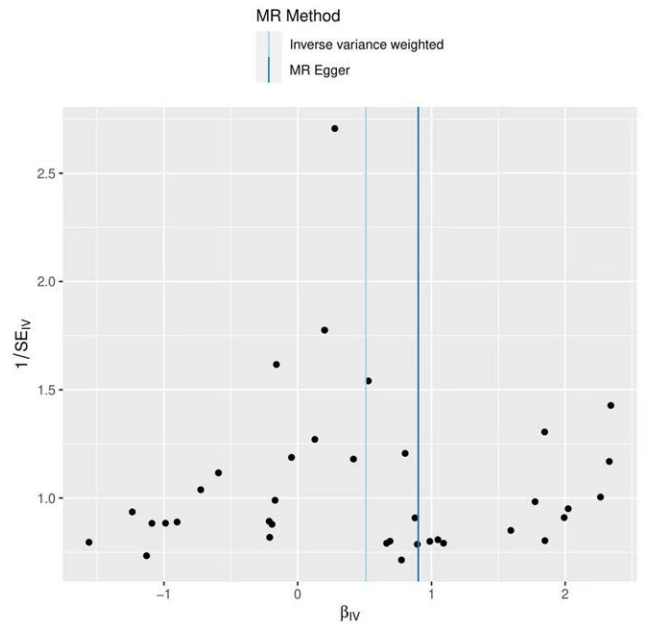

Figure 3. Funnel plot of BMI and lumbar spondylolisthesis. BMI = body mass index.

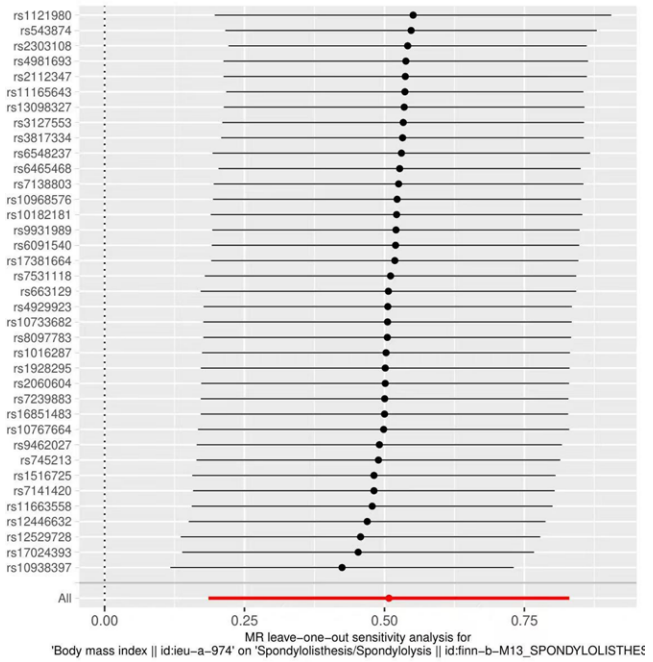

Figure 4. Analysis of BMI and lumbar spondylolisthesis by the leave-one-out method.

as an instrumental variable for the exposure of interest. This method helps minimize the effects of confounders and reverse causality, leading to more reliable and precise causal inferences in complex relationships such as that between BMI and lumbar spondylolisthesis.[29]

One plausible mechanism that links elevated BMI to lumbar spondylolisthesis involves the increased axial load placed on the lumbar spine due to excess body weight. The additional weight results in mechanical stress on the lumbar vertebrae and intervertebral discs, leading to accelerated degenerative changes and an increased risk of developing spondylolisthesis. Moreover, a high BMI is often associated with heightened levels of systemic inflammation.[30] Adipose tissue acts as a significant source of pro-inflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-6, which play a critical role in the degeneration of intervertebral discs and the destabilization of spinal joints.[31] These inflammatory mediators may contribute to the breakdown of structural proteins within the spine, weakening the overall integrity of the lumbar region and increasing the susceptibility to vertebral displacement and spondylolisthesis. In addition, the spinal alignment of obese individuals is also often changed, which is manifested by increased pelvic anterior tilt and deepening lumbar lordosis, which leads to the anterior movement of the sagittal alignment of the spine and a significant increase in the shear force on the vertebral body. Studies[29] have shown that the mismatch between the pelvic incidence angle and the lumbar lordosis angle is significantly positively correlated with the degree of lumbar spondylolisthesis.

Additionally, obesity is frequently linked to various forms of metabolic dysregulation, including conditions such as insulin resistance and hyperglycemia, which could contribute to the development of lumbar spondylolisthesis. Research has demonstrated that metabolic dysfunction can impair the efficient delivery of essential nutrients to spinal tissues and hinder the removal of metabolic waste products, which may, in turn, worsen the degenerative changes occurring in the lumbar spine. The presence of insulin resistance and elevated blood glucose levels might compromise the vascular health of the spine, affecting its ability to maintain tissue health and integrity. These metabolic disruptions could accelerate the wear and tear on intervertebral discs and vertebrae, further increasing the risk of spondylolisthesis. A deeper understanding of these underlying mechanisms will be crucial for developing targeted strategies that not only focus on managing body weight but also address metabolic health, offering a more comprehensive approach to preventing lumbar spine degeneration and related disorders.

These findings highlight the critical role that BMI management plays in preventing the development of lumbar spondylolisthesis. For individuals with an elevated BMI, particularly those who are at an increased risk of developing lumbar spinal disorders, it is essential to prioritize targeted weight management strategies. Such interventions could significantly reduce the likelihood of experiencing spondylolisthesis or other spine-related issues. To address this, clinical guidelines should consider incorporating routine BMI monitoring and lifestyle modification interventions as part of standard care, especially for patients exhibiting early signs of lumbar spine degeneration. These proactive measures could help prevent the progression of spinal conditions and improve patient outcomes. Furthermore, healthcare providers should offer tailored support to individuals at higher risk, guiding them through sustainable weight management and healthy living practices to mitigate the burden on the lumbar spine and reduce the likelihood of requiring surgical interventions in the future.

This study also emphasizes the importance of adopting a multidisciplinary approach when managing lumbar spondylolisthesis, with a focus on both weight control and the optimization of metabolic health. To reduce the risk of developing lumbar spondylolisthesis, a comprehensive strategy that includes dietary guidance, regular physical activity, and routine metabolic screenings should be considered for individuals with elevated BMI. Such interventions can play a crucial role in addressing underlying metabolic issues while helping to reduce excessive weight, thus minimizing the mechanical stress on the lumbar spine. Additionally, integrating these practices into clinical care can improve overall health outcomes by preventing further spinal degeneration and enhancing the quality of life for individuals at higher risk of developing lumbar spine disorders. By adopting a holistic approach that addresses both weight and metabolic factors, healthcare providers can offer more

effective management strategies for patients prone to lumbar spondylolisthesis.

This study does have several limitations that should be considered. First, the data utilized were exclusively derived from populations of European descent, which may limit the generalizability of the findings to other populations or ethnic groups. As such, the results may not be fully applicable to more diverse global populations. Second, despite conducting multiple sensitivity analyses to test the validity of the MR study hypotheses, the potential influence of horizontal pleiotropy—where instrumental variables may have effects on the outcome beyond their effect on the exposure—cannot be completely ruled out. While efforts were made to minimize this risk, it remains a challenge to fully exclude this possibility. Lastly, although the GWAS data used in this study were extensive, the sample size of the datasets may still be insufficient for drawing more definitive conclusions. Future research with larger, more diverse GWAS datasets will be needed to further validate and expand upon these findings. A larger pool of data may also enable the detection of subtle associations and allow for stratified analyses based on additional factors like age, gender, or other underlying health conditions. Therefore, further studies with broader populations and larger sample sizes are crucial to enhancing the robustness and applicability of the results.

5. Conclusion

In conclusion, the present MR study offers substantial evidence that a higher BMI is causally linked to an increased risk of developing lumbar spondylolisthesis. These findings emphasize the critical role of BMI management as a potential preventive strategy and suggest that incorporating weight management approaches into clinical practice and guidelines could significantly reduce the risk of lumbar spinal disorders. Given the strong association revealed in our study, it may be beneficial to prioritize weight control strategies in clinical settings, particularly for individuals at risk for spine-related issues. Moreover, further research is needed to delve deeper into the biological mechanisms underlying the relationship between BMI and lumbar spondylolisthesis. Future studies should also explore how BMI interacts with other modifiable lifestyle factors, such as physical activity, dietary habits, and metabolic health, to better understand the full spectrum of risk factors contributing to spinal health. By expanding on these findings, researchers can provide a more comprehensive framework for preventing and managing lumbar spine conditions.

Author contributions

Conceptualization: Zhan Wang, Ping-Bo Chen.
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