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Investigating the causal impact of body mass index on meniscus injuries

A 2-sample Mendelian randomization study

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Abstract

The aim of this study was to explore the possible causal association between body mass index (BMI) and meniscal injuries using Mendelian randomization (MR), a genetic research method. Relying on pooled data from a large genome-wide association study, we carefully selected a set of genetic variants as instrumental variables that were significantly associated with BMI and meniscal injuries and were independently distributed in populations of European origin. The potential impact of BMI on meniscal injuries was systematically assessed by implementing multiple MR analysis strategies including MR-Egger, weighted median and inverse variance weighting. In addition, heterogeneity and multiple validity tests were introduced in the study, together with the "leave-one-out" sensitivity analysis to ensure the robustness and reliability of the results. Inverse variance weighting analysis revealed a significant positive causal association between BMI and meniscus injury, as shown by the ratio (OR) and its 95% confidence interval of 1.46 (1.22–1.75), with a *P*-value of <.001. Further tests did not reveal significant heterogeneity and pleiotropy, and the results of the sensitivity analyses supported the robustness of the study findings. Combined with the use of 2-sample MR analysis, this study strongly confirms that BMI is an independent risk factor for meniscal injuries, and this finding provides a new genetic perspective for meniscal injury prevention and intervention.

Abbreviations: BMI = body mass index, CI = confidence interval, GWAS = Genome-Wide Association Study, IVW = inverse variance weighting, MR = Mendelian randomization, MR-PRESSO = Mendelian random polymorphism residuals and outliers, SNP = single nucleotide polymorphism.

Keywords: BMI, Mendelian randomization, meniscus

1. Introduction

The meniscus, as an indispensable component of the knee joint, plays a key role in stabilizing the joint, evenly distributing load forces and promoting intra-articular nutrient exchanges, and its presence ensures that the knee joint remains healthy and undamaged even when carrying heavy pressure for a long period of time.[1,2] Meniscus injuries, specifically trauma or tearing of the medial and lateral meniscus tissues of the knee joint, are caused by a variety of factors including, but not limited to, strenuous twisting and rotational movements, direct knee impingement, and overuse.[3,4] Globally, with the improvement of living conditions and dietary changes, the increase in energy intake is spawning a significant growth in the obese population,[5,6] and obesity not only signals an imbalance in metabolic health, but may also induce a range of chronic diseases.[7,8] The association between obesity and meniscal injuries has been explored in the research field, and although the literature suggests that obese individuals may be at higher risk of meniscal injuries compared to normal weight individuals,[9] the diversity of conclusions and methodological limitations of the studies make this topic still controversial.[10] In view of this, an in-depth analysis of the causal link between body mass index (BMI) and meniscal injuries has become an urgent need for current research, with a view to providing a solid scientific basis for the prevention and treatment strategies of obesity-related meniscal injuries.

The observed association between BMI and meniscal injuries may be limited by confounding factors and reverse causality that are difficult to avoid in traditional epidemiologic studies, which tend to weaken the reliability and accuracy of the results.[11] Mendelian randomization (MR), an innovative genetic epidemiological method, provides a powerful tool for in-depth assessment of the potential causal role of BMI on meniscal injuries.[12] The method cleverly utilizes genetic variants such as single nucleotide polymorphisms (SNPs) as "instrumental variables," which are strongly associated with variable disease risk factors such as BMI, and can provide researchers with purer causal insights.[13] Following Mendel's laws of

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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inheritance, genetic variants are randomly assigned at the onset of an individual's development, a property that makes them largely immune to external confounding factors and provides a natural "randomized control" environment for research.[14] More importantly, the stability of genotypes ensures that they do not change over the course of an individual's lifespan due to changes in disease status, thus effectively avoiding confounding by reverse causation and providing a stronger logical basis for inferring causal associations.[15]

To this end, we conducted a 2-sample MR study to examine the causal relationship between BMI and meniscal injuries. We aimed to provide significant evidence for the causal role of BMI in causing meniscal injuries.

2. Materials and Methods

2.1. Data sources

The Genome-Wide Association Study (GWAS) data on BMI and meniscal injuries used in this study were derived from the IEU OpenGWAS project (URL: mr.cieu.ac.uk), with a data acquisition date of August 19, 2024. The entire sample ultimately included in the analysis originated from European populations, with no restriction on gender. Specifically, the BMI GWAS data (ieu-a-95) encompassed 2,736,876 SNP loci involving 73,137 participants, whereas the meniscus injury GWAS data (finn-b-M13_MENISCUSDERANGEMENTS) contained 16,380,200 SNP loci. The test group consisted of 13,568 patients with meniscal injuries and the control group consisted of 147,221 healthy individuals. Given that this study was a secondary analysis of publicly available previous data, it followed the relevant ethical guidelines and did not require additional ethical approval procedures.

2.2. Conditioning on SNP as an instrumental variable

When constructing MR analyses, the instrumental variables selected need to maintain a high correlation with the exposure factor – for example, BMI – with an *F*-statistic of >10 usually being used as a criterion for determining a strong association.[16] At the same time, the principle of ensuring that the instrumental variables act only indirectly on the outcome by influencing the exposure factors and are not directly associated with the outcome itself precludes the influence of genetic pleiotropy. In this study, the presence of genetic pleiotropy was determined by whether the intercept term of the MR-Egger regression model was significant ($P < .05$), with a nonzero intercept term indicating a low likelihood that the genetic variant acted directly on the outcome.[17] To ensure the independence of instrumental variables, they should not be associated with any unmeasured confounders.[18] For in-depth validation of the specificity of the selected SNP loci, this study comprehensively searched for relevant phenotypic information for these SNPs at the genome-wide significance level using Phenoscanner V2, a human genotype-phenotype association database. This step was aimed at confirming whether these genetic variants were only associated with specific exposure factors such as BMI, while direct associations with potential risk factors for meniscus injury were ruled out, thus ensuring the validity of the study design and the reliability of the results.[19]

2.3. SNP screening

Based on the BMI-related GWAS data, SNP loci significantly associated with BMI were first screened, and the screening criteria were set at a *P*-value of $<5 \times 10^{-8}$ to ensure that the selected loci were statistically significant.[20] To ensure the independence among SNP loci, the chain imbalance coefficient (r^2) was set at 0.001 and the width of the chain imbalance region was 10,000 kb, a setting that helps to exclude genetic variation within the chain region and ensure the independence and representativeness of the selected SNPs.[21] Next, SNP loci significantly associated with BMI were precisely matched and extracted from the GWAS data of meniscal injuries, while those SNPs directly associated with meniscal injuries were excluded ($P < 5 \times 10^{-8}$), a step that ensured the specificity of the instrumental variables and the rigor of the study design. To exclude weak effect loci, we calculated the *F*-value of each SNP, and SNPs with *F*-value <10 were considered as weak instrumental variables and were excluded.[22] In addition, SNPs with potentially relevant risk

Table 1

Information on the final screening of BMI SNPs from GWAS data (n = 11).

ID	SNP	Effect_Allele	Other_Allele	β	SE	*P*	*F*
1	rs10767664	A	T	0.044	0.0075	2.84E–09	34
2	rs10938397	G	A	0.046	0.0065	1.05E–12	50
3	rs1421085	C	T	0.076	0.0063	6.00E–34	145
4	rs2206277	T	C	0.052	0.008	1.17E–10	42
5	rs2860323	G	A	0.071	0.0082	1.09E–17	74
6	rs543874	G	A	0.054	0.0078	7.11E–12	47
7	rs6091540	T	C	–0.041	0.0068	1.78E–09	36
8	rs6567160	C	T	0.055	0.0073	3.07E–14	56
9	rs713586	C	T	0.034	0.0062	3.03E–08	30
10	rs7531118	C	T	0.038	0.0064	3.04E–09	35
11	rs9816226	T	A	0.045	0.0080	2.53E–08	31

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	0.377	0.092	1.46 (1.22–1.75)	<.001
WME	0.353	0.117	1.42 (1.13–1.79)	<.001
MR-Egger	0.465	0.361	1.59 (0.78–3.23)	.230

IVW = inverse variance weighting, MR = Mendelian randomization, WME = weighted median.

factors were meticulously screened by querying the human genotype-phenotype association database, and any SNPs that were not associated with meniscal injuries or BMI would be excluded, a process that further purified the pool of SNPs and ensured that the genetic loci ultimately used in the analyses were highly specific and associated.[23]

2.4. Causality validation methods

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

2.5. Sensitivity analysis

To ensure the robustness and reliability of the study results, a series of methods were used to conduct in-depth sensitivity analysis. First, heterogeneity among the SNP estimates was assessed by the Cochran Q test; if the result of this test is statistically significant, it indicates that there is significant heterogeneity in the results, suggesting that the researcher needs to interpret the conclusions with caution. Second, the robustness of the results of the IVW model was tested by applying the Mendelian random polymorphism residuals and outliers (MR-PRESSO) tool, which identifies and corrects for the effects of outliers. If outliers are detected, these outliers are removed and reanalyzed to improve the accuracy and reliability of the results. Further, the MR-Egger intercept test is utilized to test the horizontal multiplicity of SNPs. If the intercept term shows statistical significance in the MR-Egger analysis, this may indicate horizontal pleiotropy, that is, the SNP may affect the outcome variable through other pathways than just the exposure variable. Fourth, the "leave-one-out" sensitivity analysis was implemented, that is, SNPs were excluded from the analysis 1 by 1 to assess whether a single SNP had a significant effect on the correlation between the exposure variable and the outcome variable to ensure the stability and independence of the results. Finally, funnel plots and forest plots were constructed to visually present the results of the sensitivity analyses and provide visualization support for the interpretation of the results. When the *P*-value is <.05, it suggests that there is a potential causal relationship in the MR analysis, which is statistically significant. All statistical analyses were performed with the help of the "TwoSampleMR" package in R software version 4.3.0, which ensured the professionalism and accuracy of the analysis process. Through the above comprehensive sensitivity analysis, the reliability and robustness of the results of this study were fully guaranteed.

3. Results

3.1. Instrumental variables

In this study, after rigorous screening, 11 high-quality SNP loci that were significantly associated with BMI ($P < 5 \times 10^{-8}$) and without chain imbalance ($r^2 < 0.001$, chain distance set at 10,000 kb) were finally identified. Further cross-matching with the GWAS data of meniscus injury, after excluding SNPs directly

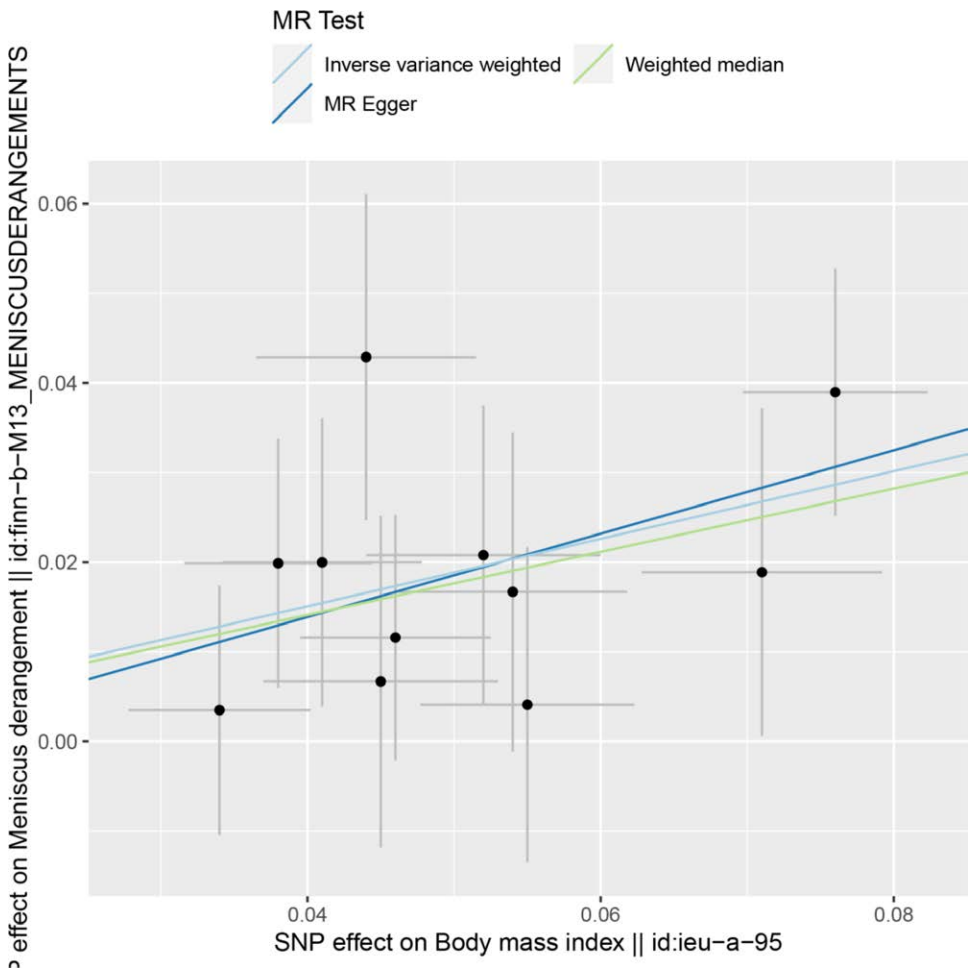

Figure 1. Scatter plot of BMI and meniscal injuries. BMI = body mass index.

associated with meniscus injury, 11 SNPs were still retained for subsequent analysis, ensuring the purity and specificity of the instrumental variables. Notably, all the selected SNPs had *F*-values higher than 10 (Table 1), which indicated that there were no weak instrumental variables, that is, the explanatory power of each SNP for BMI was strong, fulfilling the key requirement of MR analysis. In addition, an exhaustive query of the human genotype-phenotype association database did not reveal any direct association between the selected SNPs and any potentially relevant risk factors for meniscal injuries, which further ensured the rigor of the study design and the reliability of the results.

3.2. Causal relationship between BMI and meniscal injuries

Using MR analysis, we explored in-depth the causal association between obesity and meniscal injury. Both IVW and weighted median analyses consistently revealed a significant effect of obesity on the risk of meniscal injury. Specifically, IVW analysis yielded a ratio (OR) of 1.46 with a 95% confidence interval (CI) of 1.22 to 1.75 and a *P*-value of <.001, whereas the weighted median method yielded an OR of 1.42 with a 95% CI of 1.13 to 1.79 and a *P*-value of <.001, which strongly support the existence of a causal link between obesity and meniscal injuries. hypothesis of a causal link. Although the MR-Egger regression analysis (OR = 1.59, 95% CI = 0.78–3.23, *P* = .230) did not reach statistical significance, the trend was consistent with the 2 methods described above, suggesting that obesity may directly influence the risk of meniscus injuries through genetic mechanisms (Table 2). Combined with the visual presentation of scatterplot (Fig. 1) and forest plot (Fig. 2), the positive causal relationship between BMI and meniscal injury was further visualized and verified.

3.3. Sensitivity analysis

The heterogeneity test using the IVW method-specifically, Cochran's Q test-showed a *P*-value of .894, which was much larger than the .05 significance level, strongly indicating that the selected genetic variants loci were not significantly heterogeneous among them. To further visualize the results of this analysis, we plotted a funnel plot (Fig. 3), which clearly demonstrated the distribution of heterogeneity among the SNP loci, again verifying the conclusion of the heterogeneity test. An in-depth analysis using the MR-PRESSO tool was conducted with the aim of identifying SNPs that might introduce heterogeneity due to pleiotropy; however, the results of the analysis showed that none of the SNPs significantly affected the heterogeneity of the overall results, a finding that further solidified the robustness of the findings. The results of the global test (*G*-test) of the MR-PRESSO similarly supported the findings, with a *P*-value of .806 and a *P*-value of .999. The *P*-value of .806, which is significantly higher than the threshold of .05, excludes the effect of multiplicity on the study results. In addition, the sensitivity analysis of the "leave-one-out" method adopts the IVW method by removing SNPs 1 by 1 and observing the effect on the results. Figure 4 clearly shows that no matter which SNP is

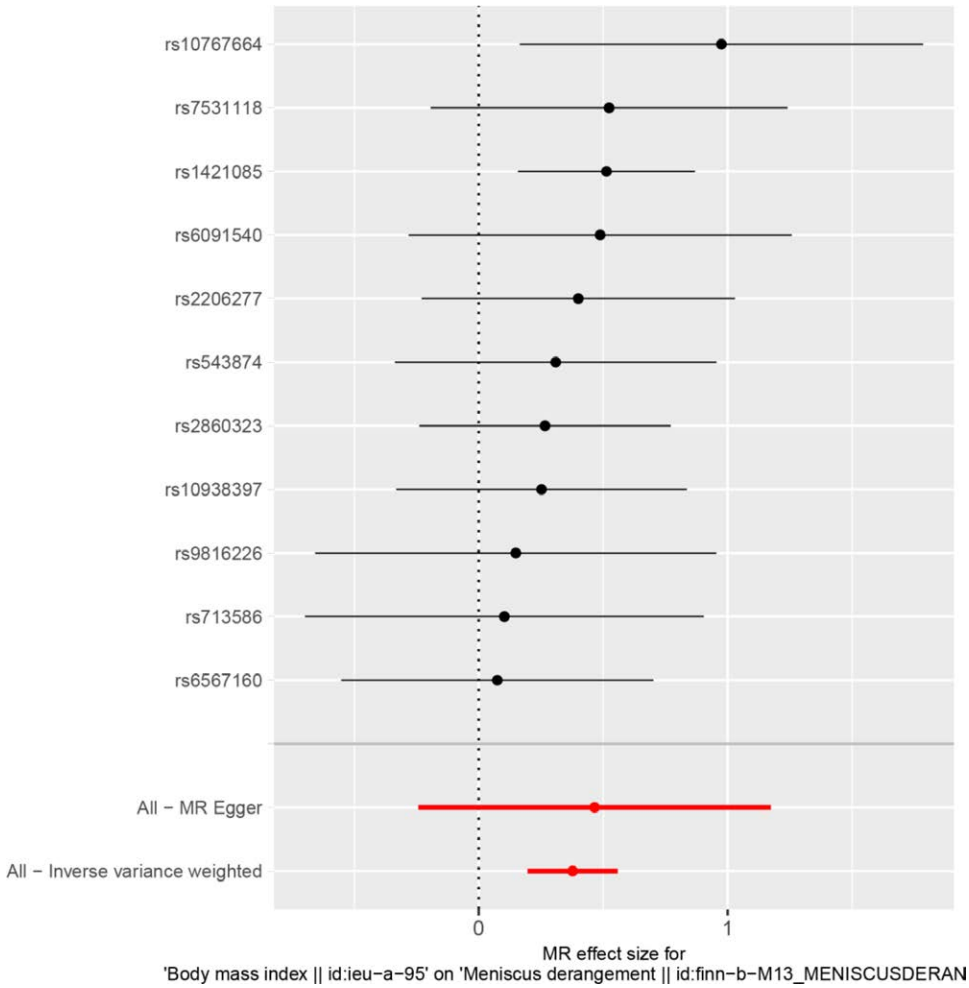

Figure 2. Forest plot of BMI and meniscal injuries. BMI = body mass index.

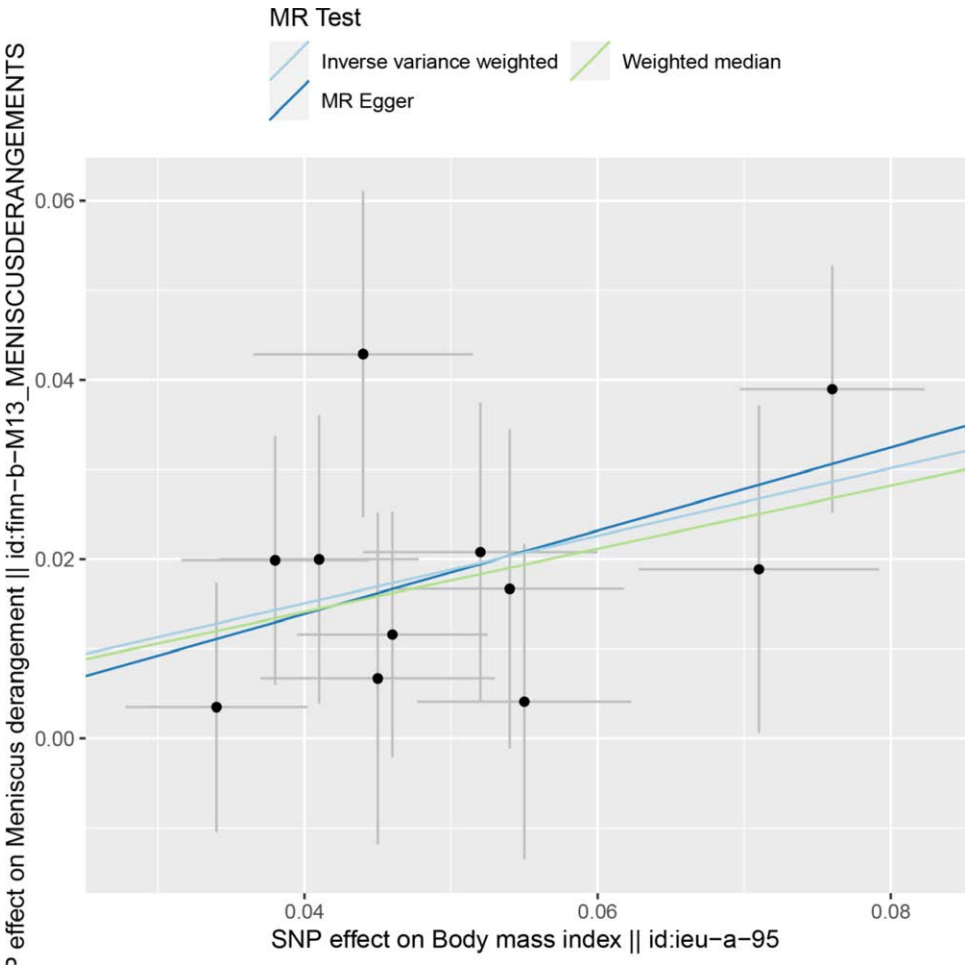

Figure 3. Funnel plot of BMI and meniscal injuries. BMI = body mass index.

removed, the overall results do not show any significant change, which strongly proves the stability and reliability of the study conclusions.

4. Discussion

Although BMI has been widely discussed as an observational risk factor for meniscal injuries, the exact causal link between the 2 has been outstanding. To delve deeper into this scientific topic, our study employed MR, a state-of-the-art genetic method, with the aim of clarifying the potential causal relationship between BMI and meniscus injury. The results of the study clearly reveal that there is a significant causality in the association between BMI and meniscal injuries. Specifically, based on the IVW method of analysis, the OR of BMI to meniscus injury and its 95% CI were 1.46 (1.22–1.75), with a *P*-value much <.001.This finding strongly suggests that individuals with higher BMI are at a higher risk of meniscus injury compared with the general population, emphasizing the role of BMI in meniscus health status and provides new scientific insight into the field of obesity and sports injuries by emphasizing the causal role of BMI in meniscus health status.

Rohde et al[9] revealed a significant association between higher BMI and increased risk of meniscal injuries through an exhaustive retrospective analysis involving 1185 cases of children and adolescents, emphasizing the importance of weight management in the prevention of sports injuries in adolescents.

Rai and his team[24] further explored the biological mechanisms of BMI and meniscal injury, and they found that the expression levels of genes related to oxygen transport, calcium binding, and maintenance of cellular homeostasis were elevated with increasing BMI, whereas the expression of genes related to extracellular matrix deposition, cell migration, and glucosamine metabolism pathways were instead suppressed. This finding implies that failure of extracellular matrix deposition and enhanced calcium ion binding may be the key biological mechanisms leading to meniscal injury.

However, Giordan et al[10] reached a different conclusion by retrospectively analyzing data from 489 patients with meniscal injuries between 2011 and 2021. They noted that the association between high BMI and meniscal injury was not significant, a finding that adds complexity to the discussion of the causal relationship between BMI and meniscal injury, suggesting that further in-depth research is still needed to reach a consensus in this area.

The present study confirmed a significant causal association between BMI and meniscal injuries at the genetic level, a finding that echoes the observations of Rohde and Rai and strongly supports the status of BMI as a risk factor for meniscal injuries, that is, that higher levels of BMI significantly elevate the incidence of meniscal injuries. In contrast, the retrospective study by Giordano et al concluded that BMI did not have a significant effect on the incidence of meniscal injuries. This discrepancy may stem from the inherent limitations of retrospective studies, including the influence of confounding factors and the difficulty of ruling out reverse causation, which diminishes the reliability of causal inferences. In contrast, MR analysis, a cutting-edge epidemiological method, provides stronger support for the assessment of causal associations by using genetic variation as an instrumental variable. This approach significantly reduces the interference of confounding

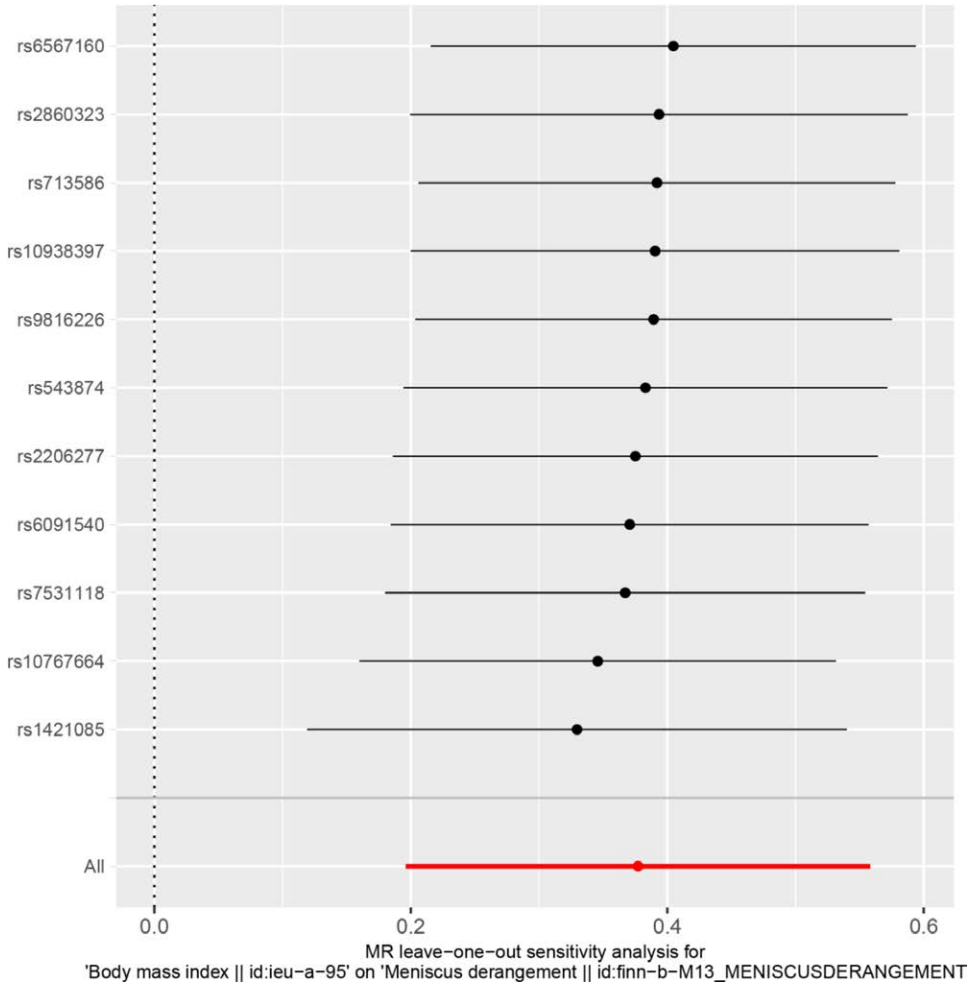

Figure 4. Analysis of BMI and meniscal injuries by the leave-one-out method. BMI = body mass index.

factors and provides purer causal insights, thus demonstrating unique advantages and higher scientific value when exploring the association between BMI and meniscus injury.[25]

Although the present study provides strong evidence of a causal association between BMI and meniscal injuries, its inherent limitations need to be recognized. The primary limitation is the homogeneity of the data source – all samples originated from populations of European origin, which limits the generalizability of the findings to other ethnic groups and emphasizes the importance of increasing sample diversity in future studies. Second, although efforts have been made in the study to validate and consolidate the assumptions of the MR study through a series of sensitivity analyses, the complete exclusion of horizontal pleiotropy of instrumental variables remains challenging. The potential existence of horizontal pleiotropy implies that SNPs may influence outcome variables through unconsidered pathways, leaving some uncertainty about the absolute precision of study conclusions. Furthermore, although the sample size of the existing GWAS is already considerable, more and larger data support is still needed to further enhance the robustness and generalizability of the findings. Future studies should aim to integrate more GWAS data, by improving the sample size and data quality, with a view to obtaining more comprehensive and precise causal association insights.

5. Conclusion

With the comprehensive use of 2-sample MR analysis, this study strongly confirmed that BMI is an independent risk factor for meniscus injury, a finding that provides a new genetic perspective for meniscus injury prevention and intervention.

Author contributions

Conceptualization: Deng Guanghua.
Data curation: Deng Guanghua.
Formal analysis: Deng Guanghua.
Investigation: Deng Guanghua.
Methodology: Deng Guanghua.
Software: Deng Guanghua.
Validation: Deng Guanghua.
Visualization: Deng Guanghua.
Writing – original draft: Deng Guanghua.
Writing – review & editing: Wen Fengli.

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