Body Mass Index and Risk of Internal Knee Derangement: A Mendelian Randomization Study

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Abstract

Background

Traditional observational studies have found an increased risk of internal knee derangement (IKD) associated with higher body mass index (BMI). Here, we hypothesized that BMI and the risk of IKD have a causal relationship, and that high BMI is more likely to suffer from IKD.

Method

By reading the results of previous studies, we can assume that high BMI can increase the risk of IKD. The instrumental variables of BMI were obtained from the GIANT GWAS meta-analysis, which included approximately 700,000 individuals of European descent (n = 681,275). The IKD genetic data from IEU database, comprising 16,380,251 SNPs of European population. We performed MR analysis mainly by inverse-variance weighted (IVW), MR-Egger, Weighted median. In order to test the robustness of the correlation, we further conducted sensitivity analysis through Cochran's Q test, MR-Egger intercept test and leave-one-out analysis.

Results

Genetic predisposition to higher BMI by 1 SD (SD = 4.8kg/m$^2$) was associated with 49% higher risk of IKD (OR = 1.491; [95%CI: 1.373–1.619]; p = 1.932e-21 0.05). Sensitivity analysis was consistent with causal interpretation, which shows that there is unlikely to be a major bias in genetic pleiotropy.

Conclusions

Our findings indicated that high BMI predicted by genes exerts a causal effect on increasing the risk of IKD. Further research is required to unravel the mechanism of BMI in IKD prevention.

Introduction

The knee joint is a complex arrangement of cruciate ligaments, meniscus, cartilage and tendon structures. With the emphasis on sports and health, the probability of knee injury has also increased. Bailey et al. pointed out that it is beneficial for teenagers to participate in various sports in youth, but it will also expose teenagers to the risk of knee injury. It is reported that the knee is one of the most vulnerable body part of gymnastics.

Internal knee derangement (IKD) is a comprehensive syndrome of knee joint disease, such as the meniscus, anterior cruciate ligament (ACL), posterior cruciate ligament (PCL), medial collateral ligament (MCL), lateral
collateral ligament (LCL) injuries. This kind of injury will permanently affect personal activity and health and bring a heavy cost burden.

Previous studies have described the risk factors of IKD include elevated body mass index (BMI), height increase, gender and other independent factors. Among them, BMI is a commonly used index to measure obesity by combining weight and height, which is easy to obtain. Large-scale population studies have shown that subjects who are underweight appear to be protected from knee injury, while overweight individuals have a much higher incidence of knee injury. Although the public is increasingly aware of the danger of high BMI, the number of people with high BMI is developing.

There are many observational studies have discussed the effect of BMI on IKD, but the reported results have been controversial. Additionally, these types of studies cannot determine the causal relationship between exposure and outcomes. Mendelian Randomization is a powerful epidemiological study method based on Mendel's genetic law which has been widely used in exploring the causal impact of exposure on outcomes. It can use single-nucleotide polymorphisms (SNPs) as instrumental variables (IVs) to simulate the design of a randomized controlled trial. These genetic variations are randomly assigned before birth and fixed during pregnancy according to Mendel’s law, so MR can avoid a bias caused by confounders or reverse causations, and further overcome the limitations of traditional observation studies.

So, the purpose of this study is to increase the understanding of the BMI-IKD association through assessing the causal relationship between BMI and IKD via a MR analysis using large genome-wide association study (GWAS) summary statistics and to prove hypothesis that BMI and the risk of IKD have a causal relationship, and that high BMI is more likely to suffer from IKD.

**Material And Method**

**Study outline**

This study was performed completely in accordance with the relevant guidelines and regulations of Mendelian Randomization study.

In this study, MR method was used as a method to determine whether there is a causal association between BMI and IKD, and the aggregated data of SNPs exposure (BMI) and SNPs outcomes (IKD) based on GWAS were used. The basic conditions for a genetic variation to be an IV are summarized as: . The variant is associated with exposure; . The variant does not affect the outcome directly, only possibly indirectly via the exposure; . The variant is not associated with the outcome via a confounding pathway, which follows the basic principles of MR research. We performed MR analysis by inverse-variance weighted (IVW), MR-Egger, Weighted median. In order to test the robustness of the correlation, we further conducted sensitivity analyses through Cochran’s Q test, MR-Egger intercept test and leave-one-out analyses. Statistical analyses were performed using R studio v.4.2.1 (the R studio Foundation: Open source...
& professional software for data science teams. https://www.rstudio.com/; the R Foundation: The R project for Statistical Computing. https://www.R-project.org/). An R package-TwoSampleMR v.0.5.6 was used for conducting the two-sample MR.

Ethics Approval

Our research is based on the currently publicly available statistical data, and no human patients are included in the research, so it doesn't need to be approved by the ethics review committee.

Genetic Instruments For Body Mass Index

The GWAS summary dataset for BMI was extracted from the Genetic Investigation of Anthropometric Traits (GIANT) consortium (https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files/), and identified from the meta-analysis of 681,275 individuals of European ancestry.

Genetic Summary Data For Internal Knee Derangement

The genetic summary data for IKD can be obtained from the UK Medical Research Council Integrative Epidemiology Unit Open GWAS Project database (https://gwas.mrcieu.ac.uk). Developed by the MRC Integrative Epidemiology Unit (IEU) at the University of Bristol, this resource is a manually collected complete GWAS summary datasets, which can be downloaded as an open-source files or obtained by querying the database of complete data. The relevant ethics committees approved all studies that provided data for these analyses, and all participants provided written informed consent.

Ivs Filtering And Harmonization

, we select the genetic instruments for BMI via the following steps: . Instruments were selected based on their genome-wide significance (p-value $5\times10^{-8}$) and independence (linkage disequilibrium [LD] $r^2$ of 0.001, and 1MB from the index variant). To evaluate the strength of IVs, we calculate the F-statistic for each SNP using the following formula: $F$-statistic = $R^2 \times (N-2) / (1 - R^2)$, where $R^2$ is the variance of the phenotype explained by each genetic variant in exposure, and $N$ is the sample size. $R^2$ was calculated using the following formula: $R^2 = 2 \times (1-EAF) \times EAF \times \beta^2$, where EAF is the effect allele frequency and beta is the per allele effect size of the association between each SNP and phenotype. F-statistic larger than the conventional value of 10, which means the instruments used strongly predict the BMI.

After selecting genetic instruments for BMI, we then extracted BMI-associated SNPs from the IKD data. Since IVs cannot be directly related to the outcome, we manually eliminate SNPs with $P \leq 5 \times 10^{-8}$. In addition, to test whether confounding factors violate the significant estimate, we check in PhenoScanner (https://www.phenoscanner.medsch1.cam.ac.uk), a comprehensive information platform on genotype and
phenotype association, to see whether these SNPs are related to the potential risk factors and remove SNPs associated with any of these potential confounders in a genome-wide sense.

Finally, we harmonized the aggregated data for exposure and outcome so that the effect alleles reflected the allele associated with exposure. When SNPs are palindromic, just like A/T or G/C, we used the allele frequency information to resolve chain ambiguity. If they were missing a P, β, or a se for the data, we excluded SNP-trait associations from the GWAS catalog. Proxy SNPs were not included in analyses 19.

**Mendelian Randomization Analyses**

After filtering and harmonizing IVs, to assess causal associations between BMI and IKD, we performed MR analyses. We performed MR analysis mainly by inverse-variance weighted (IVW), MR-Egger, Weighted median. The results are expressed in odd ratios (OR) and 95% confidence intervals (CI), which provided an estimate of the relative risk caused by the increase of each standard deviation increase in the BMI.

The inverse-variance weighted (IVW) model was conducted to examine the causal association, and this approach was considered as the main analysis because of the potential observed heterogeneity 20. The IVW method combines individual MR effects across SNPs to obtain an overall weighted effect of the potential causal association. MR-Egger and weighted median were used to improve the IVW estimates as they could provide more robust estimates in a broader set of scenarios 21.

In order to detect and correct the pleiotropy in the IVW analyses, MR-Egger and Weighted median analyses were then conducted. The MR-Egger allows all genetic variants to have pleiotropy but requires that the pleiotropic effects be independent of the variant-exposure association. MR-Egger methodology tests and explains the existence of unbalanced pleiotropy by introducing this biased parameter and combining outline information estimates of causative effects from multiple individual variants 22.

Weighted median method orders the estimates in MR using each instrument weighted for the inverse of their variance, and the median result is selected and show the single MR estimate with confidence intervals based on bootstrapping technique 23. The weighted median requires and assumes that at least half of the instruments are valid. Compared with MR-Egger analysis, the weighted median calculator has the advantage of maintaining larger precision within the estimates 24. When the p values 0.05, the test is statistically significant.

**Sensitivity Analyses**

In order to test the robustness of the correlation, we further conducted sensitivity analyses through Cochran’s Q test, MR-Egger intercept test and leave-one-out analyses. The Cochran’s Q test was used to identify heterogeneity 25. For significant estimates, we further assessed horizontal pleiotropy using the MR-Egger intercept test and leave-one-out analyses which we sequentially omitted one SNP at a time, to evaluate whether the MR estimate was driven or biased by a single SNP. Th value of the intercept provides
an estimate of the degree of pleiotropy affecting the result, and the beta (slope) coefficient represents the causal effect between exposure and outcome adjusted for pleiotropy. As the intercept neared zero in the MR-Egger intercept test, horizontal pleiotropy was reduced. A funnel plot was also used to assess the probable directional pleiotropy 26. In all these three statistical methods, the threshold of statistical significance for evidence of pleiotropy is p 0.05.

Submit Statements

All authors claim that this manuscript has not been repeatedly submitted and published in any other journals. If it is accepted, it will not be published in any other journals. All authors participated in the editing of the manuscript, strictly examined the accuracy of the data and agreed to the final manuscript.

Results

Study outline

The research framework is shown in Fig. 1.

Genetic Instruments For Body Mass Index

The GWAS summary dataset for BMI was extracted from the GIANT consortium. Yengo et al conducted a meta-analysis of genome-wide association studies for height and body mass index in approximately 700,000 (n = 681,275) individuals of European ancestry. Each participating study obtained written informed consent from all participants and received approval from the appropriate local institutional review boards. It has 2,336,260 SNPs for you to study and the SNP coefficients were per standard deviation (SD) units of BMI (SD = 4.8kg/m$^2$) 27.

Genetic Summary Data For Internal Knee Derangement

The genetic summary data for IKD (GWAS ID: finn-b-M13_KNEEDERANGEMENTS; n = 166,848) can be obtained form the UK Medical Research Council Integrative Epidemiology Unit Open GWAS Project database (https://gwas.mrcieu.ac.uk). Summary statistics for IKD were included 16,380,251 SNPs with 19,627 cases and 147,221 control in European populations.

Ivs Filtering And Harmonization

After obtaining two genetic samples, 510 SNPs were finally screened through the above screening steps. Through harmonizing the 510 SNPs, we removed rs10838202, rs10887578, rs12517185, rs13047416, rs138289, rs1521527, rs189843, rs2163188, rs2268082, rs2284746, rs355777, rs3857068, rs6011457,
rs6595205, rs676749, rs7568228, rs8027205 for being palindromic with intermediate allele frequencies. Finally, 493 SNPs were included in the main analysis. The parameters of some SNPs are written in Table 1.
Table 1
SNP partially used for body mass index-internal knee derangement two-sample Mendelian randomization analysis and its parameters

<table>
<thead>
<tr>
<th>No.</th>
<th>SNP</th>
<th>effect allele</th>
<th>other allele</th>
<th>beta</th>
<th>beta</th>
<th>se</th>
<th>se</th>
<th>P</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rs1003081</td>
<td>T</td>
<td>C</td>
<td>0.0121</td>
<td>0.0137</td>
<td>0.0016</td>
<td>0.0123</td>
<td>3.95E-14</td>
<td>0.2656</td>
</tr>
<tr>
<td>2</td>
<td>rs10099330</td>
<td>A</td>
<td>G</td>
<td>-0.0112</td>
<td>0.0123</td>
<td>0.0017</td>
<td>0.0118</td>
<td>4.45E-11</td>
<td>0.2969</td>
</tr>
<tr>
<td>3</td>
<td>rs10110189</td>
<td>T</td>
<td>C</td>
<td>-0.0164</td>
<td>-0.0047</td>
<td>0.003</td>
<td>0.0269</td>
<td>4.59E-08</td>
<td>0.8627</td>
</tr>
<tr>
<td>4</td>
<td>rs10118701</td>
<td>A</td>
<td>G</td>
<td>-0.0163</td>
<td>-0.0136</td>
<td>0.0018</td>
<td>0.012</td>
<td>1.36E-19</td>
<td>0.2552</td>
</tr>
<tr>
<td>5</td>
<td>rs10132280</td>
<td>A</td>
<td>C</td>
<td>-0.0223</td>
<td>0.0076</td>
<td>0.0018</td>
<td>0.0123</td>
<td>3.00E-35</td>
<td>0.536</td>
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<tr>
<td>6</td>
<td>rs10169594</td>
<td>T</td>
<td>C</td>
<td>-0.0121</td>
<td>-0.0069</td>
<td>0.0018</td>
<td>0.0122</td>
<td>1.79E-11</td>
<td>0.5737</td>
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<td>7</td>
<td>rs10182181</td>
<td>A</td>
<td>G</td>
<td>-0.0325</td>
<td>-0.0166</td>
<td>0.0016</td>
<td>0.0119</td>
<td>9.97E-92</td>
<td>0.1634</td>
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<td>8</td>
<td>rs1020548</td>
<td>A</td>
<td>G</td>
<td>-0.0132</td>
<td>-0.0165</td>
<td>0.0023</td>
<td>0.015</td>
<td>9.52E-09</td>
<td>0.2701</td>
</tr>
<tr>
<td>9</td>
<td>rs1021066</td>
<td>T</td>
<td>G</td>
<td>-0.0096</td>
<td>-0.0189</td>
<td>0.0017</td>
<td>0.0123</td>
<td>1.63E-08</td>
<td>0.1248</td>
</tr>
<tr>
<td>10</td>
<td>rs10211055</td>
<td>T</td>
<td>C</td>
<td>-0.0157</td>
<td>-0.0203</td>
<td>0.0018</td>
<td>0.0126</td>
<td>2.73E-18</td>
<td>0.1083</td>
</tr>
<tr>
<td>11</td>
<td>rs10236214</td>
<td>T</td>
<td>C</td>
<td>0.0128</td>
<td>0.0099</td>
<td>0.0017</td>
<td>0.0128</td>
<td>5.10E-14</td>
<td>0.4372</td>
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<tr>
<td>12</td>
<td>rs10247983</td>
<td>A</td>
<td>G</td>
<td>0.0201</td>
<td>0.0004</td>
<td>0.0033</td>
<td>0.0211</td>
<td>1.12E-09</td>
<td>0.9865</td>
</tr>
<tr>
<td>13</td>
<td>rs10248136</td>
<td>T</td>
<td>C</td>
<td>-0.0097</td>
<td>-0.0119</td>
<td>0.0017</td>
<td>0.0117</td>
<td>1.16E-08</td>
<td>0.3096</td>
</tr>
<tr>
<td>14</td>
<td>rs1025850</td>
<td>T</td>
<td>C</td>
<td>-0.0108</td>
<td>-0.0244</td>
<td>0.0017</td>
<td>0.0125</td>
<td>2.11E-10</td>
<td>0.0509401</td>
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<tr>
<td>15</td>
<td>rs10269783</td>
<td>A</td>
<td>G</td>
<td>0.0133</td>
<td>0.0014</td>
<td>0.0017</td>
<td>0.0118</td>
<td>5.14E-15</td>
<td>0.903</td>
</tr>
<tr>
<td>16</td>
<td>rs1040101</td>
<td>T</td>
<td>G</td>
<td>-0.0101</td>
<td>-0.0011</td>
<td>0.0017</td>
<td>0.0118</td>
<td>2.83E-09</td>
<td>0.9239</td>
</tr>
<tr>
<td>17</td>
<td>rs1048932</td>
<td>A</td>
<td>C</td>
<td>-0.016</td>
<td>0.0087</td>
<td>0.0017</td>
<td>0.0118</td>
<td>4.88E-21</td>
<td>0.464</td>
</tr>
</tbody>
</table>
Mendelian Randomization Analyses

When BMI-IKD was analyzed, as shown in Table 2, in MR analysis by IVW method, we observed that genetic predisposition to higher BMI by 1 SD (4.8kg/m²) was associated with 49% higher risk of IKD (OR = 1.491; [95%CI: 1.373–1.619]; p = 1.932e-21). Moreover, results from the MR-Egger (OR = 1.260; [95%CI: 1.012–1.570]; p = 3.945e-02), weighted median (OR = 1.433; [95%CI: 1.245–1.649]; p = 5.038e-07), weighted mode (OR = 1.518; [95%CI: 1.169–1.972]; p = 1.834e-03) were consistent (all P < 0.05). We visualize the MR analyses results through the scatter plot (Fig. 2) and the forest plot (Fig. 3).

<table>
<thead>
<tr>
<th>Method</th>
<th>SNP</th>
<th>OR</th>
<th>95%CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVW</td>
<td>493</td>
<td>1.491</td>
<td>1.373–1.619</td>
<td>1.932e-21</td>
</tr>
<tr>
<td>MR Egger</td>
<td>493</td>
<td>1.260</td>
<td>1.012–1.570</td>
<td>3.945e-02</td>
</tr>
<tr>
<td>Weighted median</td>
<td>493</td>
<td>1.433</td>
<td>1.245–1.649</td>
<td>5.038e-07</td>
</tr>
<tr>
<td>Weighted mode</td>
<td>493</td>
<td>1.518</td>
<td>1.169–1.972</td>
<td>1.834e-03</td>
</tr>
</tbody>
</table>

Sensitivity Analyses

We detected heterogeneity between estimates from individual SNPs (Q statistic = 634.860, P heterogeneity=1.355e-05 [IVW]) and Q statistic = 631.490, P heterogeneity=1.766e-05[MR-Egger]) as shown in Table 3. But it can be seen in Fig. 4 that there was no funnel plot asymmetry and indicated no proof heterogeneity. Besides we found that the P-pleiotropy for the intercept were large and the estimates adjusted for pleiotropy suggested null effects (MR-Egger intercept = 0.0029226; P pleiotropy=0.106 0.05) (Table 4). In a leave-one-out sensitivity analysis, we found that no single SNPs strongly drives the overall impact of BMI on IKD (Fig. 5). Therefore, we deemed that the conclusion would not be biased significantly.
by the heterogeneity of the analysis because several robust methods were performed, which could provide reliable inferences and statistical support. To sum up, our MR study indicated that genetically determined high BMI exerts a causal effect on increasing the risk of IKD.

Table 3
The Cochran’s Q test analysis of causal effects between body mass index-associated SNPs and risk of internal knee derangement.

<table>
<thead>
<tr>
<th>heterogeneity</th>
<th>Q</th>
<th>Q_pval</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVW</td>
<td>634.860</td>
<td>1.355e-05</td>
</tr>
<tr>
<td>MR-Egger</td>
<td>631.490</td>
<td>1.766e-05</td>
</tr>
</tbody>
</table>

Table 4
The MR-Egger intercept analysis of causal effects between body mass index-associated SNPs and risk of internal knee derangement.

<table>
<thead>
<tr>
<th>MR-Egger intercept</th>
<th>se</th>
<th>pval</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0029226</td>
<td>0.0018053</td>
<td>0.1061164</td>
</tr>
</tbody>
</table>

Discussions

The global obesity is a major public health problem which causes 2.8 million preventable death every year. Obesity related comorbidity leads to a significant loss of disease-free life, which brings a significant economic burden to health services and the health care costs related with obesity are on the rise globally. The relationship between high BMI and IKD is an important public health issue. BMI is not only related to the occurrence of IKD, but also has a great impact on its postoperative. Literature studies has shown that the increase of BMI is a predictor of meniscus injury and cartilage injury during reconstruction, and the risk of postoperative arthritis in adults with BMI 25kg/m² may also raise. There are similar trends in adolescents and children. Childhood obesity is also the focus of attention in modern society. In a study, Ogden et al. reported the prevalence of obesity among children and adolescents in the United States from 1998 to 2014. Among teenagers aged 12 to 19, the prevalence of obesity increased from 10.5–20.6% during the study period. In the same age group, the extreme obesity rate increased from 2.6–9.1%. Interestingly, several investigations have also recorded an increase in ACL injuries in children over a similar period. And Neeraj et al. found that compared with normal children, obese and overweight children may experience more terrible meniscus tear after anterior cruciate ligament rupture.

When clinical trials are challenging, Mendelian randomization test has certain advantages in testing causal effects. In this MR study, we found that higher BMI was related to raise the risk of internal knee derangement by using six complementary methods (IVW, MR-Egger, Weighted median, Cochran’s Q test,
MR-Egger intercept test, leave-one-out). IVW showed that each additional 4.8kg/m² increase in BMI was significantly associated with a rise IKD risk (OR = 1.491; [95%CI: 1.373–1.619]; p = 1.932e-21 0.05), whose estimate is further confirmed through other sensitivity analyses. All these findings show that the causal association between genetically increased EA and developed IKD risk is robust. Therefore, our results do seem to hint at how may help protect against IKD.

Our study has essential strength. We investigated the causal relationship between a common factor (BMI) and a common disease (IKD). We used the mendelian randomization, which, combined with results from other study designs, can improve our understanding of causality by reducing bias caused by confounders. By integrating the aggregated data from approximately 700,000 individuals, our study can do a good job of obtaining robust causal effect estimates, and can also support multiple sensitivity analyses, which often require large sample sizes. We thoroughly searched for the possibility of pleiotropy through the most advanced state of the art methodological developments in our genetic variation, for which we found almost no evidence.

The most obvious advantage of our research included the enormous sample size and complementary MR methods used in the analysis. However, our research may have some limitations. First, it is unlikely to avoid heterogeneity for potential pleiotropic effects or different mechanisms of association with the exposure by using so many SNPs as instruments. Although the heterogeneity in causal estimates is worthy of attention, if pleiotropic effects of genetic variants are also negative or positive, the overall estimate based on all the genetic variants may be unbiased. Here we deal with heterogeneity through a random-effects model in IVW methods, but MR-Egger intercept suggested there is no obvious evidence to show the existence of horizontal pleiotropy. Second, because we studied only European populations, our findings might not be extended to other ethnic groups, such as the Asian population. Third, BMI is a common measure of obesity by calculating height and weight. However, BMI is an easily available but inaccurate indicator of obesity. Existing evidence suggested that measuring and reproducing obesity by body characteristics such as waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR), WC adjusted by BMI (WCadjBMI), HC adjusted by BMI (HCadjBMI) and WHR adjusted by BMI (WHRadjBMI) might be more accurate than BMI.

Conclusions

Genetically predicted body mass index exerts a causal effect on the risk of internal knee derangement. This result should be considered for future research in internal knee derangement and for the elaboration of prevention or therapeutic strategies for the internal knee derangement. Body mass index can be modifiable in a certain extent. In order to decrease the global health burden and disability caused by internal knee derangement, we should try to intervene patients with high body mass index by giving them educational sessions about the harm of high body mass index and internal knee derangement. The strategies to lessen the future burden of IKD should focus on earlier. Screening and improved provision of treatment options for those who with higher BMI.

Declarations
Acknowledgements

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Authors’ contribution

Q.Z. and Z.C. conceived the idea for the study. Y.F., Q.L. and T.L. obtained the genetic data. M.C., Y.L. and H.F. performed the data analyses. B.X. and C.Z. interpreted the results of the data analyses. K.C. wrote the manuscript. All authors read and approved the final manuscript.

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Ethics approval and consent to participate

Not applicable.

Consent to Participate

Not applicable.

Consent to Publish

All authors have seen the manuscript and approved it to submit to your journal.

Competing interests

The authors declare that they have no conflict of interest.

Availability of data and material

All data generated or analysed during this study are included in this published article and its supplementary information files.

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Figures

Figure 1

Mendelian Randomization framework for studying the causal association between body mass index and internal knee derangement.
Figure 2

Scatter plot of causal effect between body mass index-associated SNPs and risk of internal knee derangement.
Figure 3

Forest plot of causal effects between body mass index-associated SNPs and risk of internal knee derangement.
Figure 4

The funnel plot of causal effect between body mass index-associated SNPs and risk of internal knee derangement.
Figure 5

The leave-one-out analysis of causal effect between body mass index-associated SNPs and risk of internal knee derangement.