Causal association between body mass index and risk of perianal abscess: A Mendelian randomization study

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Keywords: BMI, perianal abscess, mendelian randomization study

Posted Date: September 19th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3252190/v1

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Additional Declarations: No competing interests reported.
Abstract

Background

Perianal abscess is a common infectious disease affecting the perianal region. Body mass index (BMI) is a widely used indicator for assessing weight and obesity. Although obesity is known to be associated with multiple health issues, the understanding of the relationship between BMI and perianal abscess is limited. Whether BMI influences the risk of perianal abscess remains a subject of debate.

Method

A two-sample Mendelian randomization (MR) analysis using the inverse-variance weighted (IVW), weighted median, weighted mode and MR-Egger regression methods was performed. We used the publicly available summary statistics data sets of genome-wide association studies (GWAS) meta-analyses for BMI in individuals of South Asian (n = 8,658) as the exposure and a GWAS for abscess of anal and rectal regions from the individuals included in OpenGWAS database (total n = 183,710; case = 1,287, control = 182,423) as the outcome.

Results

We selected 29 single nucleotide polymorphisms (SNPs) at genome-wide significance from GWASs on BMI as the instrumental variables. The IVW method showed there is no evidence to support a causal association between BMI and perianal abscess (Beta = -0.093, SE = 0.097, P = 0.340). MR-Egger regression revealed that directional pleiotropy was unlikely to be biasing the result (intercept = 0.024; P = 0.285), and it also showed no causal association between BMI and perianal abscess (Beta = -0.254, SE = 0.177, P = 0.162). Moreover, the weighted median and weighted mode also approach no evidence of a causal association between BMI and perianal abscess (weighted median: Beta = -0.126, SE = 0.139, P = 0.363; weighted mode: Beta = -0.207, SE = 0.182, P = 0.813). Cochran's Q test and the funnel plot indicated no evidence of heterogeneity and asymmetry, indicating no directional pleiotropy.

Conclusion

The results of MR analysis did not yield sufficient evidence to suggest a causal association between BMI and an elevated risk of perianal abscess.

Background

Perianal abscess is a common infectious disease affecting the perianal region. It is caused by infection or obstruction of the perianal glands[1]. Perianal abscess can lead to severe pain, swelling, and inflammation, significantly impacting the quality of life for affected individuals[2]. Body mass index (BMI) is a widely used indicator for assessing weight and obesity. It is calculated by dividing a person's weight by the square of their height. Obesity is defined as having a BMI above 30 and has been associated with an increased risk of various chronic conditions, such as cardiovascular disease, diabetes, and certain types of cancer[3, 4]. Although obesity is known to be associated with multiple health issues, the understanding of the relationship between BMI and perianal abscess is limited. The development of perianal abscess involves multiple factors, including infection, trauma, and local immune status. Whether BMI influences the risk of perianal abscess remains a subject of debate.

To gain deeper insights into the causal relationship between BMI and perianal abscess, this study will employ a Mendelian randomization research design. Mendelian randomization utilizes the random distribution of genotypes to simulate the characteristics of a randomized controlled trial, reducing the interference of genetic and environmental factors on the outcomes[5]. A two-sample MR estimates causal effects where data on the exposure and outcome have been measured in different samples[6]. Through the collection of data from a large-scale population cohort, we will gather information on participants' BMI, the occurrence of perianal abscess, and other relevant factors. Participants will be randomly assigned to either the high BMI group or the normal BMI group, and long-term follow-up observations will be conducted. Clinical data, lifestyle habits, genetic information, and other factors
will be considered comprehensively, and statistical analysis will be performed to evaluate the impact of increased BMI on the risk of perianal abscess.

The results of this study are expected to provide new evidence for a better understanding of the relationship between BMI and perianal abscess. These findings can guide the prevention and treatment strategies for perianal abscess and offer more specific recommendations for obesity management. Furthermore, the study results may have important implications for public health policies and individual healthcare management, aiming to reduce the incidence and associated risks of perianal abscess.

**Methods**

**Data sources and selection of genetic variants**

We conducted a search in the Open Genome-Wide Association Studies (OpenGWAS) database, developed by the MRC Integrative Epidemiology Unit (IEU) at the University of Bristol. OpenGWAS is a comprehensive collection of GWAS summary datasets that have been curated manually. These datasets are publicly available and can be downloaded as open-source files or accessed by querying the database for complete data ([https://gwas.mrcieu.ac.uk](https://gwas.mrcieu.ac.uk))[7, 8].

We utilized publicly available summary statistics datasets from genome-wide association studies (GWAS) meta-analyses to obtain data on body mass index (BMI) in individuals of South Asian descent (n = 8658; GWAS ID: ukb-e-23104_CSA) as the exposure. We conducted a two-sample Mendelian randomization (MR) study, using genetic variants associated with BMI as instrumental variables (IVs), applying a P-value threshold of 1.00E-05. We obtained summary statistics (beta coefficients and standard errors) for 29 single nucleotide polymorphisms (SNPs) associated with BMI as the IVs from GWAS studies on BMI. Furthermore, we obtained publicly available summary statistic datasets from a GWAS on abscesses of the anal and rectal regions from individuals included in OpenGWAS (total n = 183,710; cases = 1,287; controls = 182,423; GWAS ID: finn-b-K11_ABSCANAL) as the outcome (Table 1).

<table>
<thead>
<tr>
<th>Variants content</th>
<th>GWAS ID</th>
<th>Sample Size</th>
<th>SNP</th>
<th>First Author</th>
<th>Consortium</th>
<th>year</th>
<th>Population Studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure Body Mass Index (BMI)</td>
<td>ukb-e-23104_CSA</td>
<td>8658</td>
<td>9811391</td>
<td>Pan-UKB team</td>
<td>NA</td>
<td>2020</td>
<td>South Asian/Males and Females</td>
</tr>
<tr>
<td>Outcome abscess of anal and rectal regions (perianal abscess)</td>
<td>finn-b-K11_ABSCANAL</td>
<td>1287</td>
<td>16380365</td>
<td>NA</td>
<td>NA</td>
<td>2021</td>
<td>European/Males and Females</td>
</tr>
</tbody>
</table>

Table 1 Details of Studies and Datasets Used in the Study

Abbreviations: BMI, body mass index; GWAS, genome-wide association study; SNP, single nucleotide polymorphisms

**Statistical analysis for Mendelian randomization**

Mendelian randomization analysis requires genetic variants to be related to, but not potential confounders of an exposure[9]. To ensure this, we followed a three-step approach. Firstly, we assessed the independent association of each single nucleotide polymorphism (SNP) with BMI. Secondly, we examined the association between each SNP and the risk of perianal abscess. Lastly, we combined these findings to estimate the unbiased causal association between BMI and the risk of perianal abscess using Mendelian randomization analysis. For the analysis, we employed the two-sample Mendelian randomization method, which utilizes summary statistics from different genome-wide association studies (GWASs)[10]. This approach allows us to estimate the causal effect of the exposure (BMI) on the outcome (perianal abscess). We used summary data from GWASs on BMI and perianal abscess, utilizing 29 SNPs as IVs in the analysis (Table 2).
Table 2

<table>
<thead>
<tr>
<th>MR method</th>
<th>nSNP</th>
<th>Beta</th>
<th>SE</th>
<th>P-val</th>
<th>OR</th>
<th>Low95%</th>
<th>Up95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR Egger</td>
<td>29</td>
<td>-0.254</td>
<td>0.177</td>
<td>0.162</td>
<td>0.776</td>
<td>0.549</td>
<td>1.097</td>
</tr>
<tr>
<td>Weighted median</td>
<td>29</td>
<td>-0.126</td>
<td>0.139</td>
<td>0.363</td>
<td>0.881</td>
<td>0.672</td>
<td>1.157</td>
</tr>
<tr>
<td>Inverse variance</td>
<td>29</td>
<td>-0.093</td>
<td>0.097</td>
<td>0.340</td>
<td>0.911</td>
<td>0.754</td>
<td>1.102</td>
</tr>
<tr>
<td>Weighted mode</td>
<td>29</td>
<td>-0.207</td>
<td>0.181</td>
<td>0.265</td>
<td>0.813</td>
<td>0.570</td>
<td>1.162</td>
</tr>
</tbody>
</table>

Note: Beta, beta coefficient; MR, Mendelian randomization; SE, standard error; SNP, single nucleotide polymorphism.

The inverse-variance weighted (IVW) method, employed in this study, utilizes a meta-analysis approach to combine the Wald ratio estimates of the causal effect obtained from different genetic variants\[^{11}\]. It provides a consistent estimate of the causal effect of the exposure variable on the outcome when each of the genetic variants satisfies the assumptions of an instrumental variable. In order to address potential pleiotropy, where genetic variants may have effects on multiple variables, two additional methods were used: MR-Egger regression and the weighted median estimator. MR-Egger regression accounts for unbalanced pleiotropy by introducing a parameter for bias, using summary data estimates of causal effects from individual variants\[^{12}\]. It applies a weighted linear regression of the gene-outcome coefficients on the gene-exposure coefficients, with the slope representing the causal effect estimate. The intercept provides an estimate of the average horizontal pleiotropic effect across the genetic variants\[^{13}\]. The weighted median estimator, on the other hand, provides a consistent estimate of the causal effect even if up to 50% of the information comes from genetic variants that are not valid instrumental variables\[^{14}\]. It retains greater precision in the estimates compared to MR-Egger analysis. Statistical significance was determined at a threshold of $P < 0.05$. All Mendelian randomization analyses were conducted using the MR Base platform (App Version: 1.4.3 8a77eb (25 October 2020), R Version: 4.0.3)\[^{8}\].

**Heterogeneity and sensitivity test**

We examined the heterogeneity between single nucleotide polymorphisms (SNPs) using Cochran's Q-statistics\[^{15}\] and $I^2$ statistic\[^{16, 17}\]. Additionally, we conducted a "leave-one-out" analysis to explore the potential influence of individual SNPs on the causal association\[^{18}\].

**Results**

**Studies included in the meta-analysis**

**Instrumental variables for Mendelian randomization**

We identified a set of 29 independent SNPs from genome-wide association studies (GWASs) on BMI as IVs in our analysis. All of these SNPs were found to be significantly associated with BMI at the genome-wide level of significance (Table 2 and Fig. 1). When assessing their association with perianal abscess, we observed positive associations for all 29 SNPs, although these associations did not reach statistical significance (Table 2). The genetic variants used as IVs explained approximately 0.23% of the variance in the exposure (as indicated by the $R^2$ statistic). Importantly, the $F$ statistic, which indicates the strength of the IVs, was equal to or greater than 10 for each individual variant. Typically, an $F$ statistic below 10 is considered indicative of a 'weak IV'. Therefore, the risk of weak instrument bias was minimal in our analysis.

Overall, these findings demonstrate that the selected SNPs used as IVs exhibited strong associations with BMI and demonstrated negligible weak instrument bias, supporting their suitability as instrumental variables in our Mendelian randomization analysis.

**Mendelian randomization results**

The IVW method did not provide evidence to support a causal association between BMI and perianal abscess ($Beta = -0.093$, $SE = 0.097$, $P = 0.340$; as shown in Table 2, Figs. 1 and 2). The intercept in the MR-Egger test, which represents the average pleiotropic effect across the genetic variants (the average direct effect of a variant with the outcome), was not significantly different from zero (intercept = 0.024; $P = 0.285$), indicating that directional pleiotropy was unlikely to bias the results. Furthermore, the MR-Egger analysis
also did not show a causal association between BMI and perianal abscess \((Beta = -0.254, SE = 0.177, P = 0.162;\) as presented in Table 2, Figs. 1 and 2). In addition, both the weighted median and weighted mode approaches did not yield evidence of a causal association between BMI and perianal abscess (weighted median: \(Beta = 0.126, SE = 0.139, P = 0.363;\) weighted mode: \(Beta = -0.207, SE = 0.182, P = 0.813;\) as shown in Table 2, Fig. 2). Importantly, the associations between BMI and perianal abscess were consistent across the MR-Egger, weighted median, and weighted mode methods. The results of the MR analysis do not support a potential causal association between BMI and perianal abscess.

**Heterogeneity and sensitivity test**

Cochran's Q test was performed to assess heterogeneity between instrumental variable estimates based on individual genetic variants, and the results indicated no significant evidence of heterogeneity (Table 3 and Fig. 3). Heterogeneity refers to the variability in causal estimates obtained from each SNP, and low heterogeneity suggests increased reliability of MR estimates. The \(I^2\) values also indicated low heterogeneity, further supporting the increased reliability of MR estimates (Table 3). In the "leave-one-out" analysis, each SNP was removed individually to evaluate its influence on the overall IVW point estimate. The results demonstrated that no single SNP had a significant impact on the IVW point estimate, suggesting that the overall result was not driven by any particular genetic variant. The funnel plot, which assesses publication bias and directional horizontal pleiotropy, did not exhibit any significant asymmetry (Fig. 4). Additionally, the MR Egger regression test also showed no evidence of asymmetry, further indicating the absence of bias due to directional horizontal pleiotropy. Taken together, the absence of significant heterogeneity, the low \(I^2\) values, the results of the "leave-one-out" analysis, and the absence of asymmetry in the funnel plot and MR Egger regression test provide reassurance regarding the reliability of the MR estimates and reduce concerns about potential biases in the analysis.

**Table 3**

<table>
<thead>
<tr>
<th>Heterogeneity test</th>
<th>Methods</th>
<th>(Q)</th>
<th>(df)</th>
<th>(Q)-val</th>
<th>(I^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR Egger</td>
<td>22</td>
<td>27</td>
<td>0.738</td>
<td>0.227</td>
<td></td>
</tr>
<tr>
<td>Inverse variance weighted</td>
<td>23.19</td>
<td>28</td>
<td>0.724</td>
<td>0.207</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sensitivity test</th>
<th>Egger regression intercept</th>
<th>Standard error</th>
<th>Directionality</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.024</td>
<td>0.022</td>
<td>0.285</td>
<td></td>
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</tbody>
</table>

**Discussion**

Obesity has been considered as increasing the risk for perianal abscess[2]. However, it is uncertain whether obesity has a causal relationship with perianal abscess. Our MR analysis aimed to investigate the potential causal association between body mass index (BMI) and perianal abscess. The study utilized a set of 29 independent SNPs identified from GWASs on BMI as IVs. Our findings did not provide evidence to support a causal relationship between BMI and perianal abscess. The selection of strong instrumental variables is crucial for reliable MR analysis. In our study, all 29 SNPs used as IVs exhibited significant associations with BMI at the genome-wide level, confirming their suitability as instrumental variables. The low risk of weak instrument bias, as indicated by the F statistics, further supported the robustness of our IVs. These findings highlight the importance of rigorous selection and validation of instrumental variables to strengthen the validity of MR analyses.

The IVW method, which combines the estimates from individual SNPs, did not demonstrate a causal association between BMI and perianal abscess. Similarly, the MR-Egger regression analysis, which accounts for potential directional pleiotropy, did not reveal a causal relationship. The absence of significant intercepts in the MR-Egger test suggests that directional pleiotropy is unlikely to have biased the results. Furthermore, the weighted median and weighted mode approaches also failed to yield evidence of a causal association. The absence of significant heterogeneity, as indicated by Cochran's Q test and \(I^2\) values, supports the reliability of our MR estimates. The "leave-one-out" analysis further confirmed that no single SNP had a significant impact on the overall IVW point estimate, indicating that the results were not driven by any individual variant. The absence of asymmetry in the funnel plot and the non-significant intercept in the MR-Egger test suggest the absence of publication bias and directional horizontal pleiotropy, respectively.
Our study has several strengths. Firstly, we employed a comprehensive set of independent genetic variants as instrumental variables, minimizing the risk of confounding and increasing the reliability of the MR estimates. Secondly, we conducted sensitivity analyses and heterogeneity tests to assess the robustness of our findings and minimize potential biases. Additionally, the large sample size and the use of publicly available summary statistics from GWASs enhanced the generalizability and reproducibility of our results. Lastly, to the best of our knowledge, this is the first such study on the causal relationship between BMI and perianal abscess. However, our study also has limitations that should be acknowledged. Firstly, BMI is influenced by genetic factors. Despite the success of genome-wide association studies (GWAS), the combined effects of the established genetic loci explain less than 2% of the interindividual variability in BMI. Secondly, sex and age are associated with differences in obesity and body composition. Karin et al. confirmed that abscesses are more common among men, and that they are more common among younger than among older people[2]. Thirdly, causality may depend on ethnicity and selection bias, so further MR studies are required for other populations.

In conclusion, our Mendelian randomization analysis did not provide evidence to support a causal association between BMI and perianal abscess. These findings suggest that factors other than BMI may play a more significant role in the development of perianal abscess. Future research should explore additional risk factors and mechanisms involved in the pathogenesis of perianal abscess to provide a more comprehensive understanding of its etiology. Furthermore, considering the multifactorial nature of perianal abscess, interventions and preventive strategies should focus on comprehensive management approaches that target a wide range of risk factors rather than solely focusing on BMI reduction.

**Abbreviations**

BMI: Body Mass Index;  
MR: Mendelian Randomization;  
IVW: Inverse-Variance Weighted;  
GWAS: Genome-Wide Association Studies;  
SNP: Single Nucleotide Polymorphisms;  
OpenGWAS: Open Genome-Wide Association Studies

**Declarations**

**Author contributions**

Long Wu and Huan Wu contributed equally to this work and should be considered co-first authors. Long Wu, Huan Wu, and Fei Huang wrote the first version of the article. Yunhuan Zhen and Haiyang Li revised the second and third versions of this study and helped with the English editing. Long Wu, Huan Wu, and Xiaoyun Li participated in the conception and design of the study and the drafting of the article. Long Wu and Huan Wu designed the study and revised the manuscript. All authors reviewed and approved the final version of the article.

**Acknowledgements**

This study was supported in part by the Science and Technology Fund Project of Guizhou Health Commission in 2023 (No. gzwjk2023-042) and the National Natural Science Foundation of China (No. 82061006).

**Data availability statement**

Publicly available datasets were analyzed in this study. The datasets supporting the conclusions of this article are available in OpenGWAS database website (https://gwas.mrcieu.ac.uk/). The other data generated or analyzed during this study are available in those published articles.

**Ethics approval and consent to participate**
Not applicable

**Conflicts Of Interest**

The authors have no financial or nonfinancial conflicts of interest to declare.

**Fundings:**


2. National Natural Science Foundation of China, No. 8206100697.

**Author contributions**

Long Wu and Huan Wu contributed equally to this work and should be considered co-first authors. Long Wu, Huan Wu, and Fei Huang wrote the first version of the article. Yunhuan Zhen and Haiyang Li revised the second and third versions of this study and helped with the English editing. Long Wu, Huan Wu, and Xiaoyun Li participated in the conception and design of the study and the drafting of the article. Long Wu and Huan Wu designed the study and revised the manuscript. All authors reviewed and approved the final version of the article.

**References**


Figure 1

Forest plot of single nucleotide polymorphisms (SNPs) associated with body mass index (BMI) and the risk of perianal abscess. The significance of red lines are MR results of MR-Egger test and IVW method.
Figure 2

Scatter plots of genetic associations with body mass index against the genetic associations with perianal abscess. The slopes of each line represent the causal association for each method. The blue line represents the inverse-variance weighted estimate, the green line represents the weighted median estimate, the dark blue line represents the Mendelian randomization-Egger estimate, and the dark green line represents the weighted mode estimate.
Figure 3

Funnel plot to assess heterogeneity. The blue line represents the inverse-variance weighted estimate, and the dark blue line represents the Mendelian randomization-Egger estimate.
Figure 4

Leave-one-out of SNPs associated with BMI and their risk of perianal abscess. Each black point represents result of the IVW MR method applied to estimate the causal effect of BMI on perianal abscess excluding particular SNP.