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Causal association between adiposity and hemorrhoids: a Mendelian randomization study

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Background: Hemorrhoids are a very common anorectal disorder affecting a large number of individuals throughout the world. This study aimed to evaluate the causal effects of four adiposity traits including body mass index (BMI), body fat percentage, waist circumference, and waist-to-hip ratio on hemorrhoids by Mendelian randomization (MR).

Methods: We used summary statistics of BMI ($N = 461,460$), body fat percentage ($N = 454,633$), waist circumference ($N = 462,166$), waist-to-hip ratio ($N = 212,244$), and hemorrhoids ($N = 337,199$) from large-scale genome wide association studies of European ancestry. Univariable and multivariable MR were carried out to infer causality. The MR Steiger directionality test was used to test the causal direction.

Results: The primary MR analysis using the inverse variance weighted (IVW) method showed that there were positive effects of genetically determined BMI [odds ratio (OR) = 1.005, 95% confidence interval (CI): 1.003−1.008, per standard deviation (SD), $p = 7.801 \times 10^{-5}$], body fat percentage (OR = 1.005, 95% CI: 1.001−1.008, per SD, $p = 0.008$), waist circumference (OR = 1.008, 95% CI: 1.005−1.011, per SD, $p = 1.051 \times 10^{-6}$), and waist-to-hip ratio (OR = 1.010, 95% CI: 1.003−1.017, per SD, $p = 0.003$) on hemorrhoids. These findings were robust in multivariable MR adjusting for physical activity. The Steiger directionality test showed evidence against reverse causation.

Conclusion: Our MR study supports a causal role of adiposity in the development of hemorrhoids. Adiposity prevention may be an important strategy for reducing hemorrhoids risk.

KEYWORDS

adiposity, hemorrhoids, Mendelian randomization, risk, body mass index

Introduction

Hemorrhoids are one of the most common anorectal disorders encountered in colorectal practice. According to epidemiological data, as many as half of the population suffers from hemorrhoids before reaching the age of 50 (1). Both males and females are affected equally (2). In hemorrhoids, the most common symptom is painless rectal bleeding during defection (3). Depending on their location, hemorrhoids are generally divided into external, internal, and mixed type (3). Hemorrhoids treatment may include a variety of non-operative and surgical options. Approximately 10% of cases require surgical procedures (4). In the United Kingdom

(UK), more than 20,000 hemorrhoidal procedures are performed annually (5). Given that hemorrhoids are associated with a heavy healthcare and economic burden, increasing attention has been given to hemorrhoids prevention in recent years (5).

The cause of hemorrhoids remains unclear. Epidemiological studies have suggested several risk factors for the development of hemorrhoids including adiposity (6). However, evidence concerning the relationship between adiposity and hemorrhoids is scarce and inconclusive (7–11), and it is not yet established whether the association is causal. The practical inability to perform randomized controlled trials (RCTs) for evaluating the causality between adiposity and hemorrhoids makes it necessary to conduct a Mendelian randomization (MR) analysis. MR is a form of causal inference method that utilizes single nucleotide polymorphisms (SNPs) as instrumental variables to explore the potential causal relationship between an exposure and a disorder (12). In MR, the biases including residual confounding and reverse causation are significantly reduced (13). Because identifying modifiable risk factors can offer potential for hemorrhoids prevention, it is of importance to infer causation between adiposity and hemorrhoids. The aim of this study is to apply the MR causal framework to evaluate whether four adiposity traits including body mass index (BMI), body fat percentage, waist circumference, and waist-to-hip ratio have causal effects on hemorrhoids development.

Methods

Study design

This was a two-sample MR study utilizing publicly available data for all analyses. Our paper was constructed in accordance with the suggestions provided in the Strengthening the Reporting of Observational Studies in Epidemiology-Mendelian randomization (STROBE-MR) guidelines. Supplementary Table S1 shows our STROBE-MR checklist.

Data sources for exposures

The summary-level data for BMI ($N = 461,460$), body fat percentage ($N = 454,633$) and waist circumference ($N = 462,166$) were obtained from the Medical Research Council-Integrative Epidemiology Unit (MRC-IEU) consortium. According to the consortium's instructions, body composition measures were taken manually.[1] For BMI, units of measurement were Kg/m^2. Regarding body fat percentage, units of measurement were percent. For waist circumference, units of measurement were cm. Waist-to-hip ratio data were derived from a genome wide association study (GWAS) meta-analysis of the Genetic Investigation of Anthropometric Traits (GIANT) consortium, which was based on 212,244 participants of European descent (14). Table 1 shows the details on the GWAS summary statistics for the exposures.

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1   https://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=100010

Outcome data

For hemorrhoids, we used summary-level data computed by the Neale Lab, which included 8,190 cases and 329,009 controls. Diagnostic code applied for identifying hemorrhoids cases was I84 in international Classification of diseases (ICD)-10.

Instrument construction

For constructing genetic instruments for each exposure, we selected SNPs strongly associated with the exposure at genome-wide significance ($p < 5 \times 10^{-8}$). Selected SNPs were then taken forward to linkage disequilibrium clumping to remove SNPs that were correlated ($r^2 \geq 0.001$). A European reference panel of the 1,000 Genomes Project was used as reference population (15). We harmonized SNP-exposure and SNP-hemorrhoids associations to align the effect sizes and to exclude palindromic SNPs. In the hemorrhoids GWAS dataset, we used proxy SNPs ($r^2 > 0.8$) when particular SNPs were absent. The SNP extraction from GWAS summary-level data, clumping, and harmonization were performed using the TwoSample MR package in R version 4.1.0 (16, 17). The F-statistic was used to quantify instrument strength. It was calculated using the equation: $F = (R2/K)/[(1-R2)(N-K-1)]$ (18). Where R2 is the variance explained by the instruments, K is the number of instruments, and N is the sample size.

Statistical analyses

Using two-sample MR, we generated estimates of the causal effect of the adiposity measures on hemorrhoids (OR per SD unit increase). We used the inverse variance weighted (IVW) method as the primary MR analysis (19); it assumes that the genetic instruments as a whole meets the key MR assumptions. To further evaluate the causal assessments identified in the primary MR analysis, additional sensitivity analyses using MR-Egger, maximum likelihood, weighted median, and MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) methods were undertaken. Certain MR assumptions were relaxed using these methods; they are more robust to potential pleiotropic effects (20, 21). For investigating horizontal pleiotropy, the intercept term from MR-Egger regression was used (22). The intercept $p > 0.05$ indicates the absence of pleiotropy. Furthermore, we used the MR-PRESSO as an additional method for detecting pleiotropy; this method can exclude outlier genetic instruments having pleiotropic effects and carry out causal effect estimates after excluding outlying genetic instruments (23). We investigated the causal direction between the adiposity measures and hemorrhoids using the MR Steiger directionality test (16, 24). For accounting for physical activity's effects on our MR assessments, multivariable MR analyses were undertaken using the TwoSampleMR package. Summary-level data for physical activity were obtained from the Within family GWAS consortium involving 24,264 participants of European descent (Table 1).

We did not pre-register the study protocol. All tests were two-sided and conducted using the TwoSampleMR and MR-PRESSO packages in R version 4.1.0. Statistical significance was set at $p < 0.05$. Ethical approval and informed consent were obtained in all original

Results

A summary of the instrument SNP selection process is shown in Figure 1. Of the 458 SNPs that predicted BMI, 19 SNPs were removed after linkage disequilibrium clumping. Harmonization with the corresponding hemorrhoids summary-level data resulted in 421 independent SNPs for the MR analysis (F-statistic = 61.13). Of the 395 SNPs predicting body fat percentage, linkage disequilibrium removed 18 SNPs. Three hundred and sixty-six SNPs were obtained for the MR analysis after harmonizing the body fat percentage dataset with
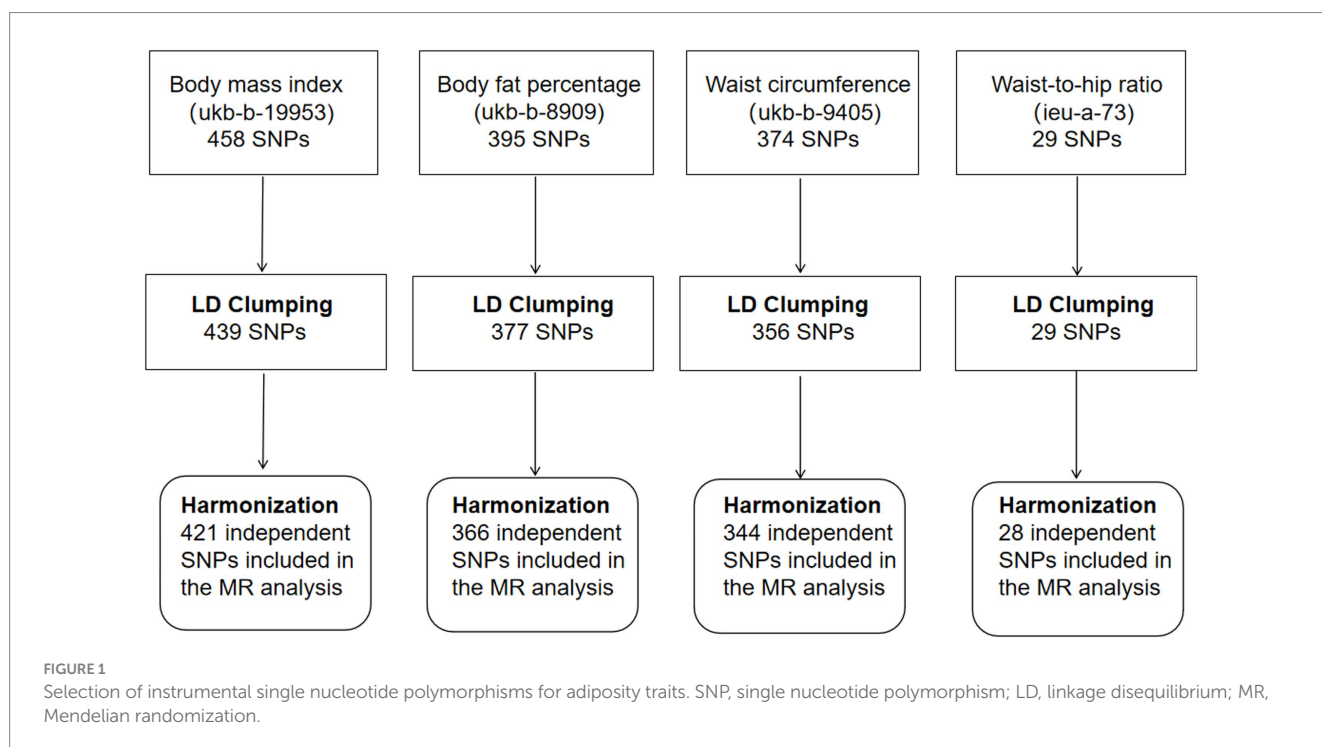
the hemorrhoids dataset (F-statistic = 32.86). Of the 374 SNPs that predicted waist circumference, 18 correlated SNPs were removed after linkage disequilibrium clumping. Harmonization with the corresponding hemorrhoids summary statistics produced 344 SNPs for the MR analysis (F-statistic = 45.00). The 29 SNPs predicting waist-to-hip ratio were uncorrelated ($r^2 < 0.001$). Harmonization with the corresponding hemorrhoids summary statistics obtained 28 SNPs for the MR analysis (F-statistic = 76.56). The SNPs for each exposure had enough strength; the F-statistics were greater than 10. Supplementary Tables S2–S5 show the details on the instrumental genetic variants for each exposure.

For each 1-SD kg/m² increase in genetically determined BMI, the IVW MR analysis indicated enhanced risk of hemorrhoids [odds ratio (OR) = 1.005, 95% confidence interval (CI): 1.003–1.008, $p = 7.801 \times 10^{-5}$] (Figures 2A, 3A). This finding was consistent across

TABLE 1 The GWAS datasets included in this MR study.

Trait	Sample size	Population	Unit	Sex	GWAS-ID	Consortium	Year
Body mass index	461,460	European	SD	Males and females	ukb-b-19953	MRC-IEU	2018
Body fat percentage	454,633	European	SD	Males and females	ukb-b-8909	MRC-IEU	2018
Waist circumference	462,166	European	SD	Males and females	ukb-b-9405	MRC-IEU	2018
Waist-to-hip ratio	212,244	European	SD	Males and females	ieu-a-73	GIANT	2015
Hemorrhoids	8,190 cases and 329,009 controls	European	NA	Males and females	ukb-a-539	Neale Lab	2017
Physical activity	24,264	European	NA	Males and females	ieu-b-4859	Within family GWAS consortium	2022

GWAS, genome-wide association studies; GIANT, Genetic Investigation of Anthropometric Traits; MRC-IEU, Medical Research Council-Integrative Epidemiology Unit; SD, standard deviation.
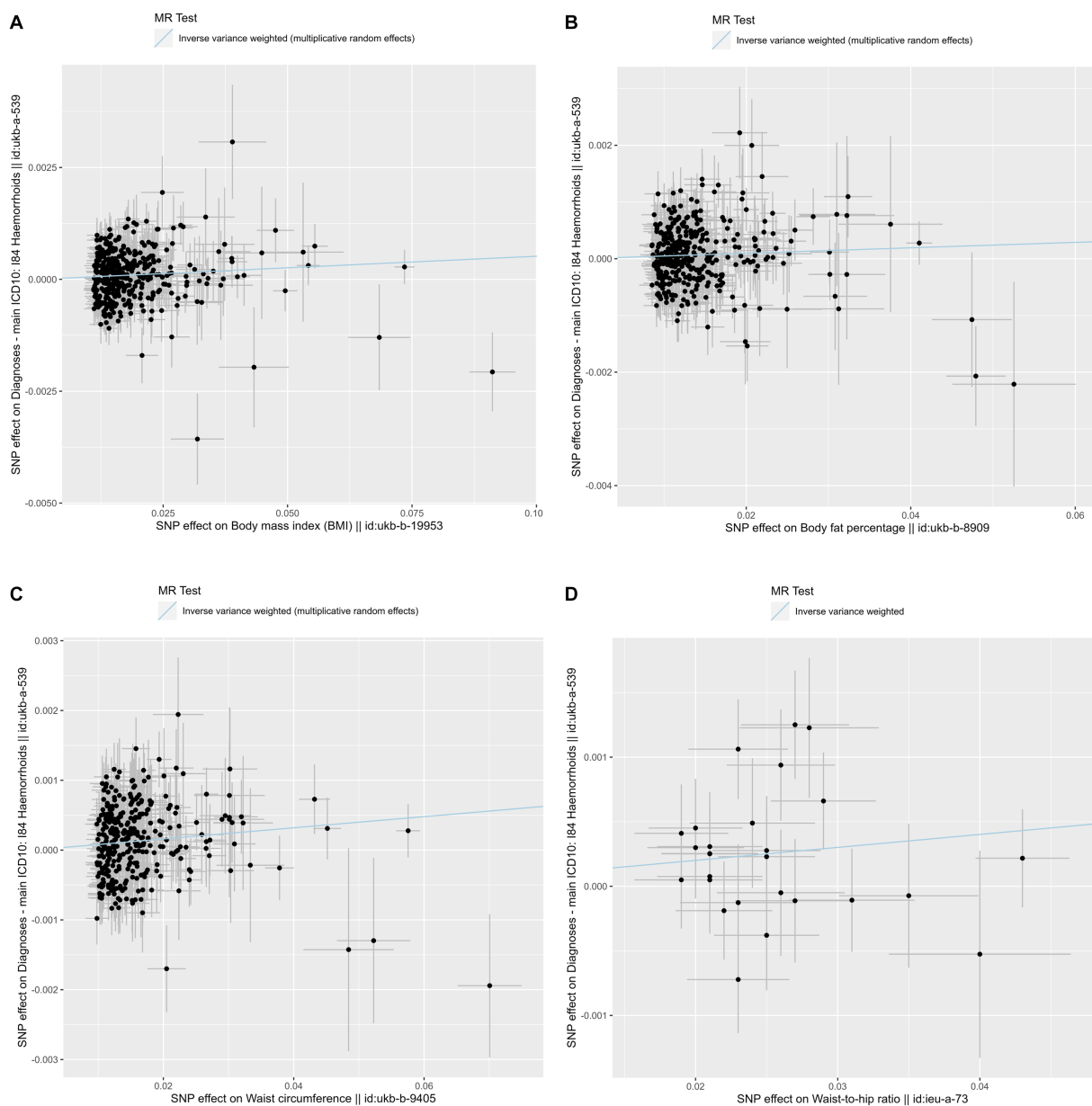

FIGURE 1
Selection of instrumental single nucleotide polymorphisms for adiposity traits. SNP, single nucleotide polymorphism; LD, linkage disequilibrium; MR, Mendelian randomization.

FIGURE 2
Scatter plots of the primary Mendelian randomization analysis assessing the causal effect of four adiposity traits on hemorrhoids. **(A)** Scatter plot for the causal effect of body mass index on hemorrhoids. **(B)** Scatter plot for the causal effect of body fat percentage on hemorrhoids. **(C)** Scatter plot for the causal effect of waist circumference on hemorrhoids. **(D)** Scatter plot for the causal effect of waist-to-hip ratio on hemorrhoids. The genetic association with exposure is represented by the x-axis, while the genetic association with hemorrhoids risk is represented by the y-axis. Results were obtained using inverse variance weighted Mendelian randomization. SNP, single nucleotide polymorphism; MR, Mendelian randomization.

sensitivity analyses applying the maximum likelihood (OR = 1.004, 95% CI: 1.002–1.006, $p = 0.001$) and MR-PRESSO (OR = 1.004, 95% CI: 1.002–1.006, $p = 9.470 \times 10^{-5}$) models. We observed heterogeneity across the SNPs (Cochran's Q $p = 9.470 \times 10^{-5}$). The MR-Egger intercept was centered around zero (intercept = 2.845×10^{-5}, $p = 0.658$), which was suggestive of the absence of a directional pleiotropic effect. MR-PRESSO detected one outlying SNP, but the MR estimate was unchanged when removing it (OR = 1.005, 95% CI: 1.003–1.008, $p = 4.707 \times 10^{-5}$). Results of the leave-one-out sensitivity analysis supported the observed causal association (Supplementary Table S6).

The IVW MR analysis showed that the OR per 1-SD increase in genetically determined body fat percentage for the risk of

hemorrhoids was 1.005 (95% CI: 1.001–1.008, $p = 0.008$) (Figures 2B, 3A). The causal estimates were also significant by sensitivity analyses using the maximum likelihood (OR = 1.005, 95% CI: 1.002–1.008, $p = 0.004$) and MR-PRESSO (OR = 1.005, 95% CI: 1.001–1.008, $p = 0.008$) methods. Heterogeneity was noted among studies ($p = 0.005$). However, this was likely not due to horizontal pleiotropy, because the MR-Egger regression intercept analysis yielded a large p-value (intercept = 7.297×10^{-7}, $p = 0.992$). No outliers were identified using the MR-PRESSO method. The leave-one-out sensitivity analysis did not detect any individual SNPs that significantly affected the causal estimates (Supplementary Table S7).
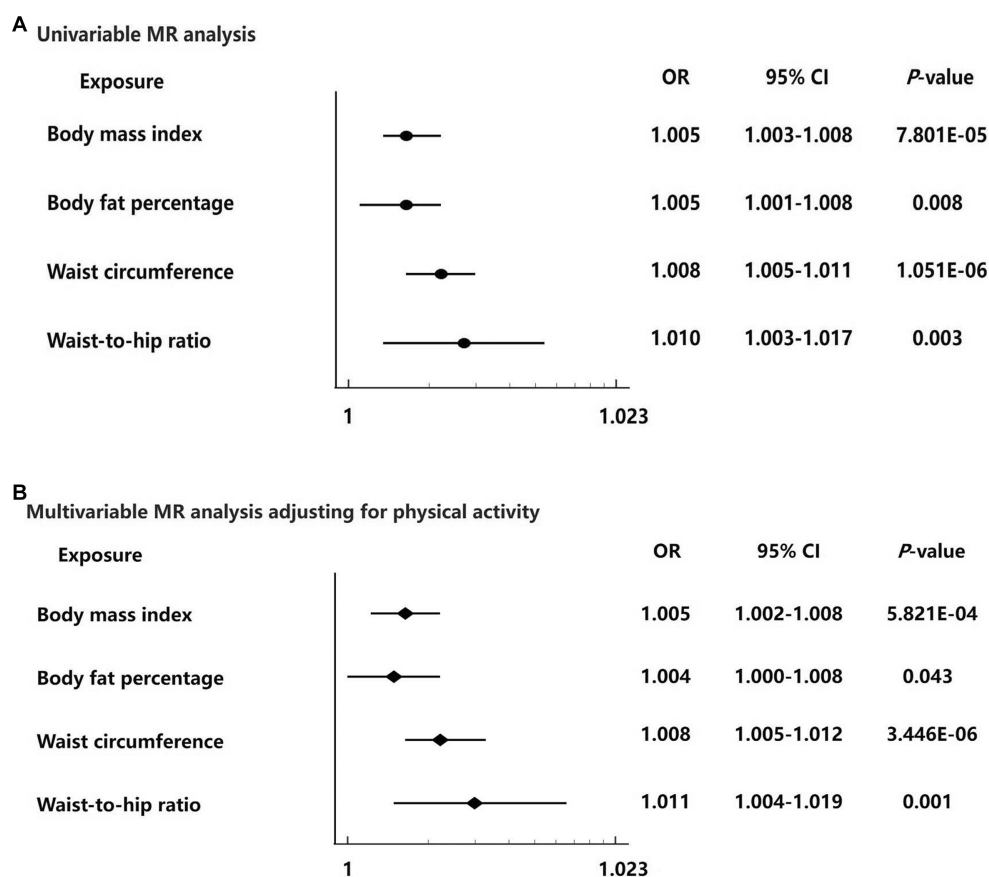
FIGURE 3
Forest plots for the univariable and multivariable Mendelian randomization analysis on the causal effect of adiposity on hemorrhoids risk.
(A) Univariable Mendelian randomization analysis from the inverse variance weighted method of four adiposity traits including body mass index, body fat percentage, waist circumference, and waist-to-hip ratio with hemorrhoids risk. **(B)** Multivariable Mendelian randomization analysis of four adiposity traits including body mass index, body fat percentage, waist circumference, and waist-to-hip ratio with hemorrhoids risk adjusting for physical activity. Data are displayed as odds ratio (OR) and 95% confidence interval (CI).

In the primary MR analysis using the IVW method, the OR per 1-SD increase in genetically determined waist circumference was 1.008 (95% CI: 1.005–1.011, $p = 1.051 \times 10^{-6}$) for hemorrhoids (Figures 2C, 3A). The sensitivity analyses based on the maximum likelihood (OR = 1.008, 95% CI: 1.005–1.011, $p = 6.891 \times 10^{-8}$), weight median (OR = 1.006, 95% CI: 1.001–1.011, $p = 0.028$), and MR-PRESSO (OR = 1.008, 95% CI: 1.005–1.011, $p = 1.614 \times 10^{-6}$) methods yielded similar results. Although the Cochran's Q test showed evidence of heterogeneity ($p = 0.002$), it was not likely because of horizontal pleiotropy (MR-Egger intercept = 2.687×10^{-6}, $p = 0.970$). MR-PRESSO did not identify potential outliers. The leave-one-out sensitivity analysis found no individual SNPs significantly affecting the causal estimates (Supplementary Table S8).

For each 1-SD increase in genetically determined waist-to-hip ratio, increased risk of hemorrhoids was identified in the IVW estimate (OR = 1.010, 95% CI: 1.003–1.017, $p = 0.003$) (Figures 2D, 3A). The maximum likelihood (OR = 1.010, 95% CI: 1.004–1.017, $p = 0.001$) and MR-PRESSO (OR = 1.010, 95% CI: 1.003–1.017, $p = 0.007$) analyses supported this association with consistent effect sizes. There was no evidence for heterogeneity ($p = 0.203$). The MR-Egger intercept indicated absence of horizontal pleiotropy (intercept = 2.670×10^{-4}, $p = 0.512$). No significant outliers were

detected using the MR-PRESSO method. The leave-one-out sensitivity analysis showed that no single SNPs could dramatically drive the observed causal association (Supplementary Table S9).

The funnel plots showed symmetry, supporting the reliability of the MR analyses (Figure 4). The MR Steiger directionality test was used to test the causal direction between the adiposity measures and hemorrhoids. Table 2 shows the results. The variance in the outcome (snp_r2.outcome) was less than each exposure (snp_r2.exposure), confirming the causal direction.

Finally, we performed multivariable MR analysis to adjust for physical activity. The results showed statistically significant causal associations of genetically determined BMI (OR = 1.005, 95% CI: 1.002–1.008, $p = 5.821 \times 10^{-4}$), body fat percentage (OR = 1.004, 95% CI: 1.000–1.008, $p = 0.043$), waist circumference (OR = 1.008, 95% CI: 1.005–1.012, $p = 3.446 \times 10^{-6}$), and waist-to-hip ratio (OR = 1.011, 95% CI: 1.004–1.019, $p = 0.001$) with hemorrhoids (Figure 3B).

Discussion

In order to evaluate the effects of adiposity traits including BMI, body fat percentage, waist circumference, and waist-to-hip ratio on
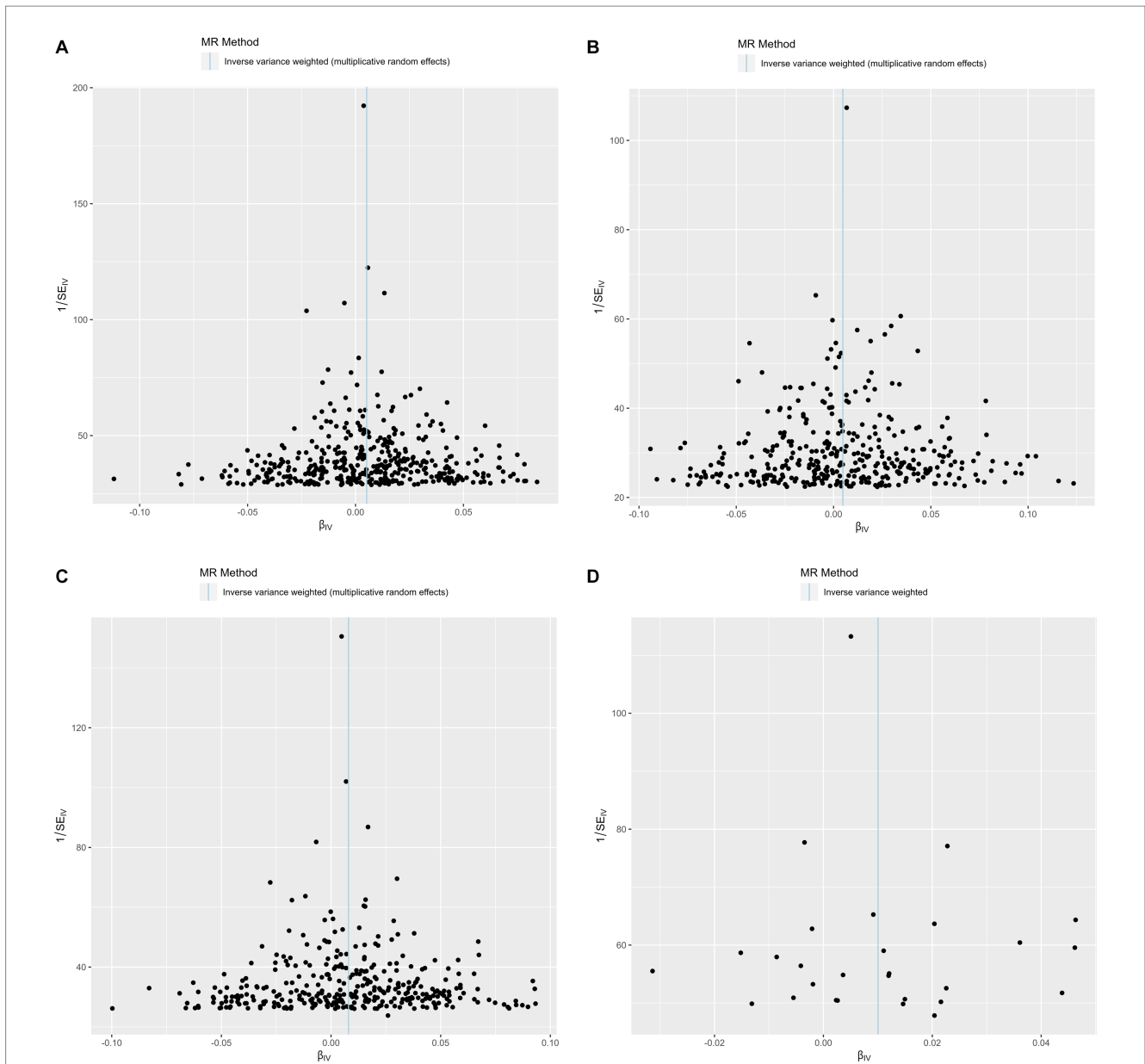
FIGURE 4
Funnel plots of precision (1/SE) versus causal estimate β for hemorrhoids. **(A)** Exposure: body mass index. **(B)** Exposure: body fat percentage.
(C) Exposure: waist circumference. **(D)** Exposure: waist-to-hip ratio.

TABLE 2 MR Steiger directionality test for evaluating the causal direction.

Exposure	Outcome	snp_r2.exposure	snp_r2.outcome	Causal direction
Body mass index	Hemorrhoids	0.06	1.71×10^{-3}	True
Body fat percentage	Hemorrhoids	0.05	1.35×10^{-3}	True
Waist circumference	Hemorrhoids	0.04	1.39×10^{-3}	True
Waist-to-hip ratio	Hemorrhoids	6.74×10^{-3}	1.38×10^{-4}	True

hemorrhoids risk, we used large-scale GWAS summary-level data within the MR framework. Our MR analyses showed that genetically determined BMI, body fat percentage, waist circumference, and waist-to-hip ratio were causally associated with increased risk of hemorrhoids. These findings indicated an important role of adiposity in hemorrhoids development. As far as we know, this is the first MR study to establish a causal relationship between adiposity and hemorrhoids.

Our results were in line with most previously published observational studies evaluating the relationship between obesity and hemorrhoids. These studies were carried out among Europeans (7, 8), Asians (9, 10), and Americans (25). Using data from the Dutch Health

Interview Surveys, Seidell and colleagues reported a positive association between severe overweight (body mass index [BMI] 30.0–40.0 kg/m²) and hemorrhoids in women (7). Similarly, in a large Italian survey study of 72,284 participants (34,787 men and 37,497 women) aged 15 years and above, Negri et al. (8) found that the prevalence of hemorrhoids or varices was significantly associated with body weight (relative risk = 1.2 for obese men, 1.5 for women). In addition to these European studies, a Korean National Health and Nutrition Examination Survey (KNHANES) study including a total of 17,228 individuals aged ≥19 years identified a link between obesity and enhanced hemorrhoids risk [odds ratio (OR) = 1.13, 95% CI: 1.01–1.26] (9). This finding was supported by another Korean study of 194,620 adults (10). However, not all observational studies reported a positive relationship between adiposity and hemorrhoids. In a cross sectional study involving 2,813 participants who underwent a colonoscopy, Peery and colleagues did not find any associations of overweight (OR = 0.89, 95% CI: 0.72–1.09) and obese (OR = 0.86, 95% CI: 0.70–1.06) with hemorrhoids risk (11). Conventional statistical approaches including the Mantel–Haenszel procedure (26) and regression models were the main methods used in these observational studies for evaluating the relationship. Large sample sizes were applied in several studies such as the study of Negri et al. (8) and Hong et al. (10), which increased the statistical power for discovering a potential relationship. However, due to the limitations of study design and conventional statistical methods, these observational studies were vulnerable to biases including confounding and reverse causation. It was unclear if their observed association between adiposity and hemorrhoids was causal.

In our study, the causal effects of adiposity on hemorrhoids were estimated in univariable and multivariable MR analyses. The MR framework effectively minimized the risk of biases that were major concerns in the previously published observational studies. Unlike these studies that mainly used BMI for evaluation, we used a range of adiposity measures including BMI, body fat percentage, waist circumference, and waist-to-hip ratio. We took into account not only total adiposity (BMI) but also specific adiposity indicators. For instance, waist circumference and waist-to-hip ratio are indicators of central adiposity, while body fat percentage is a proxy for total body fatness. The inclusion of these adiposity indicators could provide more valuable information regarding the association between adiposity and hemorrhoids. Our univariable IVW analyses revealed significant causal effects of the four adiposity indicators on hemorrhoids risk, which was supported by several sensitivity analyses and leave-one-out analyses. The causal direction was confirmed by the Steiger directionality test. Further multivariable MR suggested that the effects of BMI, body fat percentage, waist circumference, and waist-to-hip ratio on hemorrhoids were independent of physical activity. Our results encouraged future clinical studies to focus on body weight and fat reduction in hemorrhoids prevention.

The association between adiposity and hemorrhoids may be attributed to a variety of potential biological mechanisms. Firstly, adiposity was found to be associated with increased intrabdominal pressure (18, 27), which could contribute to hemorrhoids development. In individuals with excess adiposity, enhanced intrabdominal pressure may lead to impaired venous return and engorgement of the venous structure in the distal rectum. These changes could promote hemorrhoids development. Secondly, adiposity has a link with chronic inflammation and oxidative stress (28, 29). Adiposity-associated inflammation and oxidative stress triggered the synthesis of oxygen

radicals, reactive lipids, and proinflammatory cytokines including interleukin (IL)-6 and tumor necrosis factor (TNF)-α, activated tissue remodeling proteins such as matrix metalloproteinases, induced C-reactive protein production, and promoted mitochondrial dysfunction and DNA damage (30–32). Complex interactions between adiposity, chronic inflammation, and oxidative stress may have harmful effects on the supporting tissues of the anal cushions, causing their impairments. Thirdly, low fiber intake might play a role. According to a number of epidemiological studies, obese individuals usually have less intake of fiber than the general population (33–35). There was evidence showing that a low-fiber diet might be implicated in hemorrhoids development, although the reported results were conflicting (36, 37).

Our MR study has certain drawbacks that need to be acknowledged. Firstly, given that our findings are based on GWAS data derived from individuals of European ancestry, it is necessary to exercise caution when attempting to extrapolate our results and conclusions to other ethnic populations. Secondly, since we only used summary statistics for estimation, we did not evaluate the causal association in males and females separately. In a cross-sectional study of healthy young and middle-aged adults, Hong et al. (10) found a positive association of overweight with hemorrhoidal disease only in women but not in men. However, Lee and colleagues observed that high BMI (≥25) was associated with self-reported hemorrhoids in both males and females (9). The study of Negri et al. (8) also revealed a link between high BMI (≥30) and hemorrhoids or varices in both men and women. Thirdly, we mainly evaluated the effects of adiposity during adulthood on hemorrhoids in this MR study. This was consistent with most observational studies. It would be valuable to assess the impact of excess childhood adiposity at hemorrhoids in future analyses. Fourthly, we were unable to investigate the effect of adiposity on the severity of hemorrhoids.

In summary, our comprehensive MR study provided evidence for causal effects of genetically determined BMI, body fat percentage, waist circumference, and waist-to-hip ratio on hemorrhoids. These findings encouraged future clinical investigations to focus on body weight and fat reduction in the prevention of hemorrhoids.

Data availability statement

The analysis in this research relied on publicly available datasets, which can be accessed through the IEU Open GWAS Project (https://gwas.mrcieu.ac.uk/).

Ethics statement

Due to the exclusive analysis of publicly available GWAS summary-level data, ethical approval was not applicable to this Mendelian randomization study.

Author contributions

JH contributed to study concept and design, acquisition and interpretation of data, statistical analyses, and manuscript writing. YG and HQ assisted in data interpretation and reviewing the manuscript. YX supervised the study, contributed to funding acquisition, and

assisted in reviewing the manuscript. All authors read and approved the final manuscript.

Funding

Acknowledgments

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1229925/full#supplementary-material

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