Birth weight, childhood obesity, adulthood obesity and body composition, and gastrointestinal diseases: a Mendelian randomization study

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Abstract

Objective: This Mendelian randomization study aimed to investigate the associations of birth weight, childhood BMI, and adulthood BMI, waist-hip ratio, and body composition with the risk of 24 gastrointestinal diseases.

Methods: Independent genetic instruments associated with the exposures at the genome-wide significance level \((p < 5 \times 10^{-8})\) were selected from corresponding large-scale genome-wide association studies. Summary-level data for gastrointestinal diseases were obtained from the UK Biobank, the FinnGen study, and large consortia of European ancestry.

Results: Genetically predicted higher levels of birth weight were associated with a lower risk of gastroesophageal reflux. Genetically predicted higher childhood BMI was associated with an increased risk of duodenal ulcer, nonalcoholic fatty liver disease, and cholelithiasis. However, the associations did not persist after adjusting for genetically predicted adulthood BMI. Genetically predicted higher adulthood BMI and waist-hip ratio were associated with 19 and 17 gastrointestinal diseases, respectively. Genetically predicted greater visceral adiposity was associated with an increased risk of 17 gastrointestinal diseases. There were no strong associations among genetically predicted whole-body fat and fat-free mass indices with gastrointestinal diseases.

Conclusions: This study suggests that greater adulthood adiposity, measured as either BMI, waist-hip ratio, or visceral adipose tissue, is causally associated with an
INTRODUCTION

Overweight and obesity affect ~60% of adults and 30% of children, which has caused a global pandemic [1, 2]. Gastrointestinal disease is also a globally prevalent health issue that causes a large disease burden worldwide [3]. It is estimated that the annual health care expenditures on gastrointestinal diseases was ~135.9 billion dollars in the United States [4]. This heavy disease burden underscores the need for continued digging into the underlying mechanisms of gastrointestinal diseases, as well as developing effective interventions to improve patient outcomes, aimed at reducing the burden of these illnesses on individuals and society. Population-based epidemiological studies have found positive associations of adulthood obesity with the risk of many gastrointestinal diseases at different sites, including gastrointestinal reflux [5], peptic ulcer [6], diverticular disease [7], colorectal cancer [8], and nonalcoholic fatty liver disease [9], which may hint at a universal effect of excessive fat accumulation on the gastroenterological system. However, the associations of adulthood obesity with other common gastrointestinal diseases have been investigated in few studies with inconsistent findings [10]. Birth weight and childhood obesity have been associated with adulthood obesity [11]. Body composition that cannot be precisely assessed by general adiposity indicators has been revealed to be differently associated with the risk of gastrointestinal diseases [12, 13]. Nevertheless, limited data have been generated to examine the associations of birth weight, childhood obesity, and body composition with the risk of gastrointestinal diseases. In addition, observational studies are prone to be biased by reverse causation (i.e., weight loss attributed to gastrointestinal dysfunction before the diagnosis) and confounding. Whether the established associations between obesity and gastrointestinal diseases are causal remains uncertain.

Mendelian randomization (MR) is an epidemiological method that uses genetic variants as instrumental variables to infer the causality of an exposure-outcome association. Given that the exposure here is not phenotypically measured but proxied by genetic variants, it is commonly expressed as “genetically predicted” [14]. Because genetic variants are randomly assorted at conception and they cannot be modified by the onset of disease, MR investigation is less likely to be affected by confounding and reverse causality. Even though previous MR studies have identified the associations of adulthood body mass index (BMI) and waist-hip ratio (WHR) with the risk of several gastrointestinal diseases [15, 16], the MR associations of adulthood obesity with other gastrointestinal diseases such as peptic ulcer, irritable bowel syndrome, and pancreatitis remain unestablished. In addition, the associations of other obesity-related traits with the risk of gastrointestinal disease have scarcely been investigated. Here, we conducted an MR study to examine the associations of birth weight, childhood BMI, adulthood BMI and WHR, and three adulthood body composition measures (visceral adiposity, fat mass, and fat-free mass) with the risk of 24 gastrointestinal diseases.

METHODS

The study design is presented in Figure 1. This MR investigation was based on publicly available summary-level data of genome-wide association studies (GWASs), including the UK Biobank study and large consortia of European ancestry (Supporting Information Table S1). All studies have been approved by corresponding ethical boards of the relevant institutions, and participants had been given informed consent.
Genetic instrument selection

Genetic associations with birth weight and childhood BMI were extracted from the Early Growth Genetics Consortium [17, 18], with data in 298,142 European individuals for birth weight [17] and data in 35,668 European children aged 2 to 10 years for childhood BMI [18]. For adulthood phenotypes, genetic associations with BMI and WHR were obtained from a GWAS of up to 806,834 individuals of European ancestry [19]. The summary-level data on visceral adiposity were obtained from a GWAS in 396,220 European individuals in which visceral adiposity levels were estimated by a machine-learning method with a training data set of 4198 European individuals with visceral adipose tissue measured by dual-energy x-ray absorptiometry [20]. Fat mass and fat-free mass were measured using bioelectrical impedance, and corresponding genetic associations were obtained from the UK Biobank study including 331,291 individuals [21]. Fat mass index (FMI) and fat-free mass index (FFMI) were computed by dividing fat mass or fat-free mass by the square of height [21]. We extracted single-nucleotide polymorphisms (SNPs) associated with childhood BMI and adulthood BMI, WHR, visceral adiposity, and FMI and FFMI at the genome-wide significance level ($p < 5 \times 10^{-8}$) from the aforementioned GWASs. The linkage disequilibrium of selected SNPs for each trait was estimated based on the 1000 Genomes European reference panel. After removing SNPs in linkage disequilibrium ($r^2 \geq 0.01$), independent SNPs were used as instrumental variables in MR analysis. A sensitivity analysis using a strict clumping threshold ($r^2 = 0.001$) was performed. Detailed information on genetic instruments is shown in Supporting Information Table S2.

Outcome data sources

Summary-level data on 24 gastrointestinal diseases were obtained from the UK Biobank study [22], the FinnGen consortium [23], the International Inflammatory Bowel Disease Genetics Consortium (IIBDGC) [24], and Genetic Epidemiology Research on Aging (GERA) [25]. The UK Biobank is a large population-based cohort study comprising more than 500,000 individuals [22]. In the UK Biobank study, summary-level statistics of the outcomes in the European ancestry were extracted from the GWAS conducted by the Lee Lab.
in which the gastrointestinal outcomes were defined using codes of the International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) [26]. In FinnGen, summary-level data on gastrointestinal diseases were obtained from the R7 release [23]. The FinnGen study is an ongoing nationwide study combining genetic and electronic health record data. Similarly, the gastrointestinal diseases in FinnGen were defined using the ICD-8, ICD-9, and ICD-10 codes. We additionally extracted summary-level genetic data on Crohn disease (5956 cases and 14,927 controls) and ulcerative colitis (6968 cases and 20,464 controls) from the IIBDGC, in which the patients were diagnosed by radiologic, endoscopic, and histopathologic evaluations [24]. Data on irritable bowel syndrome (defined by ICD-9 codes) were additionally obtained from the GERA, which included 3117 cases and 53,520 controls [25]. Detailed ICD codes used for outcome definitions are shown in Supporting Information Table S3.

Statistical analysis

We calculated an F statistic for each association to assess the strength of the genetic instrument. Power calculation was performed using a web tool [27]. The multiplicative random-effects inverse-variance weighted method was employed to calculate the primary causal MR estimate. Estimates for each gastrointestinal end point from different sources were combined using the fixed-effects meta-analysis. Heterogeneity among SNP estimates was assessed by the Cochran Q value. Three sensitivity analyses, including the weighted median, MR-Egger, and MR pleiotropy residual sum and outlier (MR-PRESSO) methods, were performed to detect horizontal pleiotropy and examine the robustness of the results. The weighted median method can provide accurate MR estimates when up to 50% of the instruments are valid [28]. The MR-Egger intercept test can detect horizontal pleiotropic effects [29]. MR-Egger can provide estimates albeit with low precision after adjusting for directional pleiotropy. MR-PRESSO can identify horizontal pleiotropic outliers and provide estimates after the removal of the outliers [30]. The embedded global test was also used to detect directional pleiotropy, and the distortion test was used to examine the difference in estimates from the analysis before and after the removal of detected outliers [30]. We performed multivariable MR to examine whether the associations between genetically predicted birth weight and gastrointestinal diseases were independent of genetically predicted childhood BMI and adulthood BMI. We performed multivariable MR with adjustment for genetically predicted adulthood BMI for the identified associations between genetically predicted childhood BMI and gastrointestinal diseases to test whether the associations were independent of adulthood BMI. Similarly, direct effects of visceral adiposity and WHR were also investigated. Multivariable MR was also conducted to estimate the associations of genetically predicted FMI and FFMI, which are strongly correlated traits, with gastrointestinal diseases. The Benjamini-Hochberg correction, which controls the false discovery rate, was applied to correct for the multiple testing separately for each exposure. The association with \( p < 0.05 \) but Benjamini–Hochberg-adjusted \( p > 0.05 \) was regarded as suggestive, which means further studies are necessary to confirm these findings. The association with Benjamini–Hochberg-adjusted \( p < 0.05 \) was deemed significant. All analyses were performed using the TwoSampleMR and MR packages in R software (version 4.1.1).

RESULTS

The F statistic for each set of genetic instruments was greater than 10, indicating good strength of the genetic instruments used (Supporting Information Table S4). Most associations were also found to be well powered, except for several gastrointestinal outcomes with relatively smaller sample sizes (e.g., liver cancer; Supporting Information Table S4). In the case of birth weight, the smallest detectable odds ratio (OR) ranged from 1.08 to 1.45 for the included outcomes, with 80% power to detect. For childhood BMI, this range was between 1.10 and 1.74, whereas for adulthood BMI, it was between 1.05 and 1.36. Finally, for visceral adiposity, the range was between 1.07 and 1.57.

Birth weight

Genetically predicted higher levels of birth weight were associated with a lower risk of gastroesophageal reflux, duodenal ulcer, irritable bowel syndrome, and nonalcoholic fatty liver disease (Figure 2). After correction for multiple comparisons, the association for gastroesophageal reflux persisted (OR per SD 0.87; 95% confidence interval [CI]: 0.81–0.93; Figure 2 and Supporting Information Table S5). This association was consistent in all sensitivity analyses (Supporting Information Table S6). There was evidence of heterogeneity among estimates of individual SNPs in the analysis of gastroesophageal reflux (Supporting Information Table S6). Pleiotropy was detected in the analysis of gastroesophageal reflux in the FinnGen study (MR-Egger intercept \( p < 0.05 \) and global test \( p < 0.05 \), but the association remained in MR-PRESSO after removing the outlier (Supporting Information Table S6). Genetically predicted birth weight was not associated with the other studied gastrointestinal diseases (Figure 2). The associations remained directly consistent in the sensitivity analysis using a stringent threshold of linkage (Supporting Information Table S6). The association for gastroesophageal reflux did not persist after adjustment for genetically predicted childhood BMI but it remained significant after adjustment for genetically predicted adulthood BMI (Supporting Information Table S7).

Childhood BMI

Genetically predicted higher levels of childhood BMI were associated with an increased risk of esophageal cancer, duodenal ulcer, diverticular disease, nonalcoholic fatty liver disease, cholecystitis, and pancreatic cancer (Figure 3). After correction for multiple comparisons, five of these associations remained significant, and the corresponding OR was 1.31 (95% CI: 1.09–1.56) for duodenal ulcer, 1.39 (95% CI: 1.09–1.77)
for nonalcoholic fatty liver disease, and 1.43 (95% CI: 1.30–1.57) for cholelithiasis per 1-SD increase in genetically predicted childhood BMI (Figure 3 and Supporting Information Table S5). The associations remained directionally consistent in sensitivity analyses (Supporting Information Table S8). Directional pleiotropy was observed in the analysis of cholelithiasis in the UK Biobank (MR-Egger intercept p < 0.05), but no outlier was detected in MR-PRESSO (Supporting Information Table S8). Genetically predicted childhood BMI was not associated with other studied gastrointestinal diseases (Figure 3). The observed associations for genetically predicted childhood BMI attenuated and became nonsignificant in multivariable MR with adjustment for genetically predicted adulthood BMI (Supporting Information Table S9).

Adulthood BMI and WHR

Genetically predicted higher levels of adulthood BMI were positively associated with 19 of 24 gastrointestinal diseases (Figure 4). All of these associations remained significant after multiple testing correction (Supporting Information Table S5). The OR per 1-kg/m² increase in genetically predicted adulthood BMI was 1.27 (95% CI: 1.21–1.33) for gastroesophageal reflux, 1.78 (95% CI: 1.43–2.20) for esophageal cancer, 1.31 (95% CI: 1.21–1.42) for gastric ulcer, 1.34 (95% CI: 1.22–1.48) for duodenal ulcer, 1.28 (95% CI: 1.13–1.46) for acute gastritis, 1.14 (95% CI: 1.04–1.24) for chronic gastritis, 1.30 (95% CI: 1.09–1.55) for gastric cancer, 1.08 (95% CI: 1.02–1.15) for irritable bowel syndrome, 1.24 (95% CI: 1.19–1.29) for diverticular disease, 2.12 (95% CI: 1.85–2.42) for nonalcoholic fatty liver disease, 1.30 (95% CI: 1.14–1.49) for alcoholic liver disease, 1.28 (95% CI: 1.12–1.46) for cirrhosis, 1.51 (95% CI: 1.20–1.91) for liver cancer, 1.38 (95% CI: 1.16–1.64) for cholangitis, 1.87 (95% CI: 1.70–2.05) for cholecystitis, 1.73 (95% CI: 1.65–1.81) for cholelithiasis, 1.46 (95% CI: 1.34–1.60) for acute pancreatitis, 1.49 (95% CI: 1.25–1.77) for pancreatic cancer, and 1.10 (95% CI: 1.05–1.16) for acute appendicitis (Figure 4). Moderate to substantial heterogeneity was observed in the analyses; however, results were generally consistent in sensitivity analyses (Supporting Information Table S10). The MR-Egger intercept test indicated that there was pleiotropy in the analysis of gastroesophageal reflux, irritable bowel syndrome, and diverticular disease in the UK Biobank or FinnGen study (MR-Egger intercept p < 0.05; Supporting Information Table S10). MR-PRESSO detected one to fourteen outliers in these analyses, and the associations remained after the removal of outliers.

![FIGURE 2](https://example.com/figure2.png)

**FIGURE 2** Associations of genetically predicted birth weight with 24 gastrointestinal diseases. The associations were scaled to 1-SD increase in genetically predicted birth weight. *Significant association after multiple testing. OR, odds ratio
Associations of genetically predicted childhood BMI with 24 gastrointestinal diseases. The associations were scaled to 1-SD increase in genetically predicted childhood BMI. *Significant association after multiple testing. OR, odds ratio.

**FIGURE 3** Associations of genetically predicted childhood BMI with 24 gastrointestinal diseases. The associations were scaled to 1-SD increase in genetically predicted childhood BMI. *Significant association after multiple testing. OR, odds ratio.

Visceral adiposity and fat and fat-free mass indices

Genetically predicted higher levels of visceral adiposity were associated with 18 of 24 gastrointestinal diseases at the nominal significance level (Figure 5 and Supporting Information Table S12). After correction for multiple comparisons, the association per 1-kg increase in genetically predicted visceral adiposity persisted for gastroesophageal reflux (OR = 1.34; 95% CI: 1.25–1.43), esophageal cancer (OR = 1.43; 95% CI: 1.08–1.88), gastric ulcer (OR = 1.26; 95% CI: 1.11–1.42), duodenal ulcer (OR = 1.42; 95% CI: 1.23–1.63), acute gastritis (OR = 1.33; 95% CI: 1.12–1.59), diverticular disease (OR = 1.23; 95% CI: 1.15–1.31), nonalcoholic fatty liver disease (OR = 2.45; 95% CI: 2.01–2.97), alcoholic liver disease (OR = 1.38; 95% CI: 1.14–1.68), cirrhosis (OR = 1.42; 95% CI: 1.18–1.70), liver cancer (OR = 2.00; 95% CI: 1.43–2.81), cholangitis (OR = 1.33; 95% CI: 1.04–1.70), cholecystitis (OR = 1.62; 95% CI: 1.41–1.87), cholecystitis (OR = 1.77; 95% CI: 1.65–1.89), acute pancreatitis (OR = 1.50; 95% CI: 1.31–1.71), chronic pancreatitis (OR = 1.28; 95% CI: 1.07–1.53), pancreatic cancer (OR = 1.84; 95% CI: 1.45–2.33), and acute appendicitis (OR = 1.18; 95% CI: 1.10–1.26; Figure 5 and Supporting Information Table S12). Results were overall...
FIGURE 4  Associations of genetically predicted adulthood BMI and WHR with 24 gastrointestinal diseases. The associations were scaled to 1-kg/m² increase in genetically predicted adulthood BMI. The associations were scaled to 1-SD increase in genetically predicted adulthood WHR. *Significant association after multiple testing. WHR, waist-hip ratio; OR, odds ratio

<table>
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<th>Adulthood BMI OR (95% CI)</th>
<th>p value</th>
<th>Adulthood WHR OR (95% CI)</th>
<th>p value</th>
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FIGURE 5  Associations of genetically predicted visceral adiposity with 24 gastrointestinal diseases. The associations were scaled to 1-kg increase in genetically predicted visceral adiposity. *Significant association after multiple testing. OR, odds ratio
consistent in the sensitivity analyses (Supporting Information Table S12). Moderate to high heterogeneity was observed in most analyses (Supporting Information Table S12). One to seven outliers were detected in MR-PRESSO, and all of these associations remained significant after the removal of the outliers. Genetically predicted visceral adiposity was not associated with other studied gastrointestinal diseases (Figure 5). The sensitivity analysis showed consistent results when a stringent linkage disequilibrium threshold was used (Supporting Information Table S12). After adjustment for adulthood BMI, genetically predicted higher levels of visceral adiposity were associated with gastroesophageal reflux, gastric ulcer, duodenal ulcer, diverticular disease, nonalcoholic liver disease, liver cancer, cholecystitis, and acute pancreatitis (Supporting Information Table S12).

There were no associations of genetically predicted FMI or FFMI with gastrointestinal diseases after multiple testing correction (Supporting Information Table S5). Genetically predicted higher levels of FMI were suggestively associated with an increased risk of duodenal ulcer, Crohn disease, and cholecystitis (Supporting Information Table S13). Genetically predicted higher levels of FFMI were suggestively associated with an increased risk of irritable bowel syndrome and a decreased risk of Crohn disease and ulcerative colitis (Supporting Information Table S13).

DISCUSSION

We conducted a comprehensive MR investigation to examine the associations of birth weight, childhood BMI, and adulthood BMI, WHR, and FMI with 24 gastrointestinal diseases, but the associations appeared to be driven by adulthood BMI. No strong associations were observed for genetically

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<td>0.66</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>1.00</td>
<td>0.89</td>
<td>0.94</td>
<td>1.02</td>
<td>1.01</td>
<td>1.15</td>
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<tr>
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<td>1.04</td>
<td>1.06</td>
<td>1.26</td>
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<td>1.39</td>
<td>2.12</td>
<td>2.43</td>
<td>2.45</td>
<td>1.22</td>
<td>1.07</td>
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<tr>
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<td>0.89</td>
<td>1.30</td>
<td>1.55</td>
<td>1.38</td>
<td>0.85</td>
<td>1.73</td>
</tr>
<tr>
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<td>1.03</td>
<td>1.28</td>
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<td>1.51</td>
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<tr>
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<td>0.99</td>
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<tr>
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FIGURE 6 Summary of associations of genetically predicted birth weight, childhood obesity, and adulthood obesity and body composition with 24 gastrointestinal diseases. The numbers in the boxes are the odds ratios of the associations. The association with $p < 0.05$ and Benjamini–Hochberg-adjusted $p > 0.05$ was regarded as suggestive and the association with Benjamini–Hochberg-adjusted $p < 0.05$ was deemed significant. FFMI, fat-free mass index; FMI, fat mass index; WHR, waist-hip ratio [Color figure can be viewed at wileyonlinelibrary.com]
predicted birth weight, FMI, or FFMI with any of the studied gastrointestinal diseases.

We found evidence that genetically predicted birth weight was inversely associated with the risk of gastroesophageal reflux, duodenal ulcer, irritable bowel syndrome, and nonalcoholic fatty liver disease. Although the specific biological interpretation is unclear, several mechanisms might explain the associations. Birth weight reflects both intrauterine fetal growth and length of gestation. Reduced fetal growth rate may affect the relative development of organs, leading to persistent alterations in physiologic and metabolic homeostatic set points [31]. Additionally, intrauterine fetal growth has been shown to cause epigenetic changes in the fetal genome, which may contribute to the development of certain health outcomes later in life. In addition, imprint gene expression and the epigenetic alterations in early embryos may carry over into subsequent developmental stages [32]. These may explain how low birth weight can lead to insulin resistance and subsequent development of metabolic syndrome [31, 32]. Moreover, metabolic syndrome has been linked to gastrointestinal disorders, which may be attributable to chronic low-grade inflammation [33].

Studies on the associations between childhood obesity and the risk of subsequent adulthood gastrointestinal diseases are scarce. Our study, for the first time, to our knowledge, identified some positive causal associations of genetically predicted childhood obesity with duodenal ulcer, nonalcoholic fatty liver disease, and cholelithiasis. However, these associations did not persist after adjusting for genetically predicted adulthood obesity, which indicates that early-life obesity may elevate the risk of gastrointestinal diseases mainly by fat accumulation later in life. Although controlling overweight in children may have an impact on reducing the risk of several gastrointestinal diseases in adulthood, this effect is not independent of adult weight status. Adulthood weight gain can also contribute to the development of gastrointestinal diseases even in those who do not have overweight in their childhood. Therefore, it is important to maintain a healthy weight throughout the life-span to reduce the risk of developing gastrointestinal diseases.

Previous observational studies have explored the associations between obesity and gastrointestinal diseases. An umbrella review focused on gastrointestinal cancer found that excess body weight was positively associated with the risk of esophageal, gastric, colorectal, liver, and pancreatic cancer [34]. In line with these studies, our results replicated previous MR findings of positive associations between BMI and the risk of gastric [35], esophageal [35], liver [15], and pancreatic cancer [36]. However, the current MR investigation did not observe a positive association between genetically predicted BMI and colorectal cancer. Instead, we found a positive association between genetically predicted WHR and colorectal cancer. Previous observational studies have also revealed obesity as a risk factor for several non-tumor gastrointestinal diseases, including gastrointestinal reflux [5], gastric and duodenal ulcer [6], acute and chronic gastritis [37], diverticular disease [7], nonalcoholic fatty liver disease [9], alcoholic liver disease [38], cirrhosis [9], cholecystitis [39], cholelithiasis [39], and acute pancreatitis [40], which is supported by the current study. In addition, we also observed the positive associations of genetically predicted BMI or WHR with irritable bowel syndrome, cholangitis, and acute appendicitis, which have not been well established and need verification.

BMI, as an indicator of adiposity, cannot precisely measure body composition. Visceral fat appears more harmful compared with other fat sites [41]. Limited by the expensive and time-consuming technique, visceral adiposity is usually evaluated by hip circumference or WHR in observational studies. Corroborating and extending the previous observational studies, the current MR investigation demonstrated that genetically predicted visceral adiposity was associated with the risk of gastroesophageal reflux [42], esophageal cancer [43], diverticular disease [44], nonalcoholic fatty liver disease [45], cirrhosis [45], liver cancer [46], cholecystitis [47], cholelithiasis [48], acute and chronic pancreatitis [47], and pancreatic cancer [49]. We additionally found that genetically predicted visceral adiposity was associated with an increased risk of gastric ulcer, duodenal ulcer, acute gastritis, alcoholic liver disease, and acute appendicitis, which is novel and needs verification. To our knowledge, this is the first MR investigation to assess the associations between genetically predicted visceral adiposity and gastrointestinal diseases. Although a high BMI is often associated with increased visceral fat, this can be significant variation in the amount of visceral fat, even among individuals with normal or moderately elevated BMI levels. Visceral fat may be an independent risk factor for some gastrointestinal diseases independent of a high BMI, which was revealed by our multivariable MR analysis. Therefore, the findings obtained from visceral fat analysis reveal more profoundly that obesity is associated with an increased risk of gastrointestinal diseases.

The mechanisms underlying the associations between obesity and gastrointestinal disease have not been well understood. However, the obesity-related changes in anatomy and several cellular and molecular factors may be involved in explaining these associations. A low-grade chronic inflammatory state is present in obesity, which was confirmed by the increased systemic levels of pro-inflammatory markers and cytokines released from adipose tissue [50]. This inflammatory response is thought to depend on the activation of innate and acquired immune systems, which can increase intestinal permeability, bacterial translocation, and T-cell infiltration and thus contribute to gastrointestinal diseases [51, 52]. Additionally, insulin and insulin-like growth factor (IGF) signaling may also have a role in gastrointestinal diseases, especially gastrointestinal cancer. Clinical studies have supported the notion that plasma levels of insulin and free IGF-1 were higher in obesity, which triggered an intracellular cascade and stimulated the proliferation of tumor cells [53]. Moreover, there is a growing appreciation of gut microbiota in the promotion of obesity according to the different microbiomes between individuals with obesity and individuals with normal weight [54]. High-fat diet altered the composition of gut microflora and thus increased the lipopolysaccharides levels, which causes chronic inflammation and insulin resistance [55].

Overall, our results reemphasize the impact of obesity on gastrointestinal health. Going further, we specified that the visceral adiposity was a risk factor for a broad range of gastrointestinal diseases, which implied that excess visceral fat should receive adequate...
attention even in a normal BMI given that individuals without obesity may have an excess of abdominal fat [56]. Greater public education and awareness of the association of obesity with gastrointestinal diseases is vital because obesity is a modifiable behavioral risk factor that could be prevented by lifestyle factor intervention. Furthermore, although our findings highlight the potential causal impact of obesity on gastrointestinal health, it is important to note that having underweight may also be an unfavorable factor. However, the association between underweight and gastrointestinal diseases could not be investigated by MR analysis given that only a few participants with underweight were included in the exposure and outcome data resources.

The major strength of the present study is the MR design, which minimized confounding and reversed causality. Additionally, this study with a larger sample size improved the statistical efficiency. Consistent results from different large summary sources supported the robustness of our findings and improved the precision of our findings. Some limitations are worthy of note. A major limitation of the MR study was horizontal pleiotropy; however, we conducted a series of sensitivity analyses that indicated limited pleiotropic effects. Even though we used several data sources, the number of cases for certain gastrointestinal diseases was still small, which means we might have overlooked some weak associations due to inadequate power. In addition, we could not evaluate nonlinear relationships based on summary-level data. We could not perform the sex-stratified analysis either. Furthermore, although the confinement to the European populations minimized population structure bias, our findings might not be generalizable to other populations with different genetic backgrounds. It is also worth noting that genetic variants reflect the impact of a life-long difference in obesity; therefore, we could not capture the weight fluctuations in the trajectory of life. An important limitation of the analysis of FMI and FFMI is the very low variance in these traits explained by the genetic instruments. This likely explains the lack of significant associations for FMI.

In conclusion, our MR investigation found that genetically predicted higher BMI, WHR, and visceral adiposity were associated with an increased risk of a broad range of gastrointestinal diseases. These findings suggest that reducing obesity, particularly visceral adiposity, is an important strategy to lower the disease burden of gastrointestinal disorders.

AUTHOR CONTRIBUTIONS

Shuai Yuan, conceptualization: equal; methodology: equal; formal analysis: equal; data curation: equal; and writing, review and editing: equal. Xixian Ruan, conceptualization: equal; methodology: equal; formal analysis: equal; data curation: equal; and writing, original draft: equal. Yuhao Sun, conceptualization: supporting; methodology: supporting; and writing, review and editing: supporting. Tian Fu, conceptualization: supporting; methodology: supporting; and writing, review and editing: supporting. Minzi Deng, conceptualization: equal; data curation: equal; funding acquisition: equal; and writing, review and editing: equal. Jie Chen, conceptualization: leading; data curation: equal; and writing, review and editing: leading. Xue Li, conceptualization: equal; data curation: equal; funding acquisition: leading; and writing, review and editing: leading. Susanna C. Larsson, conceptualization: equal; methodology: equal; data curation: equal; and writing, review and editing: leading.

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CONFLICT OF INTEREST STATEMENT

The authors declared no conflict of interest.

DATA AVAILABILITY STATEMENT

Data can be obtained upon a reasonable request to corresponding authors.

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