Pediatric and adult obesity concerns in female health: a Mendelian randomization study

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Abstract

Purpose Adulthood and childhood obesity are both associated with reproductive diseases and gynecological cancers in females. However, the causal factors associated with these observations have yet to be identified. Mendelian randomization is a process that is independent of inverse bias and confounding and can act as a random control trial in which genetic groups are settled during meiosis, thus representing an effective tool with which to investigate causality.

Methods We carried out several Mendelian randomization trials based on the combined genetic scores of 75 adult-associated and 15 childhood-associated body mass index (BMI) single nucleotide polymorphisms (SNPs), databases for several gynecological cancers and reproductive diseases from the UK Biobank (with 194,153 participants), using the traditional inverse-variance weighted (IVW) method as the main method.

Results Elevated adult-associated BMI scores (odds ratio [OR] = 1.003; 95% confidence interval [CI]: 1.001–1.004) and childhood-associated BMI scores (OR = 1.003; 95% CI: 1.001–1.004) were related to a higher risk of the polycystic ovarian syndrome (PCOS), as determined by the traditional IVW method. The random IVW method further revealed a nominal negative causal association between childhood-associated BMI and subsequent endometriosis (OR = 0.995; 95% CI: 0.991–0.999).

Conclusions Consistent with observational consequences, our findings indicated that adulthood obesity may play role in the development of PCOS and that childhood obesity can increase the risk of PCOS but may reduce the incidence of endometriosis in later life. Further research is now needed to validate our findings and identify the precise mechanisms involved.

Keywords Mendelian randomization · Age-related obesity · Gynecological cancer · Endometriosis · Polycystic ovarian syndrome

Introduction

Obesity is characterized as a body mass index (BMI) that is ≥30 kg/m² in adults and a BMI-for-age percentile ≥95% in children. The prevalence of obesity and severe obesity has risen to approximately 17% in girls in the USA [1] and reached 39.6% in adult women between 2015 and 2016 [2]. Obesity is a prevalent global phenomenon that is associated with female infertility and gynecological cancers [3], thus leading to a number of physiological and psychological effects. Endometriosis and polycystic ovarian syndrome (PCOS) have become two major disease types that can result in female infertility. However, the etiology underlying these two diseases has yet to be fully elucidated. Endometriosis is mainly characterized as dysmenorrhea, pelvic pain, and infertility. Previous research identified an inverse relationship between current BMI and endometriosis in cases that were also infertile [4]. An ongoing
showed that a female–prospective and case-controlled cohort study further showed that a female’s current BMI and BMI at 18 years of age were significantly and inversely associated with the incidence of endometriosis [5]. This suggests that there may be an “early window of exposure” during which a lower BMI during adolescence can exert a baneful impact on endometriosis that precedes the diagnosis of this disease. PCOS is characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. Observational studies have discovered that obesity, and even childhood obesity, exerts a positive association with PCOS as well as other tumors of the female reproductive system in adulthood [6]. According to a previous systemic review and meta-analysis, there is a greater proportion of PCOS patients who are obese than non-obese [7]. On the other hand, PCOS patients with greater central adiposity were previously shown to be positively associated with a more severe metabolic phenotype, including insulin-resistant diabetes mellitus [8]. PCOS often occurs in the early stages of puberty. A longitudinal and population-based study previously concluded that obesity during adolescence could predict ovulatory dysfunction in later life [9]. Therefore, it is important that we identify the link between adulthood or childhood obesity and infertility so that we can take appropriate measures to prevent the deleterious effects of excessive weight gain on health.

Cervical cancers (CCs), endometrial carcinomas, and ovarian cancers represent the top three most common cancers in the female reproductive system; some of these cancers can be highly aggressive and invasive. Researchers have also demonstrated an association between obesity and excessive body weight, often using BMI as a proxy, and gynecological malignant tumors in females [10, 11]. Nevertheless, we do not yet know if there is a causal link between these factors.

Mendelian randomization (MR) analysis uses genetic variants, usually single nucleotide polymorphisms (SNPs), as instrumental variables to substitute for a risk factor and calculate its statistical influence on the outcome of disease in a non-experimental setting. Consequently, this technique can determine whether the observational association between exposure and outcome is consistent with causality. This research tool is similar to a normal randomized control trial (RCT) in a large population in which genotypes are randomized during meiosis and fertilization. Differences in SNP data can stratify a specific population into subsets, similar to a matched group and a treated group in an RCT. Compared to conventional artificial study designs, MR is rarely influenced by confounding elements, reverse causation, and bias. Here, we used BMI as a measure of obesity and applied MR analysis to detect whether obesity in adulthood or childhood is responsible for the morbidity of PCOS, endometriosis, or gynecological cancer.

Materials and methods

The MR process could only be established in a robust manner if a series of conditions were met. First, the SNPs that were operating as instrumental variables needed to represent the BMI. Second, the SNPs needed to be independent of confounding factors. Third, the SNPs needed to only influence outcomes via the BMI pathway and not any other potential horizontal factors [12]. Due to the inability to obtain a full dataset for a given sample, we used the traditional two-sample MR methodology [13] to obtain genetic statistics relating to exposures and outcomes from two published studies that had been proven to be efficient and useful. A weighted median (WM) method [14] was used for sensitivity analysis. Since the results of the inverse-variance weighted (IVW) method can be biased if the SNPs being used as instruments exhibit horizontal pleiotropy, we conducted the MR–Egger regression [15] and the MR–Pleiotropy Residual Sum and Outlier (PRESSO) method [16] to exclude potential bias in the sensitivity analysis. We also used leave-one-out analysis to determine whether the causal association was driven by an individual SNP.

Selection of instrumental variables

We used statistical data provided by a recent genetic study of BMI [17]; we refer to this as dataset 1. Analysis of this data identified 97 BMI-associated loci in 339,224 individuals; common variation in these loci accounted for 20% of the variation in BMI. Then, we selected SNPs from 322,154 individuals of European descent. In addition, 15 childhood BMI-associated SNPs were extracted from a previous Mendelian randomization analysis [18]; we refer to this as dataset 2. All of the selected SNPs were highly significant (P < 5 × 10^{-8}). Next, we assessed linkage disequilibrium (LD) by using a suite of web-based applications within the LDlink search system (https://ldlink.nci.nih.gov/); this analysis determined whether the selected IVs were associated with each other; correlation coefficients (r^2) that were higher than 0.1, and had the highest r values, were excluded (e.g., rs3888190 and rs11583200; Supplementary Table 1). Consequently, a total of 75 BMI-associated SNPs (Table 1) and 15 childhood BMI-associated SNPs left (Table 2) remained; rs12016871 was merged into rs9581854 in 2005.

Genetic associations with outcomes

Genetic data from different outcomes were obtained from different databases held by the UK Biobank (UKBB); over 500,000 individuals aged from 27 to 73 years old, were recruited in the UK between 2006 and 2010, thus bringing the total number of participants in our research to 194,153. Information relating to the associations between the selected
Table 1 Characteristics of adult BMI-associated SNPs from GWAS

| Gene   | SNP   | Chromosome: Position | EA | Association with exposure |
|--------|-------|----------------------|----|--------------------------|
|        |       |                      | β (SE) | P value |
| AGBL4  | rs657452 | 1:49589847            | A  | 0.023 (0.003) | 5.48 \times 10^{-13} |
| CADM1  | rs12286929 | 11:115022404         | G  | 0.022 (0.003) | 1.31 \times 10^{-12} |
| TCF7L2 | rs7903146 | 10:114758349          | C  | 0.023 (0.003) | 1.31 \times 10^{-12} |
| STXBP6 | rs10132280 | 14:25928179          | C  | 0.023 (0.003) | 1.14 \times 10^{-11} |
| HIF1AN | rs17094222 | 10:102395440         | C  | 0.025 (0.004) | 5.94 \times 10^{-11} |
| ERBB4  | rs7599312 | 2:213413231          | G  | 0.022 (0.003) | 1.17 \times 10^{-10} |
| FHT    | rs2365389 | 3:6123666            | C  | 0.02 (0.003)  | 1.63 \times 10^{-10} |
| NAV1   | rs2820292 | 1:20178287            | C  | 0.02 (0.003)  | 1.83 \times 10^{-10} |
| PRKDL1 | rs12885454 | 14:25928179          | C  | 0.021 (0.003) | 1.94 \times 10^{-10} |
| RASA2  | rs16851483 | 3:141275436         | T  | 0.048 (0.008) | 3.55 \times 10^{-10} |
| HIP1   | rs1167827 | 7:75163169            | G  | 0.02 (0.003)  | 6.33 \times 10^{-10} |
| NLRC3  | rs758747  | 16:3627358            | T  | 0.023 (0.004) | 7.47 \times 10^{-10} |
| TLR4   | rs1928295 | 9:120378438           | T  | 0.019 (0.003) | 7.91 \times 10^{-10} |
| KAT8   | rs9925964 | 16:3112958            | A  | 0.019 (0.003) | 8.11 \times 10^{-10} |
| KCNK3  | rs11126666 | 2:26928811          | A  | 0.021 (0.003) | 1.33 \times 10^{-9}  |
| SBK1   | rs2650492 | 16:28333411           | G  | 0.021 (0.004) | 1.92 \times 10^{-9}  |
| RARB   | rs6804842 | 3:25106437            | G  | 0.019 (0.003) | 2.48 \times 10^{-9}  |
| CCDC171| rs4740619 | 9:15634326            | T  | 0.018 (0.003) | 4.56 \times 10^{-9}  |
| PRKN   | rs13191362 | 6:163033350         | A  | 0.028 (0.005) | 7.74 \times 10^{-9}  |
| DMXL2  | rs3736485 | 15:51729568           | G  | 0.031 (0.005) | 7.76 \times 10^{-9}  |
| SCARB2 | rs17001654 | 7:75163169         | C  | 0.031 (0.005) | 8.45 \times 10^{-9}  |
| NT5CA  | rs11191560 | 10:10489038        | T  | 0.018 (0.003) | 1.20 \times 10^{-8}  |
| UBE2E3 | rs1528343 | 2:181550962           | T  | 0.018 (0.003) | 1.28 \times 10^{-8}  |
| RABEP1 | rs1000940 | 17:5283252            | G  | 0.019 (0.003) | 1.39 \times 10^{-8}  |
| FOXO3  | rs9400239 | 6:108975663           | C  | 0.019 (0.003) | 1.61 \times 10^{-8}  |
| LMX1B  | rs10733682 | 9:129460914          | A  | 0.017 (0.003) | 1.83 \times 10^{-8}  |
| EBBP1  | rs11688816 | 2:63053048          | G  | 0.017 (0.003) | 1.89 \times 10^{-8}  |
| CLIP1  | rs11057405 | 12:122781897        | G  | 0.031 (0.006) | 2.02 \times 10^{-8}  |
| HHIP   | rs11727676 | 4:145659064         | T  | 0.036 (0.006) | 2.55 \times 10^{-8}  |
| GBE1   | rs3849570  | 3:81792112           | A  | 0.019 (0.003) | 2.60 \times 10^{-8}  |
| FRRS1L | rs6477694 | 9:111932342           | C  | 0.017 (0.003) | 2.67 \times 10^{-8}  |
| GRID1  | rs7899106 | 10:87410904           | G  | 0.04 (0.007)  | 2.96 \times 10^{-8}  |
| HSD17B12 | rs2176598 | 11:43864278          | T  | 0.02 (0.004)  | 2.97 \times 10^{-8}  |
| PMS2L11 | rs2245368 | 7:76608143           | C  | 0.032 (0.006) | 3.19 \times 10^{-8}  |
| PGPEP1 | rs17724992 | 19:18454825          | A  | 0.019 (0.004) | 3.42 \times 10^{-8}  |
| GRP    | rs7243357 | 18:56883319           | T  | 0.022 (0.004) | 3.86 \times 10^{-8}  |
| RP11-120I21.3 | rs2033732 | 8:85079709          | C  | 0.019 (0.004) | 4.89 \times 10^{-8}  |
| FTO    | rs1558902 | 16:53803574          | A  | 0.082 (0.003) | 7.51 \times 10^{-153} |
| MC4R   | rs6567160 | 18:57829135           | C  | 0.056 (0.004) | 3.53 \times 10^{-53} |
| TMEM18 | rs13021737 | 2:632348             | G  | 0.06 (0.004)  | 1.11 \times 10^{-50} |
| NMU    | rs10938397 | 4:45182527           | G  | 0.04 (0.003)  | 3.21 \times 10^{-38} |
| SEC16B | rs543874  | 1:177889480          | G  | 0.048 (0.004) | 2.62 \times 10^{-35} |
| TFAP2B | rs2207139 | 6:50845490          | A  | 0.045 (0.004) | 4.13 \times 10^{-29} |
| BDAF   | rs11030104 | 11:27684517         | A  | 0.041 (0.004) | 5.56 \times 10^{-28} |
| NEGR1  | rs3101336 | 1:72751185           | C  | 0.033 (0.003) | 2.66 \times 10^{-26} |
BMI-related SNPs and selected disease outcomes is provided in Supplementary Tables 2 and 3.

**Statistical analysis**

We obtained exposure and outcome datasets containing β-coefficients, standard errors, p values, and effect alleles, for BMI-associated SNPs. Next, we conducted traditional IVW methodology [19], WM methods, MR–Egger regression, and MR-PRESSO, to acquire results in a robust manner. Odds ratios (ORs) with 95% confidence intervals (CIs) were converted by exponential transformation except for the original result of MR–Egger Analysis in Tables 3 and 4. All statistical analysis was carried out in RStudio version 3.6.1. As five outcomes were tested for each separate SNP, we used P < 0.01 as the significance threshold for the main IVW analyses; 0.01 < P < 0.05 was defined as nominal significant results.

**Results**

**Causal associations between BMI in adulthood and diseases**

Using the IVW approach, we calculated the estimated causal effect of BMI in adulthood on a range of female-specific diseases (Fig. 1; Table 3). A positive causal association was only detected between PCOS and BMI in adulthood (OR: 1.003; 95% CI: 1.001–1.004; P = 6.83 × 10−5). No significant causal associations were identified between BMI in adulthood and endometrial cancer (EC), CC, ovarian cancer, or endometriosis.
Causal associations between BMI in childhood and diseases

Traditional IVW analysis provided no evidence for causal relationships between BMI in childhood and CC, ovarian cancer, or EC (Fig. 2; Table 4). However, we identified a positive causal effect of BMI in childhood on PCOS (OR: 1.003; 95% CI: 1.001–1.004; \(P = 9.14 \times 10^{-4}\)) and a potential negative causal association between childhood BMI and endometriosis (OR: 0.995; 95% CI: 0.991–0.999; \(P = 1.25 \times 10^{-2}\)).

Sensitivity analysis

We first conducted the WM method for sensitivity analysis. The WM method (Tables 3 and 4) suggested a potential

| Table 2 | Characteristics of childhood BMI-associated SNPs from GWAS |
|----------|----------------------------------------------------------|
| Gene    | SNP            | Chromosome: Position | EA | Association with exposure |
|         |                |                      |    | \(\beta\) (SE) | \(P\) value |
| GNPDA2  | rs13130484 | 4:45175691 T | T | 0.067 (0.007) | 1.58 \times 10^{-23} |
| ADCY3   | rs11676272 | 2:25141538 G | G | 0.068 (0.007) | 7.12 \times 10^{-23} |
| TMEM18  | rs4854349  | 2:647861 C | C | 0.090 (0.009) | 5.41 \times 10^{-22} |
| SEC16B  | rs543874   | 1:17789480 G | G | 0.077 (0.009) | 2.20 \times 10^{-19} |
| FAIM2   | rs7132908  | 12:50263148 A | A | 0.066 (0.008) | 1.57 \times 10^{-18} |
| FTO     | rs1421085  | 16:53800954 C | C | 0.059 (0.007) | 4.53 \times 10^{-16} |
| OLFM4   | rs12429545 | 13:54102206 A | A | 0.076 (0.009) | 2.08 \times 10^{-14} |
| TFAP2B  | rs987237   | 6:50803050 G | G | 0.062 (0.009) | 1.80 \times 10^{-12} |
| TNNI3K  | rs12041852 | 1:75003500 G | G | 0.046 (0.007) | 2.28 \times 10^{-10} |
| MC4R    | rs6567160  | 2:25141538 G | G | 0.050 (0.008) | 1.21 \times 10^{-9} |
| ELP3    | rs13253111 | 8:28061974 A | A | 0.042 (0.007) | 4.89 \times 10^{-9} |
| RAB27B  | rs8092503  | 18:52479487 G | G | 0.045 (0.008) | 8.17 \times 10^{-9} |
| LMX1B   | rs3829849  | 9:129390800 T | T | 0.041 (0.007) | 8.81 \times 10^{-9} |
| ADAM23  | rs13387838 | 1:75003500 T | T | 0.139 (0.025) | 2.84 \times 10^{-8} |
| GPR61   | rs7550711  | 11:10082886 T | T | 0.105 (0.019) | 4.52 \times 10^{-8} |

| Gene nearest gene to the SNP, EA effect allele; \(\beta\) per allele effect on the exposure; SE standard error; \(P\) value p value for the genetic association

| Table 3 | Inverse-variance weighted method, weighted median approach, MR-Egger analysis for genetic associations between 75 adult BMI and indicated diseases |
|----------|-------------------------------------------------------------------------------------------------------------------------------------|
| Disease traits | Analysis method | Effect | Standard error | 95% CI | \(P\) value |
| Cervical cancer | Inverse-variance weighted | 0.998 | 1.28 \times 10^{-3} | (0.995–1.000) | 6.57 \times 10^{-2} |
| | Weighted median | 0.996 | 2.08 \times 10^{-3} | (0.992–1.000) | 4.17 \times 10^{-2} |
| | MR–Egger intercept | 6.03 \times 10^{-5} | 9.12 \times 10^{-5} | (−1.18 \times 10^{-4} to 2.39 \times 10^{-4}) | 0.51 |
| Endometrial cancer | Inverse-variance weighted | 1.000 | 1.01 \times 10^{-3} | (0.998–1.002) | 0.99 |
| | Weighted median | 0.998 | 1.65 \times 10^{-3} | (0.994–1.001) | 0.15 |
| | MR–Egger intercept | 6.83 \times 10^{-5} | 7.28 \times 10^{-5} | (−7.45 \times 10^{-5} to 2.11 \times 10^{-4}) | 0.35 |
| Ovarian cancer | Inverse-variance weighted | 1.000 | 8.34 \times 10^{-4} | (0.999–1.002) | 0.66 |
| | Weighted median | 1.001 | 1.39 \times 10^{-3} | (0.998–1.003) | 0.66 |
| | MR–Egger intercept | 2.19 \times 10^{-5} | 5.98 \times 10^{-5} | (−5.92 \times 10^{-5} to 1.39 \times 10^{-4}) | 0.71 |
| Endometriosis | Inverse-variance weighted | 0.999 | 2.12 \times 10^{-3} | (0.995–1.003) | 0.56 |
| | Weighted median | 0.999 | 3.07 \times 10^{-3} | (0.993–1.005) | 0.67 |
| | MR–Egger intercept | 1.96 \times 10^{-4} | 1.50 \times 10^{-4} | (−9.92 \times 10^{-5} to 4.91 \times 10^{-4}) | 0.19 |
| PCOS | Inverse-variance weighted | 1.003 | 7.40 \times 10^{-4} | (1.001–1.004) | 6.83 \times 10^{-5} |
| | Weighted median | 1.003 | 1.16 \times 10^{-3} | (1.000–1.005) | 2.80 \times 10^{-2} |
| | MR–Egger intercept | −4.53 \times 10^{-5} | 5.28 \times 10^{-5} | (−1.49 \times 10^{-4} to 5.83 \times 10^{-5}) | 0.39 |

\(CI\) confidence interval; \(P\) value p value of the causal estimate

The effect and confidence interval result of the inverse-variance weighted method and weighted median approach were exponentially transformed. The result of the MR–Egger intercept was original

Causal associations between BMI in childhood and diseases

Traditional IVW analysis provided no evidence for causal relationships between BMI in childhood and CC, ovarian cancer, or EC (Fig. 2; Table 4). However, we identified a positive causal effect of BMI in childhood on PCOS (OR: 1.003; 95% CI: 1.001–1.004; \(P = 9.14 \times 10^{-4}\)) and a potential negative causal association between childhood BMI and endometriosis (OR: 0.995; 95% CI: 0.991–0.999; \(P = 1.25 \times 10^{-2}\)).

Sensitivity analysis

We first conducted the WM method for sensitivity analysis. The WM method (Tables 3 and 4) suggested a potential
negative causality between adult-BMI and CC, a positive causal association between adult-BMI and PCOS; these results were similar to those obtained from the IVW method. However, we did not identify any significant causal association between disease and BMI in childhood; this was not consistent with our primary findings. Next, we conducted MR–Egger analysis (Tables 3 and 4); almost all of the intercept terms were located around the origin, thus implying that there was no horizontal pleiotropy. Next, we used an updated MR-PRESSO global test to evaluate whether there were any outlying SNPs. As expected, there were no outlying SNPs for BMI in adulthood (Supplementary Table 4) or SNPs for BMI in childhood (Supplementary Table 5) for any of the diseases tested, apart from rs11727676 and rs12566985 for BMI in adulthood when associated with endometriosis. A nominal negative association between BMI in childhood and endometriosis was still detected, as well as a significant positive causal association between PCOS and BMI in adulthood or childhood, as determined by IVW. Next, we investigated the causal associations between childhood BMI and PCOS or endometriosis, and between adulthood, BMI and PCOS were driven by an individual SNP. In order to do this, we performed leave-one-out analyses (Supplementary Table 6); this showed that the significance of the causal effects of BMI on PCOS, both in adulthood and childhood, and the nominal causal association between childhood BMI and endometriosis were not influenced by the removal of any single SNP except rs12041852 ($P = 0.060893$), which

| Disease traits | Analysis method | Effect | Standard error | 95% CI | $P$ value |
|---------------|----------------|--------|----------------|-------|-----------|
| Cervical cancer | Inverse-variance weighted | 0.998 | $1.43 \times 10^{-3}$ | (0.995–1.001) | 0.12 |
|                | Weighted median | 0.996 | $1.93 \times 10^{-3}$ | (0.993–1.000) | 0.053 |
|                | MR–Egger Intercept | $2.40 \times 10^{-4}$ | $3.50 \times 10^{-4}$ | ($-4.45 \times 10^{-4}$ to $9.25 \times 10^{-4}$) | 0.49 |
| Endometrial cancer | Inverse-variance weighted | 0.998 | $1.30 \times 10^{-3}$ | (0.996–1.001) | 0.24 |
|                | Weighted median | 0.997 | $1.54 \times 10^{-3}$ | (0.994–1.000) | 0.08 |
|                | MR–Egger Intercept | $-1.32 \times 10^{-5}$ | $3.22 \times 10^{-4}$ | ($-6.44 \times 10^{-5}$ to $6.17 \times 10^{-4}$) | 0.97 |
| Ovarian cancer | Inverse-variance weighted | 1.000 | $8.94 \times 10^{-4}$ | (0.998–1.002) | 0.96 |
|                | Weighted median | 1.000 | $1.24 \times 10^{-3}$ | (0.998–1.003) | 0.83 |
|                | MR–Egger Intercept | $4.82 \times 10^{-5}$ | $2.14 \times 10^{-4}$ | ($-3.71 \times 10^{-4}$ to $4.67 \times 10^{-4}$) | 0.82 |
| Endometriosis | Inverse-variance weighted | 0.995 | $1.99 \times 10^{-3}$ | (0.991–0.999) | 1.25 $\times 10^{-2}$ |
|                | Weighted median | 0.996 | $2.64 \times 10^{-3}$ | (0.991–1.001) | 0.11 |
|                | MR–Egger Intercept | $-6.64 \times 10^{-5}$ | $4.94 \times 10^{-4}$ | ($-1.03 \times 10^{-3}$ to $9.01 \times 10^{-4}$) | 0.89 |
| PCOS | Inverse-variance weighted | 1.003 | $8.01 \times 10^{-4}$ | (1.001–1.004) | 9.14 $\times 10^{-4}$ |
|                | Weighted median | 1.002 | $1.06 \times 10^{-3}$ | (1.000–1.004) | 0.12 |
|                | MR–Egger Intercept | $3.10 \times 10^{-4}$ | $1.79 \times 10^{-4}$ | ($-4.13 \times 10^{-5}$ to $6.62 \times 10^{-4}$) | 8.37 $\times 10^{-2}$ |

CI confidence interval, $P$ value $p$ value of the causal estimate

The effect and confidence interval result of the inverse-variance weighted method and weighted median approach were exponentially transformed. The result of MR-Egger Intercept was original

Fig. 1 Causal effects of BMI in adulthood on the risk of several diseases. Estimated effects, 95% confidence intervals, and the $P$ values of associations are shown. Effect the combined causal effect, CI confidence interval; $P$ value refers to the causal estimate

Fig. 2 Causal effects of BMI in childhood on the risk of several diseases. Estimated effects, 95% confidence intervals, and $P$ values of associations, are shown. Effect the combined causal effect, CI confidence interval; $P$ value refers to the causal estimate
indicated that this specific SNP may be an influential SNP to the negative causality between child obesity and endometriosis. Moreover, we identified three overlapping SNPs for both age-related BMIs (rs12429545, rs543874, and rs6567160). Next, we repeated the traditional IVW approach to exclude the overlapping SNPs (Supplementary Table 7); this still identified a positive causal association between BMI in adulthood and PCOS (OR: 1.003; 95% CI: 1.001–1.004; $P = 8.73 \times 10^{-4}$), a potential positive causal association between BMI in childhood and PCOS (OR: 1.002; 95% CI: 1.000–1.004; $P = 0.013$) and a nominal negative causality between BMI in childhood and endometriosis (OR: 0.995; 95% CI: 0.990–1.000; $P = 0.033$). Moreover, when the overlapping SNPs were removed, we identified potential negative causal relationships between BMI in both childhood and adulthood and CC.

**Discussion**

In this study, we identified robust evidence relating to the causal association between BMI in both childhood and adulthood and the risk of infertility and CCs; a higher BMI in adulthood, and a higher BMI in childhood, were both associated with an increased risk of PCOS. Consistent with our conclusions, previous observational studies and meta-analyses have identified similar outcomes that women with PCOS had a higher risk of central obesity [7] and that the prevalence of PCOS was higher in women who were overweight or obese [20]. In another study, earlier adiposity rebound and a severe rise in BMI during childhood were identified as predictors of PCOS in later life [21]. The nominal negative causality between BMI in childhood and endometriosis, as detected by the IVW method in our study, was also meaningful and thought-provoking because previous observational studies also arrived at the same conclusion in that there was an inverse relationship between body size at 5, 10, and 20 years-of-age and endometriosis [22]. Genome-wide enrichment analysis further demonstrated significant enrichment of common variants that overlapped between endometriosis and waist-to-hip ratio when adjusted for BMI, thus representing fat distribution [23]. Another case–control analysis, carried out in Australia, revealed that females who self-reported being overweight at 10 years of age had a higher risk of endometriosis [24]. Nevertheless, we did not identify any positive evidence for an association between BMI and endometrial or ovarian cancers using our methods while other MR or observation studies did identify such relationships. A previous study, involving MR, analyzed four subsets of cases and controls from EC datasets from subjects with Australian and European ancestry [25]. Its final IVW results were combined using random effects meta-analysis following stratification into quartiles and then calculated separately. Consequently, it is possible that different races and different computing methods may have contributed to the observed divergence in our results. Using the same SNPs associated with BMI in adulthood, and without abandoning two loci in strong LD, with a different outcome database, Gao et al. [26] concluded adult BMI was positively association with ovarian cancer. However, after excluding overlapping loci, the significance of this relationship was lost. The authors did not detect a strong association between childhood BMI and ovarian cancer risk. Another MR study demonstrated that higher scores in BMI as an instrument for obesity, increased the risk of non-high grade serous ovarian cancer of subjects with a European ancestry, but was not associated with high grade serous ovarian cancer [27]. It is evident, therefore, that subtypes of ovarian cancer may react to obesity in a different manner and need to be considered carefully. The inverse causal relationship between CC and BMI in adulthood needs to be further confirmed; this was because the $P$ value yielded by IVW was $6.57 \times 10^{-2}$ while after removal of overlapping SNPs, the IVW result as well as the original WM method yielded a nominal significant outcome. A previous study retrospectively analyzed a cohort of patients with CC [28] who were classified as underweight (BMI <18.5 kg/m$^2$), normal weight (BMI: 18.5–24.9 kg/m$^2$), overweight (BMI: 25–29.9 kg/m$^2$), obese (BMI: 30–34.9 kg/m$^2$), and morbidly obese (BMI ≥35.0 kg/m$^2$). After controlling for prognostic factors, only patients in the morbidly obese group had an independent risk of mortality by CC. This classification suggested that the extent of obesity, or the staging of disease, could obscure the real causal association between risk factors and outcomes.

With the development of genome wide associated studies, it is now possible to take advantage of data sharing and perform more enhanced MR research on the causality of exposure and disease. Previously, researchers relied heavily upon retrospective or prospective studies. Compared to these two classical research methods, our MR analysis had several advantages. First, the MR tool is less vulnerable to reverse causation or confounding bias from economic and educational levels or lifestyle factors such as smoking or alcoholism. Second, the MR tool is not susceptible to experimental influences. Third, there is a large capacity for samples once databases have been accessed. Fourth, our results showed that in addition to obesity in adulthood, severe childhood obesity can also be used as a predictor for endometriosis and PCOS in later life. Therefore, it is vital that we prevent the trend for obesity in childhood and take appropriate measures to keep in balanced shape whenever weight is gained. Finally, rather than providing a simple correlation, MR can directly explain the causality between exposure and outcomes. There are some limitations that also need to be considered. First, BMI is not a perfect index for...
obesity; the waist-to-hip ratio and the thickness of the subcutaneous fat are also used as proxies for obesity. Fat distribution, rather than BMI, can also represent an independent risk factor for certain diseases. Second, different races can exhibit differences in instrumental variables and the genetic scores of outcomes; our present analysis only considered European subjects. Third, we did not obtain a BMI dataset that was stratified by gender. In contrast, the GWAS data used in our analysis were female specific and could have influenced the rigor of our results. Forth, results of the leave-one-out analysis (Supplementary Table 6) indicated that rs12041852 may be the one SNP that could influence the negative causality between child obesity and endometriosis. Finally, severity levels for the outcomes and stages of diseases should be stipulated and defined where possible.

Conclusions

Our analysis showed that genetic predispositions to elevated BMI during childhood and adulthood were related to a higher risk of PCOS while an increased BMI in childhood was likely to be associated with a lower risk of endometriosis. We did not identify any strong evidence for an association between BMI in adulthood or childhood with gynecological cancers. Further studies need to be carried out with a larger population size. Prospective and observational studies should also include cancers of the female reproductive system and investigate the specific mechanisms underlying the effects of BMI in childhood and adulthood on PCOS and endometriosis.

Data and material availability

Besides the selected SNPs derived from published articles [dataset 1], we also obtained access to open databases to acquire genetic statistics for diseases outcomes. The data analyzed in this article are available from the UK Biobank, as follows.

[dataset 1]: Locke, Adam E et al. “Genetic studies of body mass index yield new insights for obesity biology.” Nature vol. 518,7538 (2015): 197–206. doi:10.1038/nature14177

[dataset 2]: Geng, Tingting et al. “Childhood BMI and Adult Type 2 Diabetes, Coronary Artery Diseases, Chronic Kidney Disease, and Cardiometabolic Traits: A Mendelian Randomization Analysis.” Diabetes care vol. 41,5 (2018): 1089–1096. doi:10.2337/dc17-2141

Code availability

RStudio version 3.6.1.

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Author contributions Y.-S.Y. collected data and wrote the paper. Z.Q. analyzed and revised the data. P.-P.L. and H.-F.H. designed the study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval and consent to participate and publication We did not require ethical approval from an ethics committee, or a checklist referenced by the Equator Network, because our study did not involve human and animal research, or observational studies. We performed Mendelian randomization analysis on published data and open databases to investigate the causal associations between exposures and outcomes. All of the cited projects and datasets were approved by relevant ethics committees associated with the corresponding published articles.

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