Pediatric and Adult Obesity Concern Female Health: A Mendelian Randomization Study

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Abstract

Purpose: Adulthood and childhood obesity are associated with female reproductive endocrinology and gynecological cancers. However, the causality of such association is yet to be identified. Independent of inverse bias and confounding, mendelian randomization is like a random control trial where genetic groups are settled during meiosis, which could be effective to examine the causality.

Methods: We carried out several Mendelian randomization trials based on combined genetic scores of 75 adult-associated and 15 child-associated BMI single nucleotide polymorphisms (SNPs), diseases databases of several gynecological cancers and reproductive diseases from UK Biobank with 194,153 participants, using traditional inverse-variance weighted (IVW) method, Weighted Median (WM) approach, MR-Egger regression and updated MR-PRESSO analysis.

Results: Elevated adult-associated BMI (effect:1.003;95%CI:1.001,1.004) and child-associated BMI (effect:1.003;95%CI:1.001,1.004) genetic scores were related to higher risk of PCOS incidence by using traditional IVW method. Random IVW method showed a negative causal association between the child-associated BMI and subsequent endometriosis attack(effect:0.995;95%CI:0.991,0.999).

Conclusions: Consistent with observational consequences, our findings suggested that childhood and adulthood obesity may play roles in the development of PCOS, and children obesity can elevate the possibility of PCOS but decrease the incidence of endometriosis in later life. More researches need to be conducted for further validation and potential mechanisms.

Introduction

Obesity is characterized as body mass index (BMI) ≥ 30kg/m^2 in adults and BMI-for-age percentile ≥ 95% in children. Trends in obesity and severe obesity prevalence in US have come up to approximately 17% in in American girls(Silvestris et al., 2018) and reached 39.6% in 2015–2016 among women(Hales et al., 2018). Obesity has been a worldwide prevalent phenomenon linking to prevalence risk of female infertility and gynecological cancers(Park et al., 2014) which perplex female physiologically and psychologically. Endometriosis and polycystic ovarian syndrome (PCOS) have become two major diseases type that result in female infertility. However, both of them are etiologically unknown yet. Endometriosis is mainly characterized as dysmenorrhea, pelvic pain and infertility. A research showed an inverse relation between current BMI and endometriosis was observed when cases were concurrently infertile(Missmer et al., 2004). An ongoing prospective case-control cohort study(Shah et al., 2013) uncovered that women's current BMI and BMI at age 18 were statistically associated with the rate of endometriosis inversely, which is stronger among infertile women, and the most robust association was with BMI at age 18. It suggests us that there may be an 'early window of exposure' during which lower BMI at adolescence leaves an impact on endometriosis preceding the diagnosis of the disease. PCOS is characterized as hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology, which most attacks reproductive women with 8% morbidity. Observational studies has discovered that obesity, even

childhood obesity(Koivuaho et al., 2019a), has a positive association with PCOS as well as other female reproductive system tumors in adulthood. According to a systemic review and meta-analysis, obese patients take a larger proposition than nonobese ones in PCOS(Lim et al., 2012). On the other hand, patients with greater central adiposity positively were associated with more severe metabolic phenotype such as insulin resistant diabetes mellitus(Ollila et al., 2017). PCOS takes place early at puberty. A longitude population-based study concluded that adolescent obesity predicted ovulatory dysfunction in later life(Laitinen et al., 2003). So, it's necessary to find the causality between adult or child obesity and infertility so that we can take measures to prevent the damage of overweight to health.

Cervical cancers, endometrial carcinomas and ovarian cancers are listed as the top three popular cancers in female reproductive system malignancy, some of them can be really aggressive and invasive. Researches and reviewers have also shown association between obesity and overweight, often BMI as proxy, and female gynecological malignant tumors(Markowska et al., 2017, Modesitt and van Nagell, 2005). Nevertheless, whether the link between them is causal or not remains unknown.

Mendelian randomization(Emdin et al., 2017)(MR) analysis uses genetic variants usually single nucleotide polymorphisms(SNPs) as instrumental variables substituting a risk factor to calculate its influence value statistically on outcomes of diseases or others in a non-experimental setting, which can determine the observational association between exposures and outcomes is consistent with causality. It seems like a natural and lifetime randomized control trials (RCT) in large population where randomization of genotypes happens during meiosis and fertilization. Different defined SNPs information stratifies the specific population into subsets like matched group and treated group in a RCT. Compared to conventional artificial design of a study, MR is rarely influenced by confounding element, reverse causation and bias. Here, we use body mass index (BMI) as obese measures, MR analysis to detect whether adult or child obesity is responsible for morbidity of both PCOS or gynecological cancers.

Materials And Methods

MR process is established robustly only when following conditions are met. First, the SNPs working as instrumental variables must represent for BMI. Second, the SNPs must be independent to confounding factors. Third, the SNPs only affects the outcome through the only pathway of BMI except any other potential horizontal factors(Didelez and Sheehan, 2007). With the inaccessibility to all information within one sample, we use two-sample MR methods(Burgess et al., 2015) to obtain genetic statistics of exposures and outcomes from two different published studies which has been proved efficient and useful. Moreover, we use MR-Egger regression(Bowden et al., 2015), weighted median approaches(Bowden et al., 2016) and MR-PRESSO(Verbanck et al., 2018)(Pleiotropy RESidual Sum and Outlier) method to protect results from error of pleiotropy and too many invalid IVs, which ensures the second and third assumption stand.

SNP selection and Linkage Disequilibrium Assessment

We take advantage of statistics of a recent genetic study of BMI published in Nature(Locke et al., 2015) [dataset1]*. 97 BMI-associated loci identified in 339,224 individuals, whose common variation accounts for more than 20% of BMI variation. Then we selected 77 SNPs among them of 322,154 European descent. 15 childhood BMI-associated SNPs were extracted from a mendelian randomization analysis from Diabetes Care(Geng et al., 2018)[dataset2]*. All the SNPs selected were of great significance ($p<5*10^{-8}$). We further processed linkage disequilibrium (LD) assessment by using a suite of web-based applications named LDlink search system (https://ldlink.nci.nih.gov/) to interrogate selected IVs are not associated with each other. If any correlation coefficient of LD assessment r^2 higher than 0.1, then the one with higher p value was excluded such as rs3888190 and rs11583200 (Supplementary Table 1), so there were total 75 BMI-associated SNPs (Table 1) and 15 childhood BMI-associated ones left (Table 2), including rs12016871 was merged into rs9581854 in 2005. Genetic data of different outcomes refer to different databases in the UK Biobank (UKBB), who recruited over than 500,000 aged 27-73 years old from the United Kingdom from 2006 to 2010 bringing the total number of participants up to 194153. The association information of the selected BMI-related SNPs with selected diseases outcomes is provided as listed in Supplementary Table 2 and 3. We carried out no experiments involving animals or human subjects directly, but rather got use of and did analytical researches on open databases. The ethical approval has been received by UKBB form the NHS National Research Ethics Service North West.

Statistical Analysis

By utilizing data sets containing β-coefficient, standard error p value and effect allele of BMI-assoicated and outcomes-associated SNPs respectively, we in turn conducted the traditional inverse-variance weighted(Burgess et al., 2013)(IVW) method, weighted median methods, MR-Egger regression and MR-PRESSO for robustness of the results. No error of measurement and that all the SNPs selected are valid are with acquiescence when processing random IVW, whose fundamental principles was weighted linear regression. Since results of IVW method can be biased if instrument SNPs shows horizontal pleiotropy, acting through another unaccounted casual pathway, we further conducted sensitivity analysis such as Weighted Median methods, MR-Egger regression and MR-PRESSO. MR-Egger regression was done to make sure that no horizontal pleiotropy exists among BMI-associated SNPs. However, neither IVW or MR-Egger regression can foreclose the possibility of invalid SNPs except weighted median (WM) approaches were done, which indicates that at least half of the SNPs selected were valid instrumental variables. MR-PRESSO is an updated analysis that can evaluate whether a specific individual SNP is driving the difference in residual sum of squares (RSS). After being pre-screened for LD, SNP model was incorporated into three stages to examine the extent of horizontal pleiotropy, that is MR-PRESSO global test, MR-PRESSO outlier test and MR-PRESSO distortion test. Here we conducted MR-PRESSO method as verification for pleiotropy. Effect estimate and 95%CI was converted by exponential transformation. All the analysis was conducted in RStudio version 3.6.1 and regarded two-tailed $P<0.05$ as significance.

Results

Causal associations between adult-BMI and diseases

By means of IVW approach, WM method and MR-Egger analysis, we calculated the estimated causal effect of adulthood BMI on diseases especially for women as listed (Figure 1; Table 3). The positive causal association was found between PCOS and adult-BMI, which was confirmed by both IVW (Odd ratio [OR]= 1.003;95%CI: 1.001-1.004; $P=6.83*10^{-5}$) and WM methods (OR= 1.003;95%CI: 1.000-1.005; $P=2.80*10^{-2}$). The negative causality between cervical cancer and adult-BMI was only obtained through WM method (OR= 0.996;95%CI: 0.992-1.000; $P=4.17*10^{-2}$), although the estimate of IVW approach almost got the significance (OR= 0.998;95%CI: 0.995-1.000; $P=6.57*10^{-2}$). No significant causal associations were demonstrated between adult-BMI and endometrial cancer, ovarian cancer or endometriosis. The results of MR-Egger regression uncovered that all SNPs were plotted around origin, indicating no directional pleiotropy existed here under any conditions.

Causal associations between child-BMI and diseases

Traditional IVW approach determined the positive causal effect of child-BMI on PCOS (OR= 1.003;95%CI: 1.001-1.004; $P=9.14*10^{-4}$) and negative causal association between child-BMI and endometriosis (OR= 0.995;95%CI: 0.991-0.999; $P=1.25*10^{-2}$). Weighted median method did not obtain the same conclusion. However, WM method implied that negative causal associations between child-BMI and cervical cancer (OR= 0.996;95%CI: 0.993-1.000; P=0.053) or endometrial cancer (OR= 0.997;95%CI: 0.994-1.000; P=0.08). MR-Egger regression concluded that the consequences were not influenced by pleiotropy (Figure 2; Table 4).

We then conducted recently updated MR-PRESSO global test to exhibit whether there existed horizontal pleiotropy in selected SNPs. As expected, no outlier SNP in adult-BMI (Supplementary Table 4) or child-BMI SNPs category (Supplementary Table 5) was found in all diseases according to the analytic results except rs11727676 and rs12566985 in adult-BMI when associated with endometriosis. From the perspective of MR-PRESSO conclusion, significance was shown still in the negative association between children BMI and endometriosis as well as in the positive association between PCOS and BMI at adulthood or childhood as IVW has displayed.

Discussions

In this study, we found pieces of robust evidence about causal association between child and adult BMI and the risk of infertility and cervical cancers. In details, the higher genetic score of adult and childhood BMI was associated with increased of PCOS. Consistent with our conclusions, observational studies and meta-analyses have uncovered the same outcome that women with PCOS had higher risk of central obesity(Lim et al., 2012) and the prevalence of PCOS was increased among overweight and obese women(Alvarez-Blasco et al., 2006), earlier adiposity rebound and severe BMI rise in childhood predicted later development of PCOS(Koivuaho et al., 2019b). The negative causality between child BMI and

endometriosis through IVW method was convincing because observational studies has come up with same conclusion that there was an inverse relation between body size at 5,10,20 age and the disease(Vitonis et al., 2010). The prospective case-control aiming at more than 100,000 women from the United States for over 20 years exhibited the inverse tendency to develop endometriosis was more significantly obvious in 18-year-old BMI than current BMI, persisted noteworthy in both infertile women and those without concurrent infertile. An genome-wide enrichment analysis demonstrated a significant enrichment of common variants overlapping both endometriosis and waist-to-hip ratio adjusted for BMI, representing for fat distribution(Rahmioglu et al., 2015). There is another case-control analysis in Australia revealed that women who self-reported overweight at age 10 had an increasing risk of endometriosis(Nagle et al., 2009). However, mother-daughter pair reports came up an opposite association that underweight at 16 years old positively related to endometriosis, which consisted with ours. Nevertheless, we didn't acquire same positive findings about BMI associated with endometrial cancers, ovarian cancers using the method as other MR analysis and observation did. A MR analysis published in 2016 which uses 4 subsets of cases and controls from EC datasets of Australian and European ancestry(Painter et al., 2016). The final IVW result was combined using random effects meta-analysis after stratified into quartiles and calculated separately. So different races and computing method may contribute to the divergence in our results. While using the same adult BMI-SNPs without abandoning 2 loci in strong linkage disequilibrium and different outcome database, Gao, C., et al.(Gao et al., 2016) concluded that 1 standard deviation in genetically predicted adult BMI was associated with 35% increase risk in overall ovarian cancer. However, after excluding overlap loci, the significance disappeared. They also didn't find strong association between genetically predicted child BMI with ovarian cancer risk. Another MR study ended up with a consequence that BMI as instrumental invariables as obesity, increased risk of non-high grade serous ovarian cancer of European ancestry, but had nothing to do with high grade serous ovarian cancer(Dixon et al., 2016). This reminds us that subtypes of ovarian cancer may react to obesity differently and contribute together to nonsense of overall OC to obese. The inverse causal relationship between cervical cancers and adult BMI need to be confirmed because the p value of IVW reached 6.57*10 − 2 while WM concluded significantly. A retrospective cohort study of patients of cervical cancer(Frumovitz et al., 2014) were classified as underweight (BMI < 18.5kg/m^2), normal weight (BMI 18.5-24.9kg/m^2), overweight (BMI 25-29.9kg/m^2), obese (BMI 30-34.9 kg/m^2) and morbidly obese (BMI ≥ 35.0kg/m^2). After controlling for prognostic factors, only morbidly obese remained an independent risk for mortality of CC. So, the classification left us a hint that the extent of obesity or staging of disease could obscure the real causal association of risk factors and results.

To the best of our knowledge, it is the first mendelian randomization analysis of the causality of BMI and PCOS or endometriosis. Also, never ever had articles published the association between childhood BMI and common gynecological cancers. With the appearance of genome wide associated study, we can take advantage of information sharing to further MR research on causality of exposures and diseases. Previously, researchers get used to carrying out retrospective studies or prospective studies. Compared to the two classical research methods, strengths of our MR analysis can be listed as follow: 1) less vulnerable to reverse causation or confounding bias from economic and educational levels or lifestyle

like smoking or alcoholism; 2) insusceptible of experimental such as acting time and degree of disposal; 3) the sample capacity can be big enough as soon as getting access to database; 4) our results show besides adult obesity, severe child obese can already be predictable to endometriosis and PCOS in later life, so it's vital for us to prevent the trend of obesity in childhood and take measures to keep in balanced shape whenever weight gains, and if obese has taken place, there's a need for to lose weight; 5) MR can directly explains the causality between exposure and outcomes not only simple correlation. So, drug use and side-effect of weight gain need to be notice for future health. Of course, there is room for improvement: 1) BMI is not a perfect index for obesity, as we can see, waist to hip ratio as well as subcutaneous fat thickness is often chosen to be proxies of obesity. Fat distribution rather than BMI can also be an independent risk of diseases; 2) different races can have changes in instrumental variables and genetic score of outcome; Here in our MR analysis, results only applied to European; 3) there may be some overlapped loci in adult and child BMI associated SNPs, there's a possibility that genetic variants influence both of them; 4) we can't count out the probability of population stratification and other potential confounding, severity levels of outcomes and stages of diseases should be underlined and distinguished if possible, and our final association was not obvious.

Conclusions

Generally speaking, genetic predispositions to elevated adult and child BMI was related to higher risk of PCOS, increased child BMI was linked to lower risk of endometriosis. No strong evidence had been found of association between adult and child BMI and female gynecological cancers. These results offered us a causal relationship between BMI and PCOS or endometriosis, implying that no matter adult or child obese can leave an adverse impact on PCOS. But too thin and underweight may increase the risk of endometriosis. However, further replications need to be carried out with larger scale, prospective and observational studies about female cancers of reproductive system as well as illuminating the mechanism of how adult and child obese working on PCOS and endometriosis, as PCOS is now still a disease of unknown etiology.

Declarations

Acknowledgements

All the cited projects and datasets were approved by the relevant ethics committees in corresponding published articles. We did not apply required statements of ethics committee approval or checklist referenced at the Equator Network, because our study does not belong to traditional human and animal researches or observational studies. We did mendelian randomization analysis on published data and open databases, thus drew a conclusion on the causal association between exposures and outcomes. We were sincerely appreciated the authors of studies mentioned above for their kindness and generosity with their open dataset so that we can download their reference data.

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Conflicts of interest

The authors declared no conflicts of interest.

Availability of data and material:

Besides the selected SNPs derived from published articles [dataset 1, 2], we also got access to the open database website searching for genetic statistics of diseases outcomes. The data underlying this article are available in UKBB listed as followed.

https://www.dropbox.com/s/uirk8rmdhmyana7/20001_1041.gwas.imputed_v3.female.tsv.bgz?dl=0 for cervical cancer.

https://www.dropbox.com/s/a6hxa2xh6ke726y/20001_1040.gwas.imputed_v3.female.tsv.bgz?dl=0 for endometrial cancer.

https://www.dropbox.com/s/dkgr3ejcxza9f7o/20001_1039.gwas.imputed_v3.female.tsv.bgz?dl=0 for ovarian cancer.

https://www.dropbox.com/s/4g7f8jpq3dkn6l5/20002_1402.gwas.imputed_v3.female.tsv.bgz?dl=0 for endometriosis.

https://www.dropbox.com/s/hvpig2a6n4fpsy2/20002_1350.gwas.imputed_v3.female.tsv.bgz?dl=0 for PCOS.

[dataset1]: 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

[dataset2]: 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

Authors' contributions:

Yi-Shang Yan collected data and wrote the manuscript. Zihao Qu analyzed and revised the data. Pingping Lv and He-feng Huang designed the article.

Ethics approval and consent to participate and publication:

Ethical approval for this study and written informed consent from the participants of the study were not required in accordance with local legislation and national guidelines.

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Tables

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)	5.48×10^{-13}
CADM1	rs12286929	11:115022404	G	0.022(0.003)	1.31×10^{-12}
TCF7L2	rs7903146	10:114758349	C	0.023(0.003)	1.31×10^{-12}
STXBP6	rs10132280	14:25928179	C	0.023(0.003)	1.14×10^{-11}
HIF1AN	rs17094222	10:102395440	C	0.025(0.004)	5.94×10^{-11}
ERBB4	rs7599312	2:213413231	G	0.022(0.003)	1.17×10^{-10}
FHIT	rs2365389	3:61236462	C	0.02(0.003)	1.63×10^{-10}
NAV1	rs2820292	1:201784287	C	0.02(0.003)	1.83×10^{-10}
PRKD1	rs12885454	14:29736838	C	0.021(0.003)	1.94×10^{-10}
RASA2	rs16851483	3:141275436	T	0.048(0.008)	3.55×10^{-10}
HIP1	rs1167827	7:75163169	G	0.02(0.003)	6.33×10^{-10}
NLRC3	rs758747	16:3627358	T	0.023(0.004)	7.47×10^{-10}
TLR4	rs1928295	9:120378483	T	0.019(0.003)	7.91×10^{-10}
KAT8	rs9925964	16:31129895	A	0.019(0.003)	8.11×10^{-10}
KCNK3	rs11126666	2:26928811	A	0.021(0.003)	1.33×10^{-9}
SBK1	rs2650492	16:28333411	A	0.021(0.004)	1.92×10^{-9}
RARB	rs6804842	3:25106437	G	0.019(0.003)	2.48×10^{-9}
CCDC171	rs4740619	9:15634326	T	0.018(0.003)	4.56×10^{-9}
PRKN	rs13191362	6:163033350	A	0.028(0.005)	7.34×10^{-9}
DMXL2	rs3736485	15:51748610	A	0.018(0.003)	7.41×10^{-9}
SCARB2	rs17001654	4:77129568	G	0.031(0.005)	7.76×10^{-9}
NT5CA	rs11191560	10:104869038	C	0.031(0.005)	8.45×10^{-9}
UBE2E3	rs1528435	2:181550962	T	0.018(0.003)	1.20×10^{-8}
RABEP1	rs1000940	17:5283252	G	0.019(0.003)	

					1.28×10^{-8}
	rs2033529	6:40348653	G	0.019(0.003)	1.39×10^{-8}
FOXO3	rs9400239	6:108977663	C	0.019(0.003)	1.61×10^{-8}
LMX1B	rs10733682	9:129460914	A	0.017(0.003)	1.83×10^{-8}
EHBP1	rs11688816	2:63053048	G	0.017(0.003)	1.89×10^{-8}
CLIP1	rs11057405	12:122781897	G	0.031(0.006)	2.02×10^{-8}
HHIP	rs11727676	4:145659064	T	0.036(0.006)	2.55×10^{-8}
GBE1	rs3849570	3:81792112	A	0.019(0.003)	2.60×10^{-8}
FRRS1L	rs6477694	9:111932342	C	0.017(0.003)	2.67×10^{-8}
GRID1	rs7899106	10:87410904	G	0.04(0.007)	2.96×10^{-8}
HSD17B12	rs2176598	11:43864278	T	0.02(0.004)	2.97×10^{-8}
PMS2L11	rs2245368	7:76608143	C	0.032(0.006)	3.19×10^{-8}
PGPEP1	rs17724992	19:18454825	A	0.019(0.004)	3.42×10^{-8}
GRP	rs7243357	18:56883319	T	0.022(0.004)	3.86×10^{-8}
RP11-120I21.3	rs2033732	8:85079709	C	0.019(0.004)	4.89×10^{-8}
FTO	rs1558902	16:53803574	A	0.082(0.003)	7.51×10^{-153}
MC4R	rs6567160	18:57829135	C	0.056(0.004)	3.53×10^{-53}
TMEM18	rs13021737	2:632348	G	0.06(0.004)	1.11×10^{-50}
NMU	rs10938397	4:45182527	G	0.04(0.003)	3.21×10^{-38}
SEC16B	rs543874	1:177889480	G	0.048(0.004)	2.62×10^{-35}
TFAP2B	rs2207139	6:50845490	G	0.045(0.004)	4.13×10^{-29}
BDAF	rs11030104	11:27684517	A	0.041(0.004)	5.56×10^{-28}
NEGR1	rs3101336	1:72751185	C	0.033(0.003)	2.66×10^{-26}
RP11-70F11.7	rs7138803	12:50247468	A	0.032(0.003)	8.15×10^{-24}
ADCY3	rs10182181	2:25150296	G	0.031(0.003)	8.78×10^{-24}
E7V5	rs1516725	3:185824004	C	0.045(0.005)	

					1.89×10^{-22}
AC134300.1	rs12446632	16:19935389	G	0.04(0.005)	1.48×10^{-18}
QPCTL	rs2287019	19:46202172	C	0.036(0.004)	4.59×10^{-18}
MAP2K5	rs16951275	15:68077168	T	0.031(0.004)	1.91×10^{-17}
MTCH2	rs3817334	11:47650993	T	0.026(0.003)	5.15×10^{-17}
POC5	rs2112347	5:75015242	T	0.026(0.003)	6.19×10^{-17}
FPGT-TNNI3K	rs12566985	1:75002193	G	0.024(0.003)	3.28×10^{-15}
ZC3H4	rs3810291	19:47569003	A	0.028(0.004)	4.81×10^{-15}
NRXN3	rs7141420	14:79899454	T	0.024(0.003)	1.23×10^{-14}
CADM2	rs13078960	3:85807590	G	0.03(0.004)	1.74×10^{-14}
LINGO2	rs10968576	9:28414339	G	0.025(0.003)	6.61×10^{-14}
GNAI3	rs17024393	1:110154688	C	0.066(0.009)	7.03×10^{-14}
OLFM4	rs12429545	13:54102206	A	0.033(0.005)	1.09×10^{-12}
SLC39A8	rs13107325	4:103188709	T	0.048(0.007)	1.83×10^{-12}
EEF1A1P11	rs11165643	1:96924097	T	0.022(0.003)	2.07×10^{-12}
snoU13	rs17405819	8:76806584	T	0.022(0.003)	2.07×10^{-11}
LINC01122	rs1016287	2:59305625	T	0.023(0.003)	2.25×10^{-11}
TRIM66	rs4256980	11:8673939	G	0.021(0.003)	2.90×10^{-11}
DNAJB4	rs12401738	1:78446761	A	0.021(0.003)	1.15×10^{-10}
ILRUN	rs205262	6:34563164	G	0.022(0.004)	1.75×10^{-10}
MTIF3	rs12016871	13:28017782	T	0.03(0.005)	2.29×10^{-10}
RPTOR	rs12940622	17:78615571	G	0.018(0.003)	2.49×10^{-9}
PRKD1	rs11847697	14:30515112	T	0.049(0.008)	3.99×10^{-9}
TOMM40	rs2075650	19:45395619	A	0.026(0.005)	1.25×10^{-8}
LRP1B	rs2121279	2:143043285	T	0.025(0.004)	2.31×10^{-8}
KCTD15	rs29941	19:34309532	G	0.018(0.003)	

					2.41×10^{-8}
NPC1	rs1808579	18:21104888	C	0.017(0.003)	4.17×10^{-8}

Gene = nearest gene to the SNP; EA = effect allele; β = per allele effect on the exposure; SE = standard error; P value = p-value for the genetic association.

Table 2

Characteristics of child BMI-associated SNPs from GWAS

				Association with exposure	
Gene	SNP	Chromosome: Position	EA	β(SE)	P value
GNPDA2	rs13130484	4:45175691	T	0.067(0.007)	1.58×10^{-23}
ADCY3	rs11676272	2:25141538	G	0.068(0.007)	7.12×10^{-23}
TMEM18	rs4854349	2:647861	C	0.09(0.009)	5.41×10^{-22}
SEC16B	rs543874	1:177889480	G	0.077(0.009)	2.20×10^{-19}
FAIM2	rs7132908	12:50263148	A	0.066(0.008)	1.57×10^{-18}
FTO	rs1421085	16:53800954	C	0.059(0.007)	4.53×10^{-16}
OLFM4	rs12429545	13:54102206	A	0.076(0.01)	2.08×10^{-14}
TFAP2B	rs987237	6:50803050	G	0.062(0.009)	1.80×10^{-12}
TNNI3K	rs12041852	1:75003500	G	0.046(0.007)	2.28×10^{-10}
MC4R	rs6567160	18:57829135	C	0.05(0.008)	1.21×10^{-9}
ELP3	rs13253111	8:28061974	A	0.042(0.007)	4.89×10^{-9}
RAB27B	rs8092503	18:52479487	G	0.045(0.008)	8.17×10^{-9}
LMX1B	rs3829849	9:129390800	T	0.041(0.007)	8.81×10^{-9}
ADAM23	rs13387838	2:207281447	A	0.139(0.025)	2.84×10^{-8}
GPR61	rs7550711	1:110082886	T	0.105(0.019)	4.52×10^{-8}

Gene = nearest gene to the SNP; EA = effect allele; β = 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	IVW	0.998	$1.28*10^{-3}$	(0.995,1.000)	$6.57*10^{-2}$
	WM*	0.996	$2.08*10^{-3}$	(0.992,1.000)	**$4.17*10^{-2}$**
	MR-Egger	1.000	$9.12*10^{-5}$	(0.9999,1.0002)	0.51
Endometrial cancer	IVW	1.000	$1.01*10^{-3}$	(0.998,1.002)	0.99
	WM	0.998	$1.65*10^{-3}$	(0.994,1.001)	0.15
	MR-Egger	1.000	$7.28*10^{-5}$	(0.9999,1.0002)	0.35
Ovarian Cancer	IVW	1.000	$8.34*10^{-4}$	(0.999,1.002)	0.66
	WM	1.001	$1.39*10^{-3}$	(0.998,1.003)	0.66
	MR-Egger	1.000	$5.98*10^{-5}$	(0.9999,1.0001)	0.71
Endometriosis	IVW	0.999	$2.12*10^{-3}$	(0.995,1.003)	0.56
	WM	0.999	$3.07*10^{-3}$	(0.993,1.005)	0.67
	MR-Egger	1.000	$1.50*10^{-4}$	(0.9999-1.0005)	0.19
PCOS	IVW***	1.003	$7.40*10^{-4}$	(1.001,1.004)	**$6.83*10^{-5}$**
	WM*	1.003	$1.16*10^{-3}$	(1.000,1.005)	**$2.80*10^{-2}$**
	MR-Egger	1.000	$5.28*10^{-5}$	(0.9999,1.0001)	0.39

CI = confidence interval; P value = p-value of the causal estimate.

Table 4

Inverse-variance weighted method, weighted median approach, MR-Egger analysis for genetic associations between 15 child BMI and indicated diseases

Disease traits	Analysis method	effect	Standard Error	95%CI	P value
Cervical Cancer	IVW	0.998	$1.43*10^{-3}$	(0.995,1.001)	0.12
	WM	0.996	$1.93*10^{-3}$	(0.993,1.000)	0.053
	MR-Egger	1.000	$3.50*10^{-4}$	(0.9996,1.0009)	0.49
Endometrial Cancer	IVW	0.998	$1.30*10^{-3}$	(0.996,1.001)	0.24
	WM	0.997	$1.54*10^{-3}$	(0.994,1.000)	0.08
	MR-Egger	1.000	$3.22*10^{-4}$	(0.9994,1.0006)	0.97
Ovarian Cancer	IVW	1.000	$8.94*10^{-4}$	(0.998,1.002)	0.96
	WM	1.000	$1.24*10^{-3}$	(0.998,1.003)	0.83
	MR-Egger	1.000	$2.14*10^{-4}$	(0.9996,1.0005)	0.82
Endometriosis	IVW*	0.995	$1.99*10^{-3}$	(0.991,0.999)	**$1.25*10^{-2}$**
	WM	0.996	$2.64*10^{-3}$	(0.991,1.001)	0.11
	MR-Egger	1.000	$4.94*10^{-4}$	(0.9990,1.0009)	0.89
PCOS	IVW***	1.003	$8.01*10^{-4}$	(1.001,1.004)	**$9.14*10^{-4}$**
	WM	1.002	$1.06*10^{-3}$	(1.000,1.004)	0.12
	MR-Egger	1.000	$1.79*10^{-4}$	(1.0000,1.0007)	$8.37*10^{-2}$

CI = confidence interval; P value = p-value of the causal estimate.

Figures

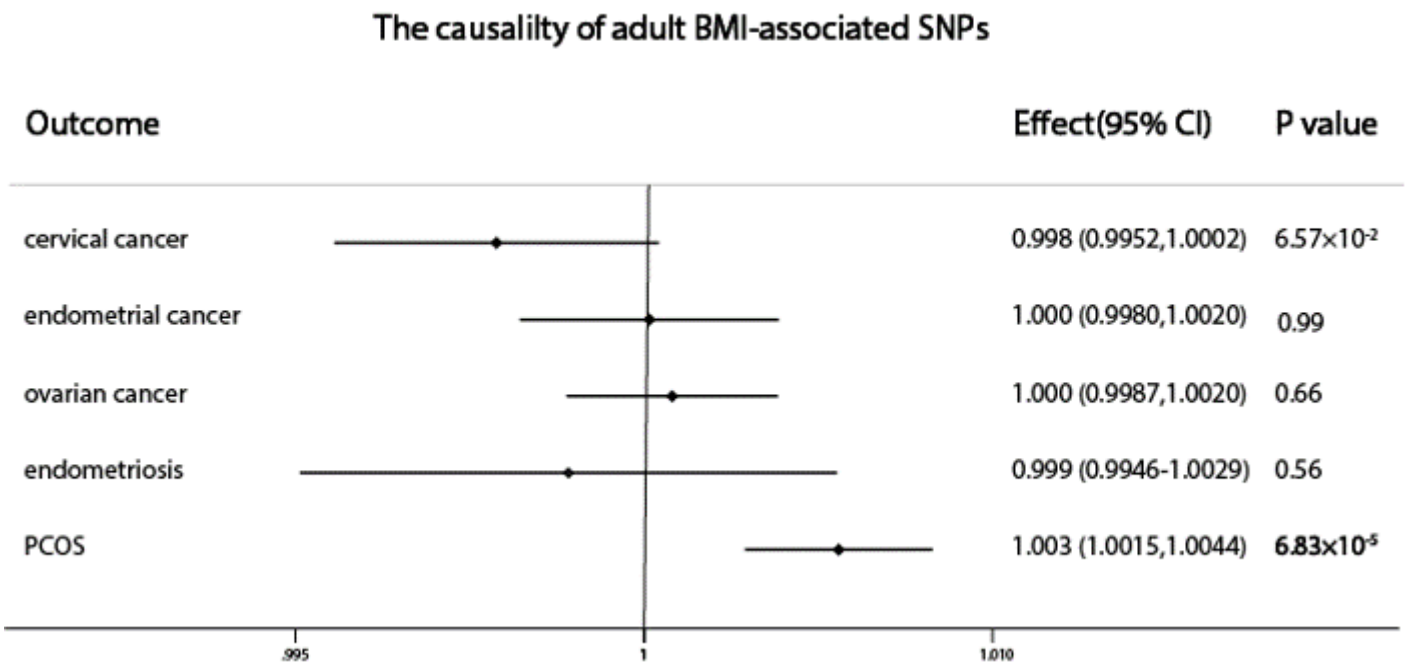

Figure 1

Causal effects of adult BMI on the risk of indicated diseases. The estimated effects, 95% confidence intervals and p-values of associations were contained. Effect = the combined causal effect; CI = confidence interval; P value = p-value of the causal estimate.

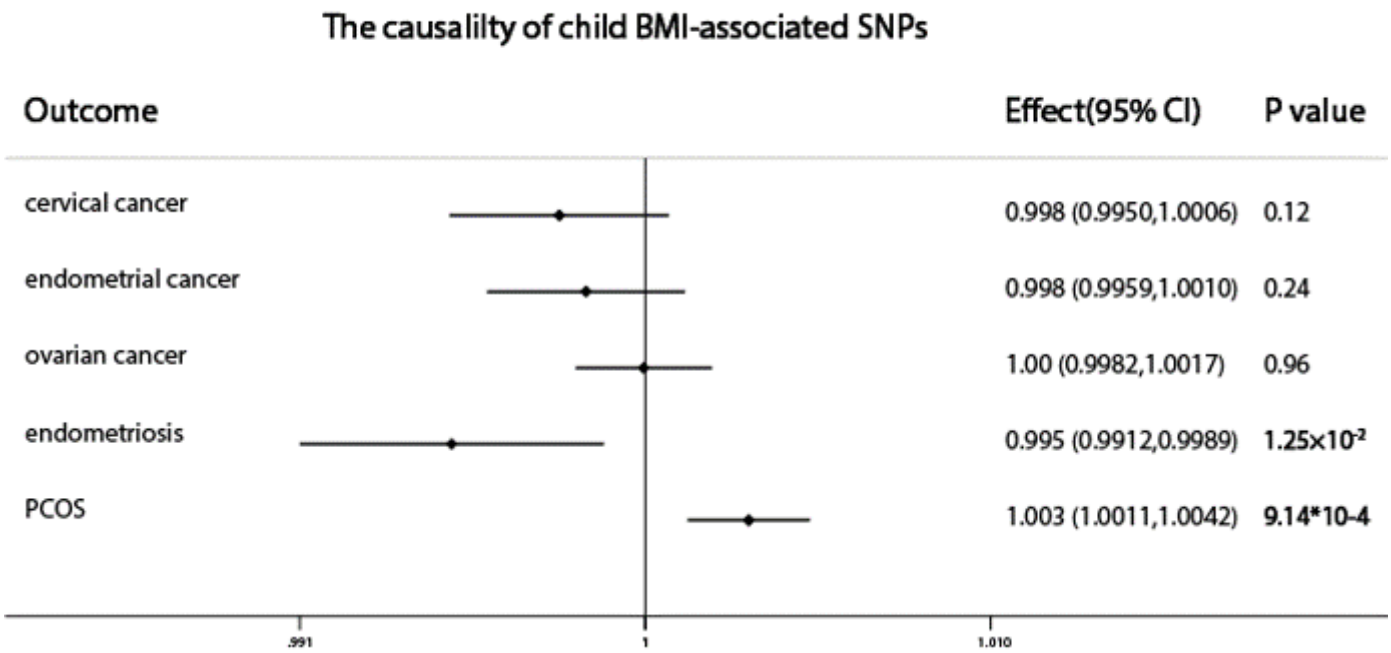

Figure 2

Causal effects of child BMI on the risk of indicated diseases. The estimated effects, 95% confidence intervals and p-values of associations were contained. Effect = the combined causal effect; CI = confidence interval; P value = p-value of the causal estimate.

Supplementary Files

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- SupplementaryMaterials.docx