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Association between childhood adiposity and gynecologic cancers: a mendelian randomization analysis

Mengyue Zhu[2†], Yuchen Zhang[2†], Xiangxiang Bao[4†], Haiyan Zhu[1*] and Wei Jin[3*]

Abstract

Purpose The causal relationship between childhood adiposity and gynecologic cancers remains unclear. We performed a two-sample Mendelian randomization (MR) study to elucidate the association between childhood adiposity and the risk of gynecologic cancers.

Methods The three distinct indicators of childhood adiposity that constitute the exposures were childhood body mass index (CBMI), childhood body size at age 10 (CBS-10) and childhood obesity (COBE). In tandem, the study scrutinized the outcomes encompassing gynecologic cancers, including ovarian cancer (OC), endometrial cancer (EC), cervical cancer (CC) and their subtypes.

Results The results of the inverse variance weighted (IVW) method suggested that CBMI was positively associated with OC (OR = 1.219, 95% CI, 1.084–1.370, q-value = 9.45E-04), EC (OR = 1.417, 95% CI, 1.272–1.702, q-value = 2.04E-07) and some of their subgroups. There were positive association between CBS-10 and invasive mucinous ovarian cancer (IMOC) (OR = 1.923, 95% CI, 1.184–3.125, q-value = 0.008), EC (OR = 1.727, 95% CI, 1.396–2.137, q-value = 4.80E-07) and its subtypes as indicated by IVW. And it is suggested by IVW that COBE was positively associated with EC (OR = 1.088, 95% CI, 1.019–1.163, q-value = 0.012). Additionally, there was no association between CBMI, CBS-10 and COBE and the risk of CC.

Conclusions Overall, this study indicates that childhood adiposity is causally associated with ovarian and endometrial cancers at the genetic level, but childhood adiposity is not causally associated with cervical cancer.

Keywords Childhood adiposity, Ovarian cancer, Endometrial cancer, Cervical cancer, Two-sample mendelian randomization analysis

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Introduction

Ovarian cancer, endometrial cancer, and cervical cancers are three major gynecological malignancies that seriously endanger women's reproductive and general health. Ovarian cancer (OC) has the highest mortality rate among gynecological cancers [1] and ranks seventh in the global incidence of malignant tumors in women. Endometrial cancer (EC) is the sixth most common cancer in women and ranks fifteenth globally [1]. Cervical cancer (CC) is the fourth most commonly diagnosed cancer, also ranks fourth in terms of cancer-related death among women [1]. Given the high rates of morbidity and mortality linked to these three main gynecological cancers, a thorough study of the variables influencing their development is crucial.

Obesity has become a prevalent global health concern, with numerous recent studies highlighting its correlation with ovarian, endometrial, and cervical cancers. Various observational studies have consistently demonstrated a heightened risk of developing these cancers in individuals with a high body mass index (BMI) or obesity [2, 3]. Additionally, prior research has indicated that obese patients diagnosed with ovarian, endometrial, and cervical cancers typically have a poorer prognosis compared to those of normal weight [4–6]. Moreover, weight loss has the potential to reduce the incidence and mortality of ovarian, endometrial, and cervical cancers [6–8]. The escalating prevalence of obesity globally has led to an increasing concerns about childhood adiposity [9]. Childhood adiposity is considered to be one of the causative factors in the development of several tumors, and childhood adiposity escalates the risk of diseases such as leukemia, Hodgkin's disease, colorectal cancer and breast cancer [10, 11]. Several observational studies have investigated the potential link between childhood adiposity and gynecologic cancers [12, 13]. However, establishing a conclusive association between childhood adiposity and gynecologic cancers is complicated by potential confounding variables and the possibility of reverse causality. Factors such as genetic predisposition, environmental influences, and lifestyle factors [14] may blur the lines and thus require careful consideration in drawing robust conclusions.

Mendelian randomization (MR) aims to elucidate the causal relationships between exposure factors and disease outcomes, similar to randomized clinical trials (RCTs) [15]. MR holds several distinct advantages over observational epidemiology. Firstly, MR partially mitigates the bias stemming from reverse causality, even though complete avoidance remains elusive [16]. Secondly, MR studies exhibit robustness against prevalent confounders in behavior, physiology, and socioeconomic factors, owing to the random allocation of alleles during meiosis. This trait bolsters the reliability of findings concluded by MR. Thirdly, genetic variants, being accurately measured and reported, are less prone to bias and errors in most cases. This facet proves particularly valuable when assessing risk factors with enduring effects [17].

The primary aim of this research is to investigate the potential causal association between childhood adiposity and gynecologic cancers through the utilization of Mendelian randomization (MR) methodology. Through this investigation, the study aims to provide new empirical evidence and strategic viewpoints that may enhance the academic discussion and practical approaches in the field of gynecologic cancers prevention and treatment.

Materials and methods

Study design

This study rested upon the foundation of summary data derived from a genome-wide association study (GWAS), with identified Single Nucleotide Polymorphisms (SNPs) serving as instrumental variables for Mendelian randomization (MR) analysis. The primary objective of this study was to elucidate the genetic causal relationships between the specified exposures and outcomes. The three distinct indicators of childhood adiposity that constituted the exposures in this study were childhood body mass index (CBMI), childhood body size at age 10 (CBS-10), and childhood obesity (COBE). In tandem, the study scrutinized the outcomes encompassing gynecologic cancers, including ovarian cancer (OC), endometrial cancer (EC), and cervical cancer (CC), alongside their respective subtypes. A two-sample Mendelian randomization analysis method was employed to systematically evaluate the discrete associations between each exposure and each outcome. This study rigorously adhered to the fundamental tenets of Mendelian randomization (MR) analysis, including the three pivotal assumptions: (1) the relevance assumption, as underscored by the strong correlation between the chosen instrumental variables and exposures ($P < 5 \times 10^{-8}$ and F statistic > 10); (2) the independence assumption, ensuring the absence of associations between confounding factors influencing the relationship between exposures and outcomes, and the selected instrumental variables; (3) the exclusion assumption, elucidating that the selected instrumental variables exclusively impacted the outcome via exposure pathways, rather than alternative routes (Fig. 1). It was noteworthy that the initial studies diligently obtained ethical permissions and secured written informed consent. Furthermore, all pertinent data featured in this study were made readily accessible through online resources.

GWAS summary data on exposures

The IEU OpenGWAS database (https://gwas.mrcieu.ac.uk/) served as the source of GWAS summary data for the exposures under scrutiny. Specifically, GWAS

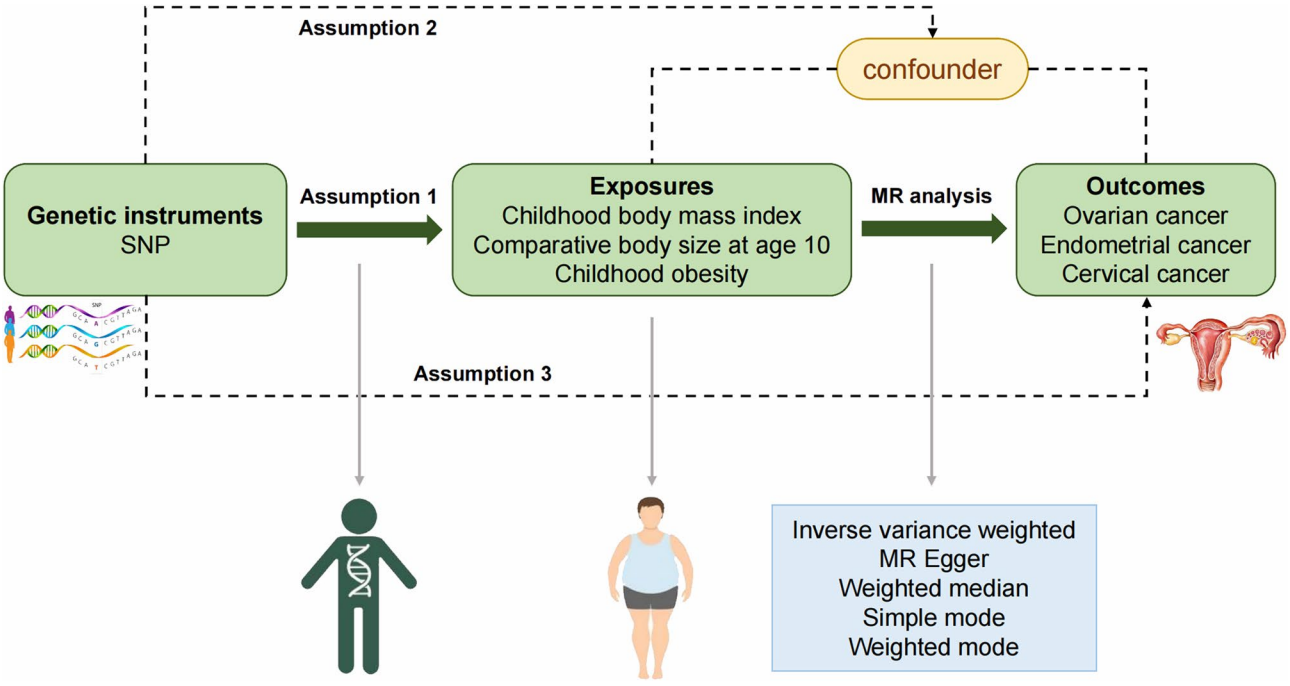

Fig. 1 Overview of the study design. SNP, single nucleotide polymorphisms; MR, Mendelian randomization

summary data for childhood body mass index (CBMI) were derived from the comprehensive GWAS meta-analysis of CBMI that was undertaken among a cohort of 61,111 children of European ancestry, aged between 2 and 10 years [18]. Subsequently, a GWAS encompassing 454,718 samples yielded the genetic associations pertaining to comparative body size at age 10 (CBS-10). CBS-10 data was gleaned from self-reported responses to a questionnaire, which proffered choices of 'thinner', 'plumper', or 'about average' relative to average body size. Notably, this assessment served to infer adiposity at an earlier chronological juncture. The seminal GWAS summary statistics of Childhood Obesity Genetic Effects (COBE) were procured from the Early Growth Genetics (EGG) Consortium. This dataset contained 13,848 samples, encompassing both male and female subjects [19]. Of pivotal significance, body mass index (BMI) stood as the most widely employed and elementary metric for assessing adiposity. This objective measure was predicated on height and weight, furnishing a direct gauge to ascertain whether a child veers into the realm of being overweight or obese. Specifically, childhood obesity was ascribed to those at or surpassing the 95th percentile threshold of BMI within their age bracket. CBS-10 was based on self-reported subjective perceptions and could indirectly show the difference in weight between children and their peers. We analyzed the association between childhood adiposity and gynecologic cancers by two different dimensions of obesity, CBMI and COBE which were calculated from weight and height and CBS-10 obtained by direct observational comparisons.

GWAS summary data on outcomes

From the Ovarian Cancer Association Consortium using an Illumina Custom Infinium array (OncoArray) came genetic associations with OC including 25,509 epithelial OC cases and 40,941 controls [20]. All participants had European descent. The OC cases were further divided into five major histological subtypes: high-grade serous OC (HGSOC, 13,037 cases), low-grade serous OC (LGSOC, 1012 cases), invasive mucinous OC (IMOC, 1417 cases), endometrioid OC (EOC, 2810 cases) and clear cell OC (CCOC, 1366 cases). From the Endometrial Cancer Association Consortium (ECAC) we obtained the GWAS summary statistics of EC [21]. The study had 121,885 participants of European ancestry, which included 12,906 EC cases and 108,979 controls. These EC cases were further divided into endometrial cancer of endometrioid histology (EEC) (8758 cases) and endometrial cancer with non-endometrioid histology (ENC) (1230 cases) according to the histological subtype of endometrial cancer [21, 22]. By using the first nine principal components, this GWAS controlled for potential population stratification. It also controlled for study-specific covariates and principal components [21]. The GWAS summary statistics of cervical cancer comprised 199,086 female participants of European ancestry, which included 563 cases and 198,523 controls. Detailed

information on the GWAS data included in this study is presented in Table 1 and Supplement 2.

Selection of instrumental variables

We screened qualified SNPs as instrumental variables through a series of strict quality controls to ensure the robustness of MR analysis results. (1) First, we selected SNPs associated with exposures at a threshold of $P < 5 \times 10^{-8}$. We firstly identified six single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) representing childhood obesity for conducting Mendelian Randomization (MR) analysis. To meet the requirement of at least 10 IVs in MR studies, we extracted a total of 15 SNPs by using a significance threshold of $p < 5 \times 10^{-6}$ [23]. (2) Second, to avoid the linkage disequilibrium, all SNPs were clumped under a strict clump window ($r^2 < 0.001$, clumping distance = 10,000 kb) [24]. (3) Third, the instrumental variables did not contain the SNPs that were linked with outcomes ($P < 5 \times 10^{-8}$). (4) Fourth, we chose SNPs with an F statistic > 10 as instrumental variables to satisfy the strong association with exposure. F statistics were computed using the formula: $F = R^2(N - K - 1)/K(1 - R^2)$. R^2 was calculated using the formula: $R^2 = 2 * MAF * (1 - MAF) * Beta^2$ [24]. (5) Fifth, to ensure that the effect of SNPs on outcomes matched the same allele as that affecting exposures, palindromic SNPs with intermediate allele frequencies were removed [25].

MR analysis

We performed two-sample MR analyses of outcomes and exposures using the TwoSampleMR package of R (version 4.2.1). The primary approach utilized was the random effects IVW, with supplementary methods including MR Egger, weighted median, simple mode, and weighted mode. The random effects IVW dominated the MR analysis results [26]. The random-effects IVW enabled each SNP to have different mean effects and could disregard the intercept term and weight the outcome variance by its inverse unlike most other fitting methods. The MR Egger method could evaluate whether genetic variants have pleiotropic effects on the outcomes. Weighted median analysis was an important method of estimating the causal effect if more than 50% of SNPs satisfy the "no horizontal pleiotropy" assumption. The simple mode was a model-based estimation method that offers the robustness for pleiotropy. The weighted mode was sensitive to the challenging bandwidth selection for mode estimation. And $p < 0.05$ indicates the causal association of the outcomes with exposures.

Sensitivity analysis

We used the Cochran's Q statistic of the MR-IVW method, and Rucker's Q statistic of the MR Egger method to assess the heterogeneity of MR analysis, where $P > 0.05$ implies no heterogeneity [27]. Moreover, we applied MR pleiotropic residual sum and outliers (MR-PRESSO) to identify and adjust for any outliers that might indicate pleiotropic bias in all reported results, where $P > 0.05$ implies no horizontal pleiotropy [28]. We removed the

Table 1 Summary information for the genetic data used in the study

exposure	Consortium	Sample size	Population	Sex	PMID	Author		
Childhood body mass index	NA	39,620	European	NA	33,045,005	Vogelezang S		
Comparative body size at age 10	MRC-IEU	454,718	European	Males and Females	NA	Ben Elsworth		
Childhood obesity	EGG	13,848	European	Males and Females	22,484,627	Bradfield JP		
outcome	**Consortium**	**Sample size**	**Population**	**Sex**	**PMID**	**Author**	**ncase**	**ncontrol**
Ovarian cancer	OCAC	66,450	European	Females	28,346,442	Phelan	25,509	40,941
High grade serous ovarian cancer	OCAC	53,978	European	Females	28,346,442	Phelan	13,037	40,941
Endometrioid ovarian cancer	OCAC	43,751	European	Females	28,346,442	Phelan	2,810	40,941
Invasive mucinous ovarian cancer	OCAC	42,358	European	Females	28,346,442	Phelan	1,417	40,941
Clear cell ovarian cancer	OCAC	42,307	European	Females	28,346,442	Phelan	1,366	40,941
Low grade serous ovarian cancer	OCAC	41,953	European	Females	28,346,442	Phelan	1,012	40,941
Endometrial cancer	ECAC	121,885	European	NA	30,093,612	O'Mara TA	12,906	108,979
Endometrial cancer (endometrioid histology)	ECAC	54,884	European	NA	30,093,612	O'Mara TA	8,758	46,126
Endometrial cancer (Non-endometrioid histology)	ECAC	36,677	European	NA	30,093,612	O'Mara TA	1,230	35,447
cervical cancer	NA	199,086	European	Females	NA	Burrows	563	198,523

OCAC Ovarian Cancer Association Consortium, *MRC-IEU* MRC Integrative Epidemiology Unit, *EGG* Early Growth Genetics, *ECAC* Endometrial Cancer Association Consortium

outliers if they were detected and performed a second round of MR analysis. We also investigated whether a single SNP influenced the genetic causal relationship between outcomes and exposures using leave-one-out analysis. To avoid false positives or false negatives as much as possible, if a single SNP affected the MR analysis results, we conducted a second round of genetic assessment after removing the single SNP that influenced the MR analysis results [29]. We performed sensitivity analyses using the TwoSampleMR and MRPRESSO packages of R (version 4.2.1).

Results

MR analysis of CBMI and gynecologic cancers

We found that childhood body mass index (CBMI) was positively associated with the risk of OC by IVW method (OR = 1.219, 95% CI, 1.084–1.370, q-value = 9.45E-04) (Figs. 2 and 3A). The Cochran's Q test and Rucker's Q test indicated that there was no heterogeneity (Table 2). MR Egger intercept test and global test of MR-PRESSO suggested no horizontal pleiotropy. The distortion test of MR-PRESSO analysis indicated that there were no outliers in the MR analysis of CBMI and OC (Table 2). Moreover, the leave-one-out analysis showed that no single SNP drove the MR analysis of childhood BMI and OC (Supplement 1). Furthermore, we also investigated the causal relationship between CBMI and the histologic subtypes of OC and detected a positive association between CBMI and the risk of EOC, IMOC and LGSOC using the IVW method (Figs. 2 and 3B-D). However, we did not find any causal associations between CBMI and HGSOC or CCOC (Fig. 2). There was no heterogeneity for any histologic subtypes of OC (Table 2). It is suggested that there was no horizontal pleiotropy for instrument SNPs of EOC, IMOC, CCOC and LGSOC, but there was pleiotropy for instrument SNPs of HGSOC (Table 2). No single SNP drove the results indicated by the leave-one-out analyses (Supplement 1).

We found a causal effect of CBMI on EC (OR = 1.417, 95% CI, 1.272–1.702, q-value = 2.04E-07) by IVW method. Furthermore, we also investigated the causal relationship between CBMI and the histologic subtypes of EC including EEC (OR = 1.493, 95% CI, 1.268–1.759, q-value = 1.55E-06) and ENC (OR = 1.716, 95% CI, 1.135–2.596, q-value = 0.010) by IVW method (Figs. 2 and 3E-G). There was no heterogeneity or pleiotropy (Table 2). Moreover, no single SNP drove the results, as revealed by the leave-one-out analyses (Supplement 1).

We found no association between CBMI and the risk of CC (OR = 0.999, 95% CI, 0.998–1.001, q-value = 0.471) by IVW method (Fig. 2). In addition, we did not find any heterogeneity or horizontal pleiotropy (Table 2). Also, the leave-one-out analyses showed that no single SNP drove the results (Supplement 1).

Additionally, other MR methods to examine the relationship between CBMI with each outcome were used as well (Table 3).

MR analysis of CBS-10 and gynecologic cancers

We found that there was no potential causal association between CBS-10 and OC risk using the IVW method (OR = 1.108, 95% CI, 0.942–1.305, q-value = 0.216) (Fig. 2). No heterogeneity and outliers were found (Table 2) but horizontal pleiotropy was detected by MR Egger intercept test ($P = 0.010$) (Table 2). Furthermore, the result of IVW indicated a positive association between CBS-10 and IMOC risk (OR = 1.923, 95% CI, 1.184–3.125, q-value = 0.008) (Figs. 2 and 3H), but no causal associations between CBS-10 and HGSOC, EOC, CCOC or LGSOC were discovered (Fig. 2). No heterogeneity except for HGSOC ($P = 0.047$) or outliers were found (Table 2) and no horizontal pleiotropy expect for IMOC ($P = 0.048$) was detected (Table 2). The leave-one-out analyses revealed that no single SNP drove the results (Supplement 1).

A potential positive association of CBS-10 with EC (OR = 1.727, 95% CI, 1.396–2.137, q-value = 4.80E-07), as well as with its subgroups including EEC (OR = 1.940, 95% CI, 1.516–2.482, q-value = 1.40E-07) and ENC (OR = 1.877, 95% CI, 1.139–3.095, q-value = 0.014) was suggested by the results of IVW method (Figs. 2 and 3K). For ENC, no heterogeneity or pleiotropy were detected (Table 2). However, heterogeneity and pleiotropy were detected in the MR analysis for EC and EEC (Table 2). Therefore, for EC and EEC, the reanalysis was conducted after removing the outliers (Table 2). After removal of outliers, the positive association of CBS-10 with EC (OR = 1.868, 95% CI, 1.534–2.274, q-value = 4.85E-10) and EEC (OR = 2.084, 95% CI, 1.653–2.628, q-value = 1.40E-07) remained unchanged (Figs. 2 and 3I-J). And no single SNP drove the results as revealed by the leave-one-out analyses (Supplement 1).

No association of CBS-10 with the risk of CC (OR = 1.000, 95% CI, 0.998–1.002, q-value = 0.927) was found by the IVW method (Fig. 2). No heterogeneity or horizontal pleiotropy were detected using Cochran's Q test, MR-Egger intercept test and MR-PRESSO (Table 2). The leave-one-out analyses revealed that no single SNP drove the results (Supplement 1).

We also used other MR methods to examine the relationship between CBS-10 with each outcome (Table 3).

MR analysis of childhood obesity and gynecologic cancers

We discovered that there was no association of COBE with the risk of OC or any histologic subtypes (Fig. 2). Heterogeneity and pleiotropy were not detected (Table 2). The MR analysis of COBE and OC was not

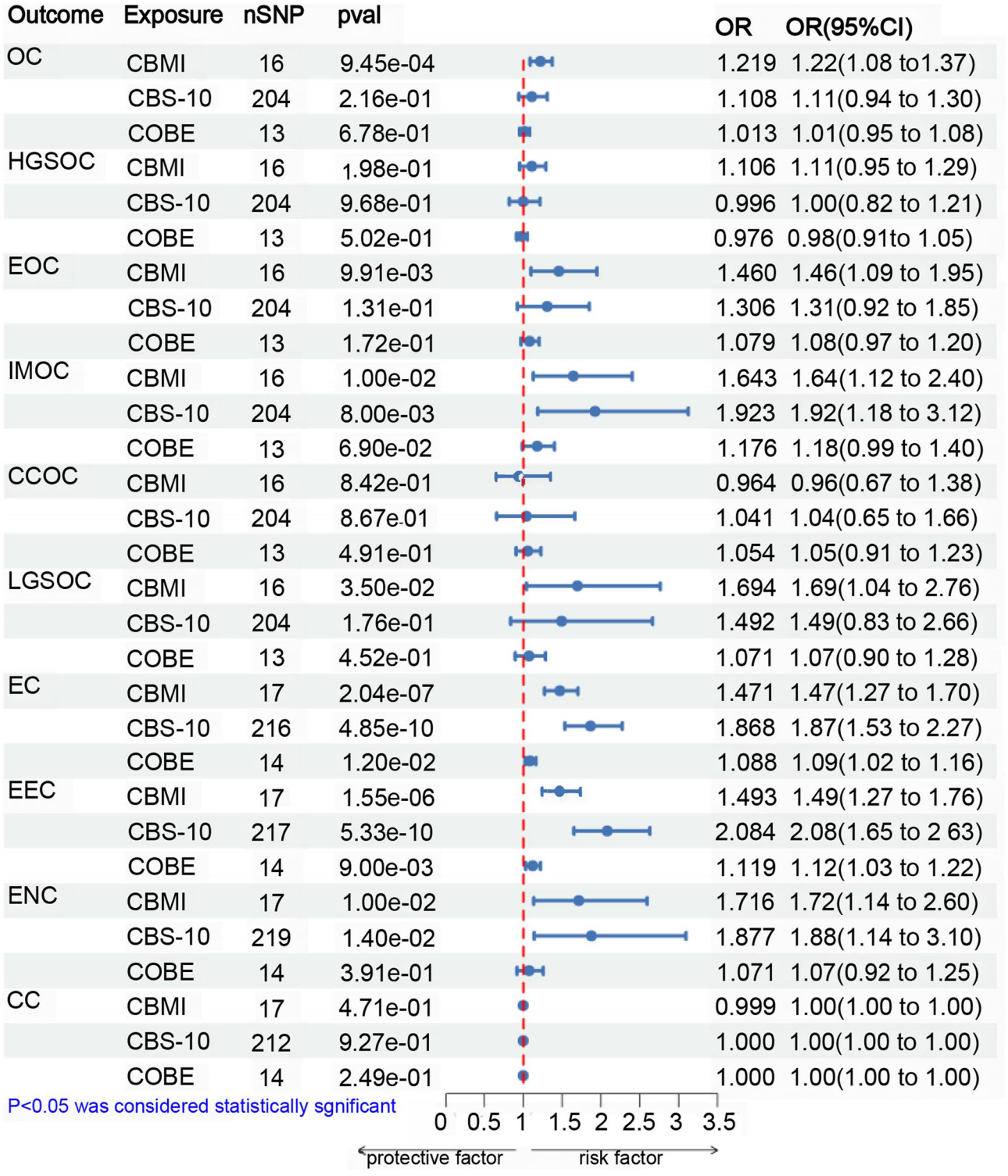

Fig. 2 Forest plot of Mendelian randomization results. OR, odds ratio; CI, confidence interval; nSNP, number of single nucleotide polymorphisms; CBMI, childhood body mass index; CBS-10, comparative body size at age 10; COBE, childhood obesity; OC, ovarian cancer; CCOC, clear cell ovarian cancer; EOC, endometrioid ovarian cancer; IMOC, invasive mucinous ovarian cancer; HGSOC, high-grade serous ovarian cancer; LGSOC, low-grade serous ovarian cancer; EC, endometrial cancer; EEC, Endometrial cancer (endometrioid histology); ENC, Endometrial cancer (Non-endometrioid histology); CC, cervical cancer

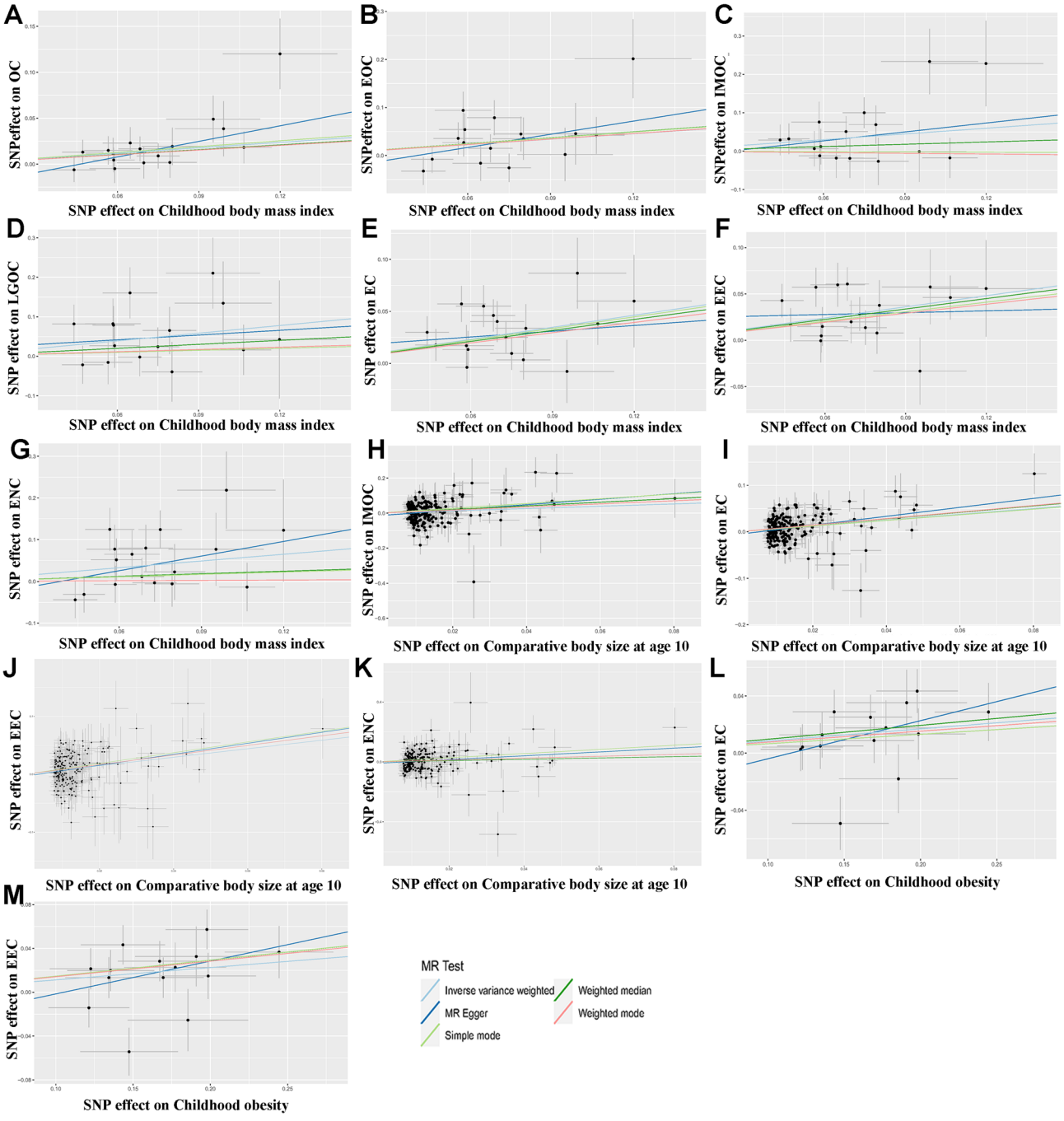

Fig. 3 Scatter plot of the causal relationships between exposures and outcomes at different sites using different MR methods. **A** Causal estimates for childhood body mass index (CBMI) on ovarian cancer (OC). **B** Causal estimates for CBMI on endometrioid ovarian cancer (EOC). **C** Causal estimates for CBMI on invasive mucinous ovarian cancer (IMOC). **D** Causal estimates for CBMI on low grade serous ovarian cancer (LGSOC). **E** Causal estimates for CBMI on endometrial cancer (EC). **F** Causal estimates for CBMI on endometrial cancer (endometrioid histology) (EEC). **G** Causal estimates for CBMI on endometrial cancer (Non-endometrioid histology) (ENC). **H** Causal estimates for comparative body size at age 10 (CBS-10) on IMOC. **I** Causal estimates for CBS-10 on EC. **J** Causal estimates for CBS-10 on EEC. **K** Causal estimates for CBS-10 on ENC. **L** Causal estimates for childhood obesity (COBE) on EC. **M** Causal estimates for COBE on EEC. The slope of each line corresponds to the causal estimates for each method. Individual SNP effect on the outcome (point and vertical line) against its effect on the exposure (point and horizontal line) is delineated in the background

Table 2 Sensitivity analysis of the MR analysis results of exposures and outcomes

Exposure	Outcome	Heterogeneity Test		Pleiotropy test	MR-PRESSO	
		Cochran's Q Test (P value)	Rucker's Q Test (P value)	Egger Intercept (P value)	Distortion Test	Global Test
		IVW	MR-Egger	MR-Egger	Outliers	*P* value
Childhood body mass index	OC	0.618	0.741	0.136	NA	0.681
	HGSOC	0.258	0.511	0.044	NA	0.305
	EOC	0.203	0.202	0.366	NA	0.219
	IMOC	0.282	0.232	0.724	NA	0.282
	CCOC	0.771	0.716	0.726	NA	0.761
	LGSOC	0.177	0.136	0.833	NA	0.215
	EC	0.193	0.170	0.525	NA	0.220
	EEC	0.284	0.285	0.342	NA	0.329
	ENC	0.211	0.191	0.477	NA	0.224
	CC	0.925	0.936	0.331	NA	0.907
Comparative body size at age 10	OC	0.074	0.126	0.010	NA	0.080
	HGSOC	0.047	0.053	0.145	NA	0.065
	EOC	0.146	0.168	0.095	NA	0.131
	IMOC	0.085	0.112	0.048	NA	0.094
	CCOC	0.398	0.425	0.123	NA	0.361
	LGSOC	0.133	0.122	0.922	NA	0.148
	EC	0.001	0.001	0.070	rs1611719 rs3129962 rs3131934 rs818902	0.002
	EEC	0.001	0.001	0.337	rs1611719 rs3129962 rs3131934	< 0.001
	ENC	0.270	0.284	0.178	NA	0.261
	CC	0.883	0.907	0.065	NA	0.908
Childhood obesity	OC	0.093	0.228	0.080	NA	0.142
	HGSOC	0.123	0.201	0.151	NA	0.183
	EOC	0.408	0.352	0.596	NA	0.443
	IMOC	0.158	0.128	0.605	NA	0.192
	CCOC	0.891	0.910	0.326	NA	0.909
	LGSOC	0.502	0.501	0.342	NA	0.412
	EC	0.112	0.128	0.296	NA	0.141
	EEC	0.043	0.043	0.404	NA	0.072
	ENC	0.446	0.476	0.261	NA	0.480
	CC	0.919	0.894	0.628	NA	0.949

P >0.05 implies no heterogeneity and horizontal pleiotropy

OC Ovarian cancer, *CCOC* Clear cell ovarian cancer, *EOC* Endometrioid ovarian cancer, *IMOC* Invasive mucinous ovarian cancer, *HGSOC* High-grade serous ovarian cancer, *LGSOC* Low-grade serous ovarian cancer, *EC* Endometrial cancer, *EEC* Endometrial cancer (endometrioid histology), *ENC* Endometrial cancer (Non-endometrioid histology), *CC* Cervical cancer

driven by a single SNP, as indicated by the leave-one-out analysis (Supplement 1).

A potential positive association of COBE with EC (OR = 1.088, 95% CI, 1.019–1.163, q-value = 0.012) and EEC (OR = 1.119, 95% CI, 1.028–1.218, q-value = 0.009) was suggested by the results of IVW method (Fig. 2). Heterogeneity and pleiotropy were not detected for EC and pleiotropy was also absent for EEC (Table 2). Heterogeneity may have influenced the result for EEC (Table 2). The MR-PRESSO test did not identify any potential outliers. No single SNP drove the results as indicated by the leave-one-out analyses (Supplement 1).

No association of COBE with the risk of CC was indicated by the IVW method (Fig. 2) or other MR methods (Table 3). No heterogeneity or horizontal pleiotropy were detected using Cochran's Q test, MR-Egger intercept test or MR-PRESSO (Table 2). No single SNP drove the results, as revealed by the leave-one-out analyses (Supplement 1).

Table 3 Mendelian randomization results of weighted median and MR-Egger methods

			Weighted median				MR-Egger			
exposure	**outcome**	**NSNP**	**pval**	**OR**	**95%LCI**	**95%UCI**	**pval**	**OR**	**95%LCI**	**95%UCI**
Childhood body mass index	OC	16	0.031	1.190	1.016	1.395	0.033	1.761	1.100	2.818
	HGSOC	16	0.259	1.120	0.920	1.364	0.026	2.037	1.165	3.561
	EOC	16	0.022	1.509	1.061	2.146	0.145	2.494	0.782	7.953
	IMOC	16	0.446	1.219	0.732	2.031	0.348	2.171	0.454	10.375
	CCOC	16	0.767	1.076	0.661	1.753	0.698	0.747	0.176	3.166
	LGSOC	16	0.309	1.382	0.741	2.580	0.769	1.365	0.178	10.445
	EC	17	2.42E-04	1.423	1.179	1.718	0.570	1.203	0.645	2.245
	EEC	17	9.14E-04	1.455	1.166	1.816	0.853	1.068	0.537	2.127
	ENC	17	0.482	1.222	0.699	2.138	0.209	3.229	0.561	18.578
	CC	17	0.562	0.999	0.998	1.001	0.433	1.002	0.996	1.008
Comparative body size at age 10	OC	204	0.108	1.248	0.953	1.635	0.004	1.653	1.176	2.323
	HGSOC	204	0.681	1.069	0.778	1.470	0.205	1.308	0.865	1.978
	EOC	204	0.151	1.537	0.854	2.764	0.030	2.268	1.091	4.717
	IMOC	204	0.014	2.822	1.235	6.447	0.003	4.794	1.730	13.284
	CCOC	204	0.205	1.626	0.766	3.450	0.150	2.074	0.772	5.575
	LGSOC	204	0.140	2.054	0.790	5.343	0.470	1.575	0.461	5.381
	EC	216	5.45E-06	2.004	1.485	2.704	8.86E-06	2.626	1.733	3.979
	EEC	217	1.74E-06	2.293	1.632	3.222	2.13E-04	2.581	1.576	4.226
	ENC	219	0.320	1.548	0.655	3.659	0.020	3.595	1.238	10.439
	CC	212	0.735	0.999	0.996	1.003	0.113	0.997	0.993	1.001
Childhood obesity	OC	13	0.113	1.057	0.987	1.131	0.073	1.312	1.003	1.718
	HGSOC	13	0.931	1.004	0.924	1.090	0.201	1.254	0.905	1.738
	EOC	13	0.325	1.078	0.928	1.251	0.435	1.252	0.727	2.155
	IMOC	13	0.077	1.215	0.979	1.507	0.394	1.481	0.622	3.526
	CCOC	13	0.366	1.095	0.900	1.332	0.275	1.530	0.741	3.159
	LGSOC	13	0.305	1.140	0.888	1.464	0.283	1.645	0.693	3.903
	EC	14	0.009	1.102	1.025	1.185	0.142	1.305	0.936	1.819
	EEC	14	0.001	1.158	1.060	1.265	0.199	1.350	0.876	2.079
	ENC	14	0.265	1.130	0.911	1.402	0.210	1.703	0.775	3.743
	CC	14	0.137	0.999	0.999	1.000	0.800	1.000	0.997	1.003

OR Odds ratio, *95%LCI* Lower limit of 95% CI, *95%UCI* Upper limit of 95% CI, *NSNP* Number of single nucleotide polymorphisms, *OC* Ovarian cancer, *CCOC* Clear cell ovarian cancer, *EOC* Endometrioid ovarian cancer, *IMOC* Invasive mucinous ovarian cancer, *HGSOC* High-grade serous ovarian cancer, *LGSOC* Low-grade serous ovarian cancer, *EC* Endometrial cancer, *EEC* Endometrial cancer (endometrioid histology), *ENC* Endometrial cancer (Non-endometrioid histology), *CC* Cervical cancer. And $p < 0.05$ indicates the causal association of the outcomes with exposures

The association between COBE and OC, EC, CC and their subgroups were also investigated by other MR methods (Table 3).

Discussion

Our investigation examined the correlation between childhood adiposity and gynecological cancers by analyzing three indicators of childhood obesity (CBMI, CBS-10, COBE) in relation to three major gynecological cancers (ovarian cancer, endometrial cancer, cervical cancer). Our findings revealed a positive association between childhood adiposity and ovarian cancer (OC), including its histological subtypes—EOC, IMOC, and LGSOC. However, we did not establish a potential causal relationship between childhood adiposity and CCOC and HGSOC. Additionally, our research findings indicate a potential positive relationship between childhood adiposity and endometrial cancer (EC), encompassing its distinct subtypes of EEC and ENC. Conversely, our analysis did not reveal any potential correlation between CBMI, CBS-10, and COBE and cervical cancer (CC).

Several previous studies have reported that the development of ovarian cancer was association with childhood overweight, with variations across histological subtypes. A recent meta-analysis suggests that obesity in children and adolescents is a risk factor for ovarian cancer, and that the risk increases with increasing BMI [30]. Consistent with previous studies, our results suggested that childhood adiposity is positively associated with the risk of ovarian cancer. Interestingly, we further analyzed the causal relationship between different histological subtypes of ovarian cancer and childhood adiposity, and we found that childhood adiposity was potentially causally associated with EOC, IMOC, and LGSOC but not with CCOC and HGSOC. Consistent with our conclusions, the study by Aarestrup et al. also indicated that the girls

with overweight had increased risks of ovarian cancer overall, mucinous, endometrioid and clear cell ovarian cancers, but not serous and other ovarian cancers [31]. Our research adds to the current body of evidence regarding the correlation between childhood adiposity and the vulnerability to ovarian cancers, thereby enhancing the understanding of this relationship.

Our current study demonstrated a notable positive correlation between childhood adiposity and endometrial cancer (EC), including its specific subtypes—EEC and ENC. And our conclusions were consistent with some previous studies. Aarestrup and colleagues performed Cox regression and identified 1,020 cases of endometrial cancer, and they discovered that increased BMI in childhood was positively associated with EC [32]. It is also indicated that BMI are more related to type 1 endometrial cancers than type 2 endometrial cancers. Another study by Aarestrup et al. indicated that endometrial carcinogenesis is linked to early-life body size and suggested that childhood BMI might aid in the early prevention of EC [33]. Thus, our study suggested a potential causal link between childhood adiposity and endometrial cancer, further supported the notion that childhood adiposity may increase the risk of endometrial cancer.

The present investigation found no correlation between childhood adiposity and the likelihood of developing cervical cancer. It is widely acknowledged that infection with high-risk human papillomavirus (HPV) is a well-established causative factor in the development of cervical cancer [34, 35]. While prior research has indicated that obese individuals may have a heightened risk of cervical cancer and potentially poorer outcomes, these findings could potentially be attributed to decreased compliance and satisfaction with cervical cancer screening among individuals with obesity [36, 37]. Moreover, there are no specific studies linking obesity to HPV infection, which may further explain why we did not find any association between childhood adiposity and cervical cancer.

The relationship between childhood adiposity and the risk of gynecologic cancers demonstrates variability across various histological subtypes, with the underlying biological mechanisms largely remaining unclear. Impaired endocrine environment caused by obesity is a possible explanation of increased cancer risk. It is suggested that high level of estradiol and local accumulation of IGF1 contribute to the development of endometrial cancers [38, 39]. In the stage of adolescence, characterized by the advent of puberty, there ensues an elevation in androgen secretion. Notably, girls experiencing obesity during puberty exhibit a distinctive elevation in total testosterone levels, relative to their normal-weight peers [40, 41]. This distinct hormonal milieu potentially serves to raise the risk of ovarian cancer and endometrial cancers [42, 43]. It is speculated that obesity in adolescence may lead to increased odds of PCOS [44, 45], and ovulatory infertility as a typical symptom of PCOS which is associated with ovarian cancer risk. Furthermore, the accumulation of excess body fat has been suggested to accelerate the onset of puberty in girls [23], leading to a higher number of ovulatory cycles throughout their lifetime. This nuanced viewpoint introduces a novel perspective on the potential impact of obesity in modulating the risk factors for both ovarian and endometrial cancers [46, 47]. In addition, significant occurrences associated with obesity such as increased estrogen levels, insulin resistance, and chronic inflammation have been suggested as potential factors that enhance the progression of proliferation, invasion, and metastasis in ovarian and endometrial cancer cells [38].

Our research is supported by several significant strengths. Specifically, we utilized two-sample Mendelian randomization analyses with a substantial amount of summary-level genetic data to mitigate potential confounding effects and reverse causation in observational studies. To enhance credibility and minimize weak instrumental bias, we employed robust and reliable instrumental variables from various databases and large-scale genome-wide association studies. Additionally, a series of sensitivity analyses were conducted to reduce bias. We utilized heterogeneity analysis to identify single nucleotide polymorphisms (SNPs) with robust associations. Subsequently, a pleiotropy test was conducted to assess the presence of horizontal pleiotropy. Furthermore, a leave-one-out study was carried out to ensure the stability of Mendelian randomization results when compared to other instrumental variables. Consequently, the findings are deemed reliable, and this represents the first relatively systematic illustration of a causal relationship between childhood adiposity and gynecologic cancers.

Despite the strengths of the study, it is important to recognize its limitations. Firstly, our GWAS data were mainly emanated from European populations, thereby necessitating validation through GWAS endeavors across diverse ethnicities. Moreover, the inclusion of both males and females in the exposure dataset may potentially weaken the observed association strengths [48]. Furthermore, the restricted number of single nucleotide polymorphisms (SNPs) that met the rigorous bioinformatic threshold of $p < 5 \times 10^{-8}$ may hinder the creation of suitable instrumental variable (IV)-outcome pairings and diminish resulting associations. In response to this limitation, we selected SNPs that met a less stringent significance threshold of $p < 5 \times 10^{-6}$. Although this strategy is consistent with suggestions from previous research [49], it is crucial to recognize that it carries the potential for introducing weak instrumental variable bias. Moreover, it is important to acknowledge that a portion of our analysis findings displayed signs of horizontal pleiotropy,

which may violate the exclusion restriction assumption. This highlights the need for increased rigor in future research endeavors. Specifically, conducting additional high-quality Genome-Wide Association Studies (GWAS) and Mendelian Randomization (MR) analyses is crucial.

Our study provides robust genetic evidence that supports the link between childhood adiposity and gynecologic cancers. The increasing global prevalence of childhood adiposity has become a major public health issue. Our results from a Mendelian randomization analysis indicate that childhood adiposity may increase the risk of developing gynecologic cancers. Therefore, healthcare professionals should be mindful that obese children may have a heightened susceptibility to gynecologic cancers and could potentially reduce this risk by addressing obesity during childhood. Prior observational studies have suggested a potential association between childhood adiposity and gynecologic cancers, yet these studies are frequently impeded by confounding factors and reverse causality. Our employment of Mendelian randomization (MR) methodology circumvents these limitations, indicating that childhood adiposity may heighten the susceptibility to specific gynecologic cancers. Nevertheless, the exact mechanisms underpinning this correlation remain ambiguous, underscoring the necessity for additional research to clarify the relationship and underlying mechanisms.

Conclusion

To conclude, ovarian and endometrial cancers were potentially causally associated with childhood adiposity at the genetic level, but there was no potential causal relationship between cervical cancer and childhood adiposity. Our study clarified the potential causal link between exposures (CBMI, CBS-10, COBE) and outcomes (OC, EC, CC) by using MR analysis. These findings have significant implications for the development of interventions aimed at preventing gynecologic cancers. Controlling childhood adiposity may help reduce the risk of ovarian and endometrial cancers. Nevertheless, due to the dynamic and intricate nature of diseases, it is imperative to continue conducting thorough investigations into their complexities and interrelationships as a vital path for further research.

Abbreviations

CBMI	Childhood body mass index
CBS-10	Comparative body size at age 10
CC	Cervical cancer
CCOC	Clear cell ovarian cancer
COBE	Childhood obesity
EC	Endometrial cancer
EEC	Endometrial cancer (endometrioid histology)
ENC	Endometrial cancer (Non-endometrioid histology)
EOC	Endometrioid ovarian cancer
GWAS	Genome-wide association study
HGSOC	High grade serous ovarian cancer
IMOC	Invasive mucinous ovarian cancer
IVW	Inverse variance weighted
LGSOC	Low grade serous ovarian cancer
MR	Mendelian randomization
MR-PRESSO	Mendelian randomization pleiotropy residual sum and outlier
OC	Ovarian cancer
SNP	Single nucleotide polymorphism

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions

M.Z. and Y.Z. designed the study and performed the analysis of data. M.Z., Y.Z. and X.B. wrote the manuscript. H.Z. and W.J. revised and edited the manuscript. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participatae

We used publicly available summary-level data. No additional patient consent and ethical approval are required.

Competing interests

The authors declare no competing interests.

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