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Causal association of childhood body mass index with risk of endometrioid endometrial cancer — A two-sample Mendelian randomization study

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Asociación causal del índice de masa corporal en la infancia con el riesgo de cáncer endometrial endometrioide: estudio de aleatorización mendeliana de dos muestras

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ABSTRACT

Objective: this study aimed to investigate if childhood body mass index (BMI) causally contributed to the risk of endometrial cancer (EC), which had not been well answered.

Methods: genetic instruments were selected using single-nucleotide polymorphisms (SNPs) associated with childhood BMI in European population from a large-scale genome-wide association studies (GWAS, n = 39,620). A two-sample Mendelian randomization (MR) study was performed to evaluate the effect of higher childhood BMI on risk of EC. The data for endometrioid EC was obtained from a GWAS dataset comprising 54,884 individuals (8,758 cases and 46,126 controls). Inverse variance weighting (IVW), weighted median, weighted mode, and MR-Egger regression approaches were applied.

Results: **w**e selected 16 SNPs with genome-wide significance in childhood BMI for the analysis. The IVW analysis provided a causal link between childhood BMI and EC (beta = 0.408, standard error [SE] = 0.088, $p < 0.001$). Similarly, the weighted median method also provided robust evidence for the causal correlation (beta = 0.390, SE = 0.119, $p < 0.001$). Although the MR-Egger regression did not achieve the same significance (beta = 0.071, SE = 0.362, $p = 0.848$), it showed a minimal intercept value indicating small bias for directionality of pleiotropic effects (intercept = 0.024; $p = 0.354$). Through Cochran's Q test and visual inspection *via* funnel plot, the assessment of heterogeneity found no evidence of heterogeneity or asymmetry in our findings, further supporting the absence of directional pleiotropy.

Conclusions: **c**hildhood BMI and risk of EC might be causally related, and early-life intervention on weight control might be considered for children to reduce the life-span risk of EC.

Keywords: Childhood body mass index. Endometrial cancer. Mendelian randomization. Risk factor. GWAS.

RESUMEN

Objetivo: este estudio tuvo como objetivo investigar si el índice de masa corporal (IMC) en la infancia contribuyó causalmente al riesgo de cáncer endometrial (CE), lo que no había recibido una buena respuesta.

Métodos: se seleccionaron instrumentos genéticos utilizando polimorfismos de un solo nucleótido (SNP) asociados con el IMC infantil en la población europea de estudios de asociación del genoma completo a gran escala (GWAS, n = 39,620). Se realizó un estudio de aleatorización mendeliana (MR) de dos muestras para evaluar el efecto de un mayor IMC infantil en el riesgo de CE. Los datos para el CE endometrioide se obtuvieron de un conjunto de datos de GWAS que comprende 54,884 individuos (8,758 casos y 46,126 controles). Se aplicaron enfoques de ponderación de varianza inversa (IVW), mediana ponderada, modo ponderado y regresión MR-Egger.

Resultados: seleccionamos 16 SNP con significancia a nivel del genoma en el IMC infantil para el análisis. El análisis IVW proporcionó un vínculo causal entre el IMC infantil y el CE (beta = 0,408, error estándar [SE] = 0,088, $p < 0,001$). De manera similar, el método de mediana ponderada también proporcionó evidencia robusta para la correlación causal (beta = 0,390, SE = 0,119, $p < 0,001$). Aunque la regresión MR-Egger no alcanzó la misma significancia (beta = 0,071, SE = 0,362, $p = 0,848$), mostró un valor de intercepto mínimo que indica un pequeño sesgo en la direccionalidad de los efectos pleiotrópicos (intercepto = 0,024; $p = 0,354$). A través de la prueba Q de Cochran y la inspección visual mediante un gráfico de embudo, la evaluación de la heterogeneidad no encontró evidencia de heterogeneidad o asimetría en nuestros hallazgos, apoyando aún más la ausencia de pleiotropía direccional.

Conclusiones: el IMC infantil y el riesgo de CE podrían estar relacionados causalmente, y se podría considerar una intervención en la vida temprana sobre el control del peso para los niños con el fin de reducir el riesgo de CE a lo largo de la vida.

Palabras clave: Índice de masa corporal en la infancia. Cáncer endometrial. Aleatorización mendeliana. Factor de riesgo. GWAS.

INTRODUCTION

The incidence of endometrial cancer (EC) has been rising significantly (1-3), which constitutes 4.5 % of female malignancies worldwide, with 417,367 new cases and 97,370 EC-related deaths globally (1,2,4). To reduce the occurrence of EC, particularly in reproductive-age women under 40 years without childbearing, it is essential to elucidate the etiology behind.

Obesity has been widely recognized as one of the most established risk factors for EC (5-8). As the global prevalence of overweight and obesity continues to rise (9), there is growing concern regarding the escalating incidence of childhood obesity. Notably, it is reported that more than 60 % of overweight pre-adolescent children carry excess weight throughout adulthood in Italy (10). On the other hand, EC has been increasingly diagnosed among young obese women (3). However, whether childhood obesity independently increases the risk of EC has not been well answered, which may provide evidence to guide early-life intervention on weight control to reduce the prevalence of EC. Considering that EC often has a long latency period, it is crucial to investigate the association between childhood BMI and the risk of EC.

By employing genetic variants as instrumental variables (IVs), Mendelian randomization (MR) can be used to estimate causal effects, that is, whether an observed association between exposure and outcome implies a causal relationship (11). Several MR studies have unveiled a positive association of obesity with susceptibility to EC (12-14). The earliest MR study on obesity and EC conducted in 2015 suggested that

each interval of 10 BMI-increasing alleles had a 13 % increased risk of EC (15). Freuer et al. provided supportive evidence that genetically elevated BMI was causally related to the risk of EC (12). Other similar studies showed consistent results (13,14). The above studies have suggested that obesity may have a causal effect on EC. Observational studies have further suggested a possible association between childhood obesity and elevated risk of EC in adulthood (16,17). However, it should be noted that observational studies may not fully take residual confounding into account (11). So far, the causal relationship between childhood BMI and susceptibility to developing EC in adulthood remains uncertain.

A two-sample MR analysis can estimate the genetic associations with both exposure and outcome separately in different samples, assuming consistent magnitudes of these associations across datasets (18). Therefore, in this study we conducted a two-sample MR analysis to explore the possible causal association between childhood BMI and the risk of EC.

MATERIALS AND METHODS

Data sources and genetic variant selection

In this MR study, childhood obesity was assessed by childhood BMI. We performed a search in the MR Base platform (http://www.mrbase.org/), which contains open-access consolidated data from large genome-wide association studies (GWAS). The dataset for childhood BMI as the exposure variable was obtained from summary statistics of systematic GWAS studies in a European population, which comprised a total of 39,620 individuals. On the basis of their significant association at the genome-wide level, a total of 16 single nucleotide polymorphisms (SNPs) linked to childhood BMI were selected and identified as instrumental variables (IVs) in the two-sample MR analysis (Table I). The *p*-value threshold was set at 5.0e-08. Our analysis included 54,884 individuals in

European population, consisting of 8,758 cases and 46,126 controls. The EC histology type was endometrioid in all patients.

Statistical analysis for Mendelian randomization

In the MR analysis, genetic variants were considered as surrogates for the exposure variable without the effect of potential confounding variables (19). Our analysis proceeded in three stages: firstly, the independent association was assessed between each SNP and childhood BMI; secondly, the relationship was investigated between SNPs and the risk of developing EC; thirdly, these findings were combined to infer causality between childhood BMI and EC development by using MR analysis (20). With the set of 16 SNPs as IVs, it was evaluated whether there exists a causal association of childhood BMI with EC development. Statistical summaries from GWAS were collated and presented in tables II and III.

The inverse-variance weighted (IVW) method was a meta-analysis that combines variant-specific Wald ratios for each mutation with an assumption that each mutation satisfies IV criteria (11). It integrated the estimated effects across different SNPs, providing a precise estimate of the effect of exposure on outcome (11). Including a large number of genetic variants could increase statistical power, however, there was a risk that they may not qualify as valid IVs (21). Pleiotropy meant a potential association between genetic variants and multiple phenotypes (22). To assess pleiotropy, MR-Egger and weighted median approaches were used as pleiotropy-robust methods. Through a weighted linear regression model, MR-Egger regression could correct for the bias due to directional pleiotropy considering the effects of multiple genetic variants across all instruments (21). The slope coefficient represented a causal effect estimation (21). The intercept represented the average pleiotropic effect estimated across genetic variants, and it indicated the overall directional pleiotropy if different from zero (21). The weighted median

approach consistently estimated causal effects even with 50 % of the information derived from valid IVs (23). It showed higher accuracy compared to MR-Egger approach (23). In order to estimate the true causal effect, we also used the weighted mode approach as an additional MR method. It assigned weights to variants, with the largest weights assigned to valid IVs among all variant subgroups (24). Although its power for detecting a causal effect in a two-sample setting was lower than that of IVW and weighted median approaches, it outperformed MR-Egger regression (24), with similar precision to that of the IVW and weighted median approaches (24). All analyses were conducted by using MR Base (the App version: 1.4.3 8a77eb [October 25, 2020], the Database version: 0.3.0 [25 October 2020], the R version: 4.0.3) (25). A level of less than 0.05 in a two-tailed *p*-value was considered statistically significant.

Heterogeneity and sensitivity test

To assess individual SNP influence on causal estimates, we conducted sensitivity analysis using leave-one-out method. Additionally, we examined heterogeneity among SNP estimates by employing Cochran's *Q*-statistics and I^2 statistics (26-28).

RESULTS

Instrumental variables for Mendelian randomization analysis

A total of 16 SNPs were identified from the GWAS in association with childhood BMI, each met the criteria for independence and causality at the genome-wide significance level (Table I; Table II; Fig. 1). None of the positive SNP associations with EC were statistically significant (Table I; Table II). The IVs together explained 2.3 % of the variance in childhood BMI and each had an *F*-statistic of over 30, which corresponded to a *p*-value of 5.0e-08 (Directionality, p = 4.13e-77). This result minimized the

concern of a weak bias of the instrument, which was taken into account when the *F*-statistic is set to < 10.

The results of Mendelian randomization analysis

Studies using the weighted median and IVW method revealed a strong association of childhood BMI with risk of EC (beta = 0.390, standard error [SE] = 0.119, $p < 0.001$; beta = 0.408, SE = 0.088, $p < 0.001$; Table II, Fig. 1 and Fig. 2). However, the MR-Egger and weighted mode methods did not provide support for a causal relationship (beta = 0.071, SE = 0.362, $p = 0.848$; beta = 0.318, SE = 0.168, $p = 0.078$; Table II, Fig. 1 and Fig. 2). The intercept analysis of MR-Egger regression suggested that directional pleiotropy was unlikely to affect the estimates (Directionality, $p = 0.354$; SE = 0.025; intercept = 0.024). Although there were inconsistencies in the estimates obtained from MR-Egger and weighted mode approaches, the weighted median and IVW method could offer more precision. Figure 2 illustrated that the intercepts of these methods approached zero, indicating consideration of horizontal pleiotropy. Thus, MR results simply implied a potential causal relationship between childhood BMI and the risk of developing EC.

Heterogeneity and sensitivity test

There was no heterogeneity detected in the causal effect estimates provided by the SNPs (Table III). In addition, confidence in the MR estimates was increased by the I^2 values, which further indicated low heterogeneity (Table II; Table III). The stability of the IVW estimates was maintained by the absence of any single SNP effect when removed, confirming the robustness of our findings. Investigation of funnel plot asymmetry revealed no bias due to directional pleiotropy within the MR analyses (Fig. 3). Consequently, the reliability of the MR estimates was substantiated, and the empirical results were exempted from directional pleiotropy influence. It was further confirmed that no single SNP

significantly altered the causal inference in the leave-one-out analysis (Fig. 4).

DISCUSSION

The present study aimed to explore the causal association between childhood BMI and risk of EC in adulthood. To achieve this, four MR statistical techniques were used, including IVW, weighted median, weighted mode and MR Egger regression (11). Our results implied that childhood BMI causally increased susceptibility to EC.

The relationship between childhood BMI and EC has not been well investigated. Previous observational studies have suggested that childhood or adolescent obesity might be a risk of EC (16,17). A large (*n* = 155,505) Danish prospective cohort study with 35 years of follow-up showed that the childhood (age 7-13) BMI was non-linearly associated with all endometrial cancers (16). Furthermore, participants with higher BMI-gain across all child's ages (6.28-14.0 years) were found to have increased prevalence of EC in later life (17). In line with previous findings, we found that childhood BMI was causally related to the risk of EC. On the contrary, one MR study showed a non-significant correlation between EC and childhood body size (29), which was collected by asking adult participants to describe themselves as thinner, plumper or about average at age 10 (29). Therefore, recall bias might be introduced. Another MR study also reported that the childhood obesity was not related with EC (30), which was inconsistent with our findings. This discrepancy might be explained by the 15 loci associated with childhood BMI used in that study had been updated to 25 genetic variants used in our study (31,32). Besides, selection of variables and data sources were also different in previous MR studies compared to our study (29,30).

The association between early-life BMI and risk of EC was considered not independent from adult BMI (29). However, recent study identified 25 genome-wide significant loci associated with childhood BMI and

addressed that genes influencing childhood and adult BMI were not completely overlapped (32). Potential age-specific differences or stronger effects of these genetic loci on childhood rather than adult BMI were suggested (32). Thus, the relationship between childhood BMI and EC remains uncertain and needs further examination. More attention should be paid to early life intervention such as childhood weight control considering its causal link to the risk of EC during the life-span.

Nowadays, the first-line management of children obesity is lifestyle intervention on eating habits and physical activities (33), particularly for children under 12 years old. However, it often fails to achieve significant and enduring weight-reduction (10,34). If necessary, anti-obesity medications or surgeries are also options. Notably, a 3-year observational study of behavioral intervention on children at 6-16 years old revealed that the BMI z-score was reduced at least 0.5 units in 58 % of the severely obese children at 6-9 years old compared with only 2 % of the adolescents at 14-16 years old (35). It was also worth noting that 92 % of these severely obese adolescents were already obese at age 7 (35), addressing the importance of early intervention on severe obesity in childhood.

MR is employed to decrease the inherent biases of observational studies but is susceptible to bias amplification, which occurs when a single genetic variant is associated with multiple phenotypes, potentially leading to bias in causal inferences (36). Incorporating a wide array of genetic variations into MR studies can increase statistical power; however, it also raises the probability of introducing pleiotropic variants that are not valid instrumental variables, which requires sensitivity analyses (18). In our study, the MR analysis employed satisfied three assumptions (11): 1) there had links between the genetic variants used as instrumental variables and childhood BMI; 2) the instrumental variables were not associated with potential confounders; 3) the instrumental variables only affected EC through childhood BMI, rather

than other pathways. To solve the problem of pleiotropy, we applied methodologies including weighted median estimator and MR-Egger regression. Although there was a lack of consistence in the outcomes from different methods, the similar results from both the weighted median estimator and IVW approach bolstered the reliability of these associations.

This study has several strengths. The nature of MR analysis decreased bias from unobserved confounding of childhood BMI and EC. Also, the large-scale sample size used in the MR analysis increased the statistical power for reliable estimation of causal effects. However, our study only included endometrioid histology type of EC, and the study participants were all European. Considering BMI differs among ethnic groups, it might impact the generalizability of our findings. Further MR studies with improvement on these aspects are needed to untangle the relationship between childhood BMI and EC.

In conclusion, applying a two-sample MR study, we found childhood-BMI causally contributed to an increased risk of EC using meta-analyses data from GWAS. Our results suggested the importance of weight control for obese children to reduce their risk of EC in adult stage.

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Table I. The association between SNPs and endometrial cancer

	SNP	effect_allele.exposure	other_allele.exposure	se.exposure	beta.exposure	pos.exposure	pval.exposure
1	rs114670539	T	C	0.0179	0.0991	207064335	3.16E-08
2	rs11676272	G	A	0.0079	0.075	25141538	2.37E-21
3	rs12042908	G	A	0.0077	-0.0586	74997762	2.77E-14
4	rs12641981	T	C	0.008	0.044	45179883	4.19E-08
5	rs13107325	T	C	0.0173	0.0953	103188709	3.51E-08
6	rs17817449	G	T	0.008	0.0683	53813367	1.69E-17
7	rs41279738	G	T	0.0211	0.1199	110082551	1.30E-08
8	rs4477562	T	C	0.0112	0.0802	54104968	8.29E-13
9	rs543874	G	A	0.0099	0.0793	177889480	1.62E-15
10	rs56133711	A	G	0.0089	0.0566	27723334	2.00E-10
11	rs571312	A	C	0.0093	0.059	57839769	2.00E-10
12	rs61765651	T	C	0.0102	-0.0584	72754314	9.50E-09
13	rs62500888	G	A	0.0076	-0.0472	28061823	6.91E-10
14	rs7138803	A	G	0.008	0.0729	5024746	7.12E-

						8	20
15	rs7199285	T	C	0.0101	-0.0647	19980931	1.34E-10
16	rs939584	T	C	0.0102	0.1066	621558	8.85E-26

SNP: single-nucleotide polymorphism; SE: standard error.

Table II. The MR estimates from each method of assessing the causal effect of childhood body mass index on the risk of endometrial cancer

MR method	**Number of SNPs**	**Beta**	**SE**	**Association *p*-value**
MR-Egger	16	0.07073	0.3624	0.848
Weighted median	16	0.3904	0.1188	0.001012
Inverse-variance weighted	16	0.4077	0.08834	0.000003927
Weighted mode	16	0.3183	0.1684	0.07824

MR: Mendelian randomization; SNP: single-nucleotide polymorphism; Beta: beta coefficient; SE: standard error.

Table III. The MR estimates with heterogeneity statistics from each Mendelian randomization method

MR method	**Cochran Q statistic**	**df**	**I^{2*}**	**Heterogeneity *p*-value**
MR-Egger	17.43	14	0.1967871	0.2339
Inverse-variance weighted	18.58	15	0.1926803	0.2336

MR: Mendelian randomization. $^{*}I^2 = (Q - \mathrm{df}) / Q$.

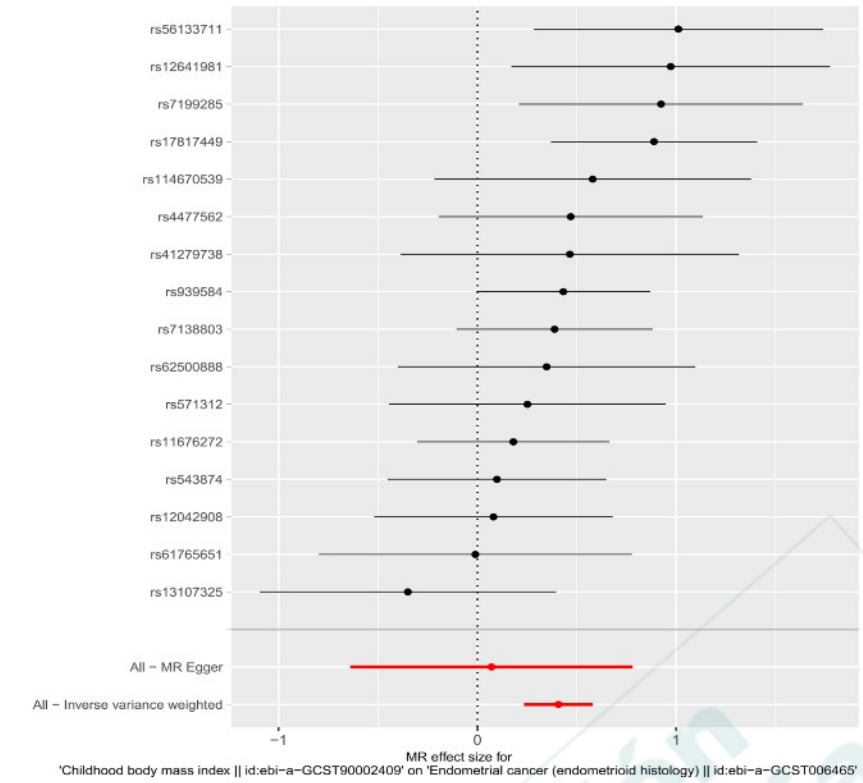

Figure 1. The forest plot of the causal effects of SNPs associated with childhood body mass index on endometrial cancer (the significance of red lines were MR results of MR-Egger and IVW methods. SNP: single-nucleotide polymorphism; MR: Mendelian randomization; IVW: inverse-variance weighted).

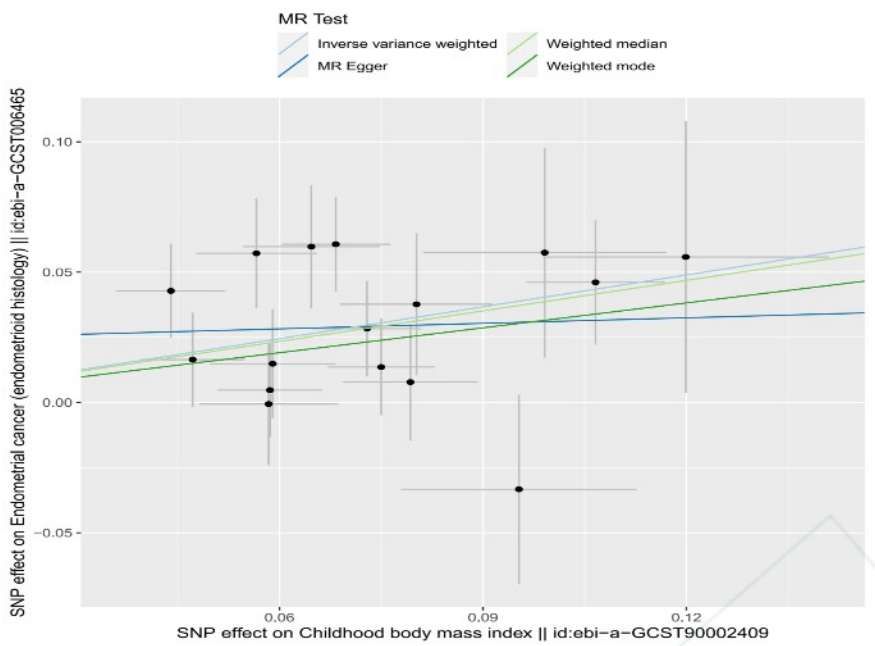

Figure 2. The scatter plot of genetic associations with childhood body mass index against the genetic associations with endometrial cancer (the slopes of each line represented the causal association for each method. The light blue line represented the IVW estimate, the light green line represented the weighted median estimate, the dark blue line represented the MR-Egger estimate, and the dark green line represented the weighted mode estimate.

IVW: inverse-variance weighted; MR: Mendelian randomization; SNP: single-nucleotide polymorphism).

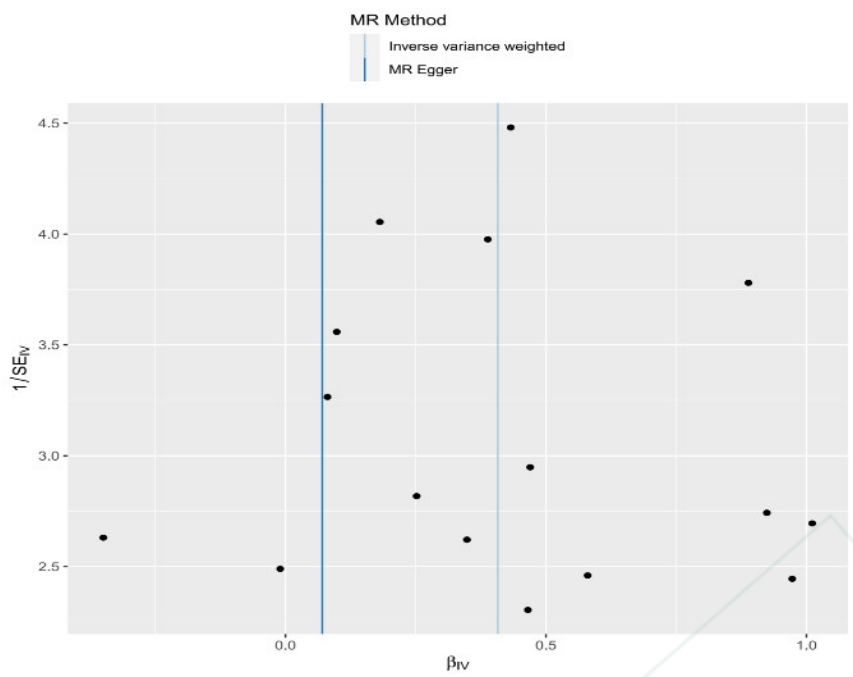

Figure 3. The funnel plot to assess heterogeneity (the light blue line represented the IVW estimate, and the dark blue line represented the MR-Egger estimate. MR: Mendelian randomization; IVW: inverse-variance weighted).

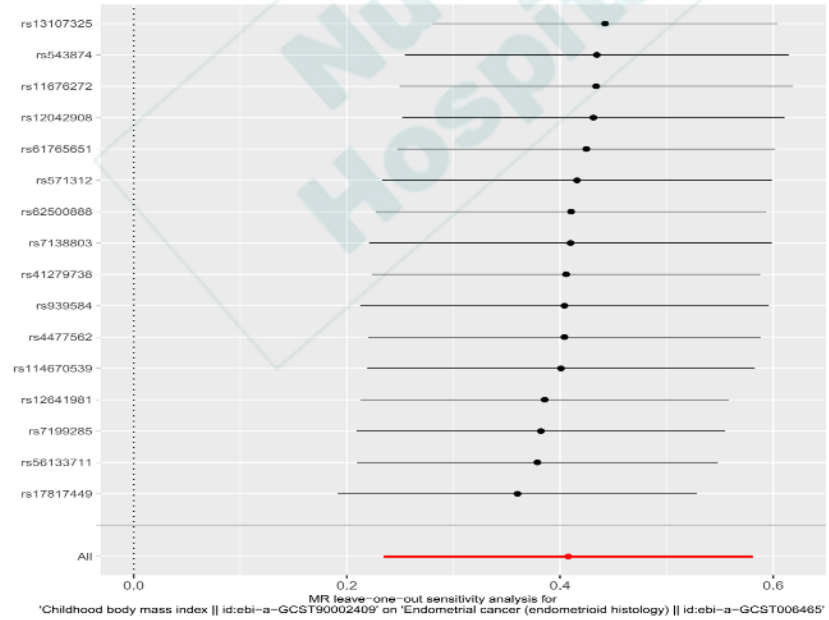

Figure 4. the leave-one-out analysis of SNPs associated with childhood body mass index and their risk of endometrial cancer (each black point

represented result of the MR analysis by using IVW applied to estimate the causal effect of childhood body mass index on endometrial cancer excluding particular SNP. Each red point depicted the IVW estimate using all SNPs. No single SNP was strongly driving the overall effect of childhood body mass index on endometrial cancer in this leave-one-out sensitivity analysis. SNP: single-nucleotide polymorphism; MR: Mendelian randomization; IVW: inverse-variance weighted).