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Body Mass Index and Risk of Female Reproductive System Tumors Subtypes: A Meta-Analysis Using Mendelian Randomization

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Abstract

Introduction: A strong association was previously established between body mass index (BMI) and female reproductive system tumors; however, the causal relationship is unclear. We conducted a Mendelian randomization (MR) study to further explore this association. **Methods:** Genetic information for BMI was retrieved from a published genome-wide association study involving 339,224 participants. Genetic associations with five common female reproductive system tumors were obtained from the FinnGen, UK Biobank studies, and other large consortia. **Results:** Genetic predisposition towards BMI exhibits a significant association with multiple tumors of the female reproductive system. Specifically, for every 1-unit increase in BMI log-transformed odds ratio (OR). The OR fluctuations overall for patients with breast cancer ranged from 0.661 to 0.996 (95% confidence interval [CI],0.544-1.000, $P < 0.05$). When stratified by estrogen receptor (ER) status, the OR for patients with ER (+) breast cancer ranged from 0.782 to 0.844 (95% CI, 0.616-0.994, $P < 0.05$) and that for those with ER (-) breast cancer ranged from 0.663 to 0.789 (95% CI, 0.498-0.991, $P < 0.05$). Additionally, ORs were as follows for cancer types: 1.577–1.908 (95% CI, 1.049-2.371, $P < 0.05$) for endometrial carcinoma; 1.216–1.303 (95% CI, 1.021-1.591, $P < 0.05$) for high-grade serous ovarian cancer; 1.217 (95% CI, 1.034-1.432, $P < 0.05$) for low-grade malignant serous ovarian cancer; and 1.502 (95% CI, 1.112-2.029, $P < 0.05$) for endometrioid ovarian carcinoma. Furthermore, our findings indicated that genetic predisposition towards BMI did not exhibit a causal association with uterine fibroids, cervical precancerous lesions, or cervical cancer itself. **Conclusion:** A genetic association was established between a high BMI and high risk of developing multiple tumors of the female reproductive system and their associated subtypes. This underscores the significance of taking measures to prevent reproductive system tumors in women who have a high BMI.

Keywords

body mass index, obesity, female reproductive system tumor, Mendelian randomization, meta-analysis

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Abbreviations:
MR, Mendelian randomization; GWAS, genome-wide association study; OR, odds ratio; ER, estrogen receptor; BMI, high body mass index; IV, instrumental variable; TSMR, Two-sample Mendelian randomization; BCAC, breast cancer association consortium; E2C2, epidemiological consortium of endometrial cancer; OCAC, ovarian cancer association consortium; CC, cervical cancer; CIN, cervical intraepithelial neoplasia; SNPs, small nucleotide polymorphisms; IVW, inverse variance weighted; RCT, randomized controlled trial

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Introduction

Obesity is increasingly recognized as a key initiating factors in many chronic diseases, according to numerous studies.[1] With 600 million obese and 1.9 billion overweight adults worldwide, obesity has been ranked as the fifth most significant risk factor for health by the World Health Organization.[2] The primary global health issues of the future are projected to be obesity and associated diseases. Moreover, obesity has been recognized as an independent risk factor for several major cancer types,[3,4] including colorectal and urothelial cancer[5,6] and it also has a substantial influence on the incidence of female-related cancers.[7,8] Obesity is particularly acute in developed countries; the obesity rate in the United States has tripled over the past three decades. The burden of morbidity and mortality from common gynecological tumors in women with high body mass index (BMI) is rapidly increasing.[9] According to the cancer statistics for 2022, in the next 20 years, the global cancer burden will increase by nearly 50%.[10] Breast cancer (BC) accounts for nearly a third of female cancer diagnoses, and cervical cancer and other common female reproductive system tumoural prevalence also increased.[11,12] Therefore, obesity poses a major threat to women's health and the economy. To our knowledge, current epidemiological and clinical trial studies have not established a causal relationship between BMI, and the incidence of common tumor precancerous lesions and related tumor subtypes in women. Therefore, it is crucial to investigate and clarify this potential association.

A randomized controlled trial (RCT) is the most effective etiology research method in epidemiological studies. In addition to avoiding the potential bias in the design and implementation of clinical trials, it can further balance confounders and improve the validity of statistical tests. However, it is difficult to widely apply this method due to the ethical problems, high cost, and long follow-up time. We used Mendelian randomization (MR) analysis to overcome these limitations in our study. An MR study is often called a 'natural RCT'. During MR, the segregation and accessible combination of alleles during meiosis is similar to randomization in an RCT.[13] MR is an epidemiological data analysis technique used to evaluate causal relationships in non-experimental data.[14] Genetic variation is used as an instrumental variable (IV) to estimate the causal relationship between the exposure factors of interest and the outcome.[15] MR analysis depends on the natural division during meiosis, using random classificationto produce a random distribution of genetic variation in the population.[16] Individuals naturally inherit a genetic variant that may or may not affect risk factors. As these genetic variants are not commonly associated with confounding factors, differences in outcomes between those with or without it can be attributed to differences in risk factors.[17] Considering the assumption of genetic variation, any association between genetic variation and disease outcome must be examined as the variation versus exposure association achieved, confirming that exposure factors are causal to disease outcome with precise timing. MR analysis effectively avoids the defects of confounding factors and unclear causal timing when demonstrating the etiologic hypothesis; it provides new ideas and methods for the demonstration of epidemiological etiology hypotheses.[18,19]

Recently, genome-wide association studies (GWAS) have enabled the establishment of millions of genetic variant-disease associations. Two-sample MR (TSMR) analysis is an optimized extension of one-sample MR.[20] TSMR analysis involves the use of published pooled data without the need for additional experiments to assess the causal effect of exposure factors on outcomes, saving study costs and improving bioinformatic availability.[21] Published GWAS databases have large sample sizes, high test efficiency, numerous selectable IVs, and strong genetic interpretation of exposure factors. This replaces exposure, ensuring precise and reliable analysis results.

The causal association between BMI and female tumor susceptibility is not fully understood despite physiological and epidemiological evidence. This study was used to analyze the relationship between BMI and female tumor susceptibility using BMI-related gene polymorphisms and associated subtypes as IVs. The aim is to clarify the causal association and provide a basis for prevention, treatment, reducing incidence, and disease burden in women prone to tumors and their subtypes.

Materials and Methods

Research Design

In this study, we used BMI as an exposure factor, related subtypes of BC and four other common female reproductive system tumor subtypes as outcome indicators, and the study mainly followed the following five steps: (1) determination of IVs (selection of IVs and verification of IVs); (2) sorting and extracting relevant data before analysis; (3) TSMR analysis; (4) data analysis and mapping ; and (5) further meta-analysis of the TSMR results to integrate the TSMR results from the

currently available prospective evidence.[22] The overall design of the study is shown in the flow chart in Figure 1.

Data Sources and Selection of the Tool Variables

The genetic information utilized in determining BMI was derived from a previously published GWAS. The genetic associations to five prevalent female reproductive system tumors were derived from the FinnGen and UK Biobank studies, along with other extensive consortia. Given that this study relies solely on previously published data, it was not necessary to obtain ethical approval or informed consent. Sample inclusion criteria included the following: available GWAS sequencing data and corresponding clinical information, including data release year, race, gender, research institution, sample size, PMID number. Detailed data sources are provided in Supplementary Table 1.[23]

BMI data were derived from a large-scale GWAS analysis of 339224 admixed population cases (https://mibiogen.gcc.rug.nl/). Data for BC and its subtypes are available from the BC Association Consortium, including 122,977 cases and 105,974 controls. All the participants were of a European population and summary statistics for both subtypes [estrogen receptor-positive (ER+) and negative (ER-) BC] are also available. In addition, we included BC cohorts from Biobank Japan, MRC-EU, Neale Lab laboratories.

Data on endometrial cancer and its histological subtypes (endometrioid and non-endometrioid subtypes) were obtained from the Consortium of Endometrial Cancer Societies (ECAC), the Epidemiological Consortium of Endometrial Cancer (E2C2) and the UK Biobank, among data from the ECAC. The E2C2 consortium contained 12 of the 270 cases and 46 of the 126 controls. Data from the UKB contained 1151 cases and 461,782 controls. To ensure the validity of

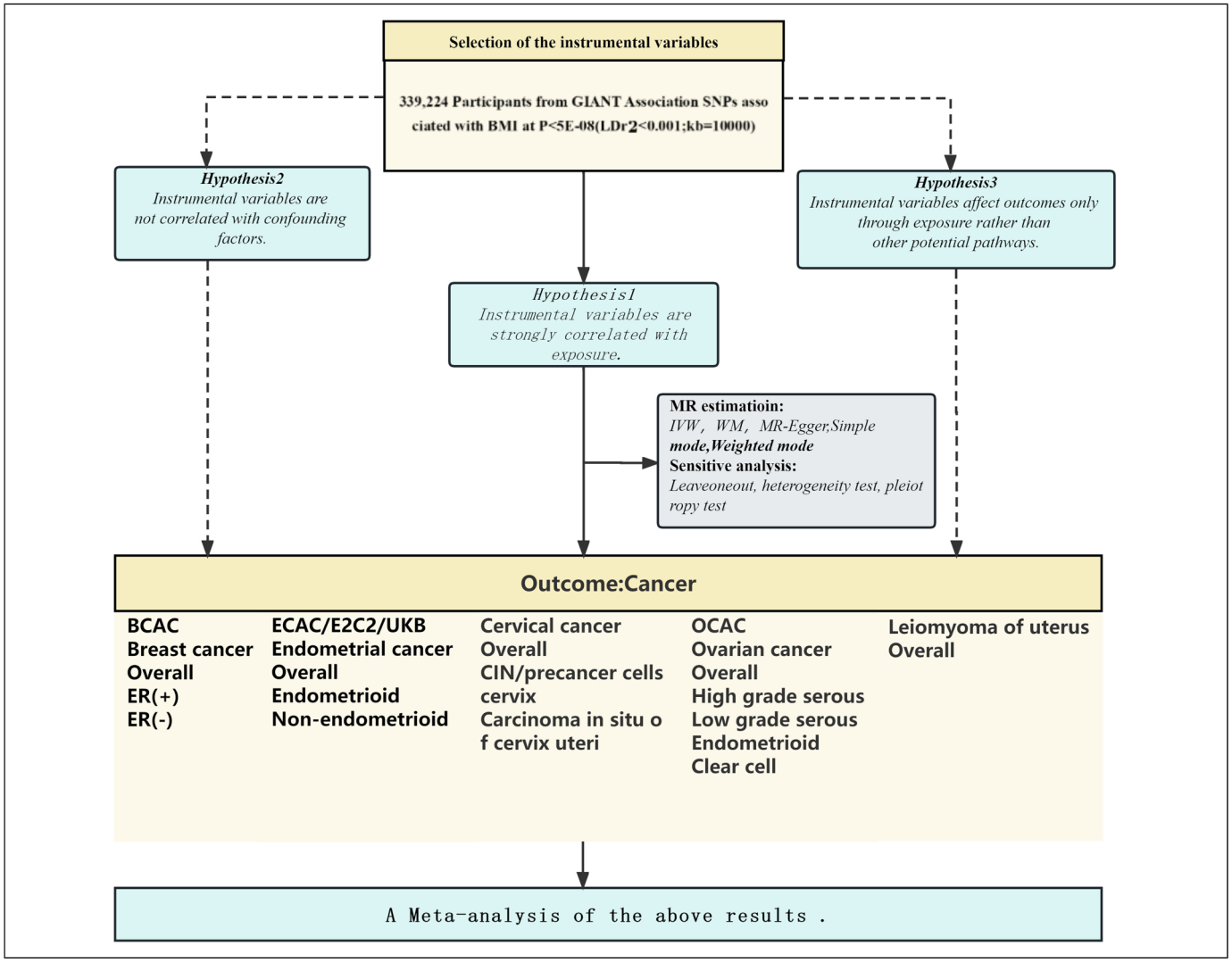

Figure 1. Flow chart of TSMR and Meta-analysis studies of BMI on subtype risk associated with female breast cancer and female reproductive system tumors. Abbreviations:BCAC, Beast Cancer Association Consortium; E2C2,Epidemiology of Endometrial Cancer Consortium; ECAC, Endometrial Cancer Association Consortium; ER-, estrogen receptor-negative; ER+, estrogen receptor-positive; OCAC, Ovarian Cancer Association Consortium; IVW, inverse variance weighted; WM, weighted median.

the study, we also included 999 cases from Biobank Japan as well as 89 of the 731 control individuals.

Cervical cancer-related data were obtained from multiple GWASs from the UKBiobank and the MRC-IEU association. The data related to precancerous lesions of cervical cancer were derived from a GWAS analysis of European populations conducted by the MRC-IEU association and the sample size varied from 102,485 to 462,933 cases.

Ovarian cancer and its subtypes were obtained from the GWAS study conducted by the OCAC consortium, which included 12,270 cases and 46,126 controls from the European female population, and ovarian cancer and its subtypes from the Finnish and UKB databases were included in the study.

Uterine leiomyomas-related data were obtained from GWAS analyses of MRC-EU and Nepalese laboratories and other unknown associations from different ethnic groups, including European, South Asian, African American, and Black Caribbean samples with sample sizes ranging from 5902 to 459,986.

In the summary data of GWAS, we selected single nucleotide polymorphisms (SNPs) that met the following criteria for MR analysis: at the genome-wide significance level ($P < 5E\text{-}08$).[24] and SNPs with linkage disequilibrium (defined as $r^2 > 0.001$ and clump distance < 10,000 kb) were excluded. The included SNPs had no moderate allele frequency, palindromes or outliers.[25]

Validation of the Tool Variables

According to the principle of MR analysis, the single-nucleotide diversity that can be used as IVs must hold the following three core assumptions[26,27]:

1. Assumption of independence: IVs are not associated with confounders other than exposure.
2. Association hypothesis:Strong correlation must exist between the IVs and the exposure factors they replace.
3. Exclusivity hypothesis (non-pleiotropic hypothesis): IVs can only affect the outcome variables only exposure factors and not other routes.

According to Mendel's law, alleles are randomly separated and combined during gamete formation, and acquired factors (such as social and natural environments) do not affect on this process.[28] Based on this characteristic, genetic variation supports the independence hypothesis. Additionally, in the initial screening phase of IVs, we screened SNPs strongly correlated with exposure factors as IVs using $P < 5E\text{-}8$ as the criteria to satisfy the association hypothesis. The filtered IVs were not associated with the outcome measures ($P > 5E\text{-}8$), confirming adherence to the association hypothesis, and indicating that the IVs did not directly influence the outcome. Finally, the premise of causality inference using MR is that there is no interference of horizontal pleiotropy, therefore we also need to test whether IVs affect outcomes through other means. In this study, we used the Mendelian random polymorphism residual and outlier (MR-PRESSO) method to assess the magnitude of horizontal pleiotropy.[29,30] $P > 0.05$ indicates no statistical significance, that is, horizontal pleiotropy has no effect in IVs. Any significant outliers detected ($P < 0.05$), they were excluded from the analysis.[31]

Two-Sample Mendelian Randomization

We used the inverse variance weighted (IVW) method with random effect as the primary MR analysis method.[32] Previous studies have demonstrated that the IVW method is extensively employed in TSMR studies due to its robust test efficacy.[33] In addition, we used four methods: weighted median, simple mode, weighted mode, and MR-Egger as complementary methods for causal inference[34,35] For each SNPs, the ratio of the causal of exposure on outcome was the ratio of the effect of the SNP on outcome to the effect of SNP on exposure. In the IVW, the overall estimates were generated using an IVW meta-analysis of the ratio estimates for all variables in the set of IVs.

The data are derived from multiple GWAS cohort studies, therefore, there may be differences in the studies, such as different gene annotation analysis platforms, different case inclusion and exclusion criteria, inconsistent population sources, and therefore TSMR there may be heterogeneity in analytical methods, leading to bias in the estimated results of causal effects. In this study, heterogeneity was tested between IVW and MR-Egger regression methods. There was no significant statistical significance in heterogeneity test results when $P > 0.05$, that is, the heterogeneity did not affect the study results. In addition, to eliminate the influence of the research method on the results and improve the accuracy of the results, the fixed effect model and random effect model in the IVW analysis method were also used. Random effects models can reduce outcome bias due to existing heterogeneity.

There must be some difficulty in avoiding random error in the process of including IV selection. Therefore, it was necessary conduct out a "leave-one-out" analysis of the individual data (leave-one-out sensitivity test), eliminate one SNP in turn, and calculate the MR analysis effect of the remaining SNP. Through the display of the forest map, we intuitively judged the influence of each SNP on the results, to judge the stability of TSMR analysis results.

A meta-Analysis Based on the TSMR

To investigate the causal link between BMI and various cancers, we conducted a meta-analysis of TSMR results using GWAS data across all tumor types and their subtypes. This systematic review was performed in accordance with the 2020 updated Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines. The study protocol was registered with INPLASY(INPLASY202440025) .Data from at least three independent studies assessing the causal effect between BMI and risk of disease with female reproductive system tumors and their subtypes, were pooled for the meta-analysis. We pooled the risk ratios for all TSMRs with a fixed-effects model and assessed the heterogeneity across

studies by examining the funnel plot of the risk ratios estimates and using the Cochrane Q test and I2 statistic ($P \leq 0.1$, or $I^2 \geq 50\%$ for any heterogeneity ; $P > 0.1$, or $I^2 < 50\%$ without heterogeneity)[36,37] To eliminate heterogeneity, we explored the source of heterogeneity from the perspective of clinical and methodological heterogeneity, and further conducted subgroup analysis based on the attribute characteristics causing heterogeneity existed in the results.[38]

Statistical Analysis

All analyses were performed using R (v4.2.2) and software packages, including Meta, TwoSampleMR, and 95% confidence interval (CI) and two-sided P-values were calculated for statistical inference. TwoSampleMR package, Meta package can be downloaded from GitHub website (https://mrcieu.github.io/TwoSampleMR/; https://github.com/meta-toolkit/meta).

Results

We included 79 of the BMI-related SNPs as IVs for MR analysis with SNP-specific F-statistics ranging from 29.9(BMI) to 716.5 (BMI) (Supplementary Table 2),[39] significantly above the traditional threshold of 10, indicating no weak instrumental bias. After a rigorous tool selection procedure, the number of SNPs associated with each tumor and its associated subtypes varied from 52–75.

Heterogeneity Test

All cancer types and their subtypes were tested for heterogeneity, and the heterogeneity test between BMI and female common tumors and their subtypes indicated $P > 0.05$ with no heterogeneity. The P-value of data heterogeneity test results between BMI and BC and its subtypes, endometrial cancer, invasive mucinous ovarian cancer, and high-grade serous ovarian cancer was less than 0.05. There was heterogeneity, therefore, the main statistical analysis method used was IVW (random effect model) (Supplementary Table 3).

Horizontal Pleiotropy

The results of the pleiotropy test (Supplementary Table 4) showed that after the MR-PRESSO test,[40] the results P of all tumor types and related subtypes were greater than 0.05, therefore, there was no pleiotropic interference in this study.

Sensitivity Analysis

There must be some difficulty to avoid random errors in the selection and inclusion of IVs. Therefore, it was necessary to conduct "leave-one-out" analysis of the data, eliminate one SNP in turn, and calculate the MR analysis effect of the remaining SNP. Through the display of forest maps, intuitively judged the influence of each SNP on the results, to judge the stability of TSMR analysis results.

TSMR Analysis and meta-Analysis of BMI Versus the Five Tumors and Their Subtypes

A meta-analysis conducted using TSMR revealed that there is a significant association between BMI and 11 types of tumors in females. The analysis revealed a positive correlation between BMI and endometrial, high-grade serous ovarian, and endometrioid ovarian cancer. However, a negative correlation was found between BMI and BC. No significant association was found between BMI and uterine fibroids, mucinous ovarian carcinoma, and cervical cancer. Other MR models (including weighted median, simple mode, weighted mode, and MR-Egger regression) also supported these findings.

Breast Cancer and its Associated Subtypes

In total, 18 GWAS datasets from different databases were included as outcome variables, including seven BC, five ER + BC, and six ER- BC datasets. The results of the TSMR correlation analysis between BMI and BC and its subtypes are shown. All included BCs and their subtypes, except for GWAS ID: ieu-a-1134 and ieu-a-160, had statistically significant casual relationships ($P < 0.05$; Figure 2A). Other MR methods for studies of disease risk associations of BC and its subtypes under BMI exposure also showed similar estimates of directionality to IVW, although some lacked statistical significance (Supplementary Table 5).We performed a meta-analysis of the relative risk (odd ratio [OR]) and 95% CIs for TSMR results, using a random- and fixed-effects model approach. The meta-analysis showed heterogeneity when all BC data and their subtypes were included (heterogeneity: $I^2 = 87\%$, $t^2 = 0.0103$, $P < 0.01$). We further examined the source of heterogeneity in the study, and the results showed that the heterogeneity was mainly related to the gender of the population where the data were included, therefore, we conducted a subgroup analysis of the samples according to the gender differences of the study individuals, and there was no heterogeneity within each subgroup after grouping (Figure 2B) (BC-M&F, Heterogeneity: $I^2 = 0\%$, $t^2 = 0$, $P = 1$; BC-F, heterogeneity:$I^2 = 51\%$, $t^2 = 0.0062$, $P = 0.11$; BC-(ER+)-F, heterogeneity:$I^2 = 0\%$, $t^2 = 0$, $P = 0.95$; BC-(ER-)-F, heterogeneity: $I^2 = 0\%$, $t^2 = 0$, $P = 0.8$). In summary, the results of TSMR meta-analysis of multi-source data sets of BC and related subtypes showed that increased BMI was negatively associated with increased risk of female BC, ER + BC, and ER- BC (BC-F, OR:0.80, 95% CI: 0.75– −0.86; BC-(ER+)-F, OR:0.83, 95% CI:0.78–0.89; BC-(ER+)-F, OR:0.80, 95% CI: 0.69–0.83). However, there was no clear causal relationship between BMI and the risk of BC in a mixed population (BC-M&F, OR:1.00, 95% CI: 0.99-1.00).

Endometrial Cancer and its Associated Subtypes

Among the GWAS data, those from the East Asian population study with the UKB database and the Japan BioBank showed no clear causal link between BMI and endometrial cancer

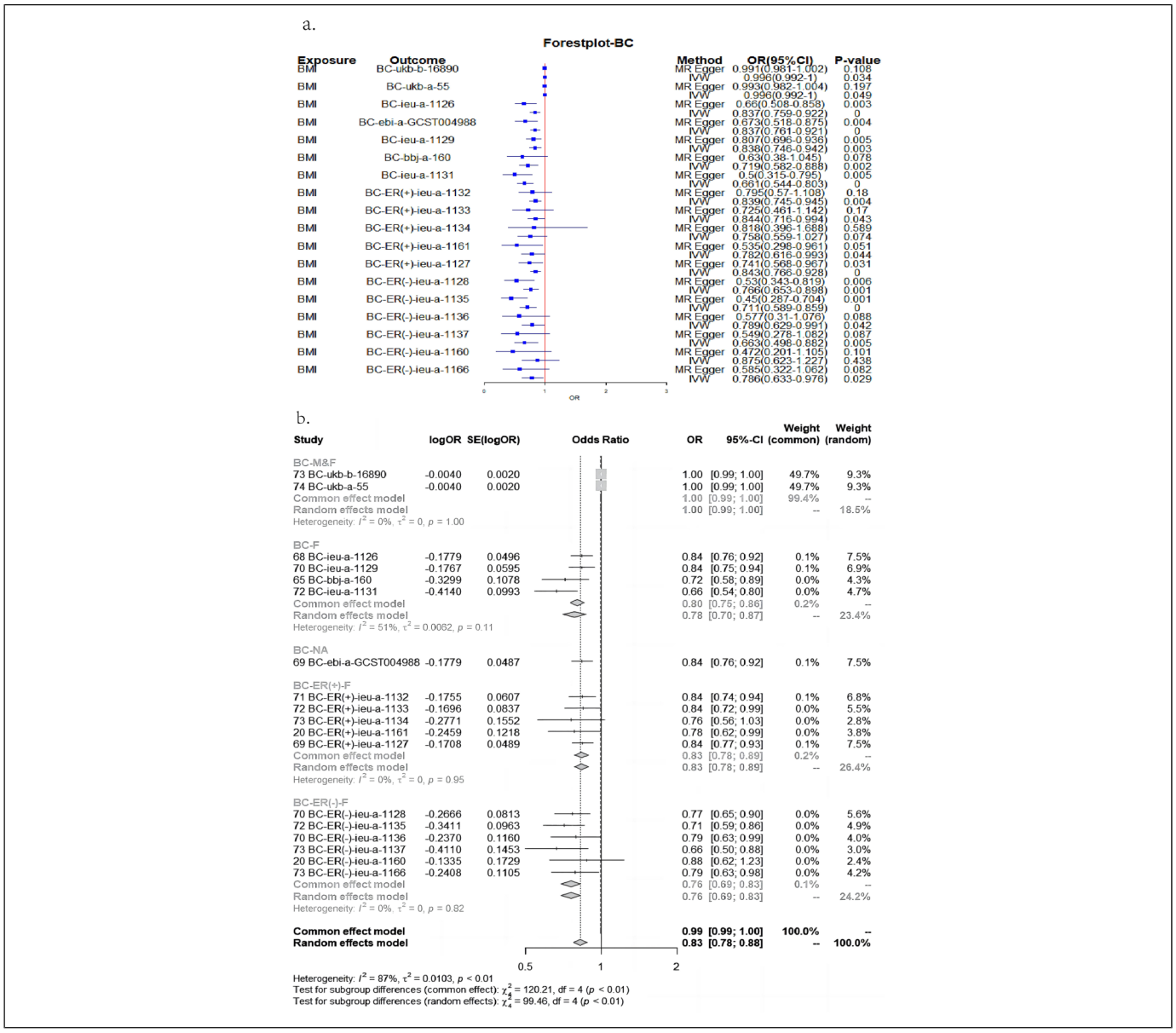

Figure 2. A. Forest plot of the causality of body mass index on the risk of breast cancer and its subtypes. B. Results of a meta-analysis of BMI and risk of breast cancer, estrogen receptor positive breast cancer and estrogen receptor negative breast cancer typed by gender in the study population(Random effect model).

risk. However, the UCEC Association cohort found that BMI was associated with a higher risk of endometrial cancer and its subtypes, based on IVW analysis ($P < 0.05$, OR > 1) (Figure 3A). Other MR methods also showed similar trends, although some lacked statistical significance (Supplementary Table 6). Meta-analysis revealed heterogeneity among study results from different data sources (heterogeneity: $I^2 = 97\%$, $t^2 = 0.0788$, $P < 0.01$). Subgroup analysis indicated that heterogeneity was linked to different database sources. The meta-analysis showed a positive association between increased BMI and endometrial cancer risk in UKB and BBJ study cohorts (UKB, OR:1.00, 95% CI:1.00-1.00; BBJ: OR:1.58, 95% CI: 0.99-2.52) (Figure 3B).

Cervical Cancer and its Precancerous Lesions. TSMR correlation between BMI and cervical cancer in the five included cervical cancer study cohorts showed no significant statistical significance ($P > 0.05$), suggesting there is no clear causal relationship between BMI and the risk of cervical cancer (Figure 4A).The results of the TSMR correlation between BMI and premalignant lesions of cervical cancer showed had no significant statistical significance ($P > 0.05$). The results of other MR methods were consistent with IVW and MR-Egger (Supplementary Table 7). Subsequently, we conducted a meta-analysis of TSMR results from different databases. Our results showed no clear causal relationship between BMI and cervical cancer

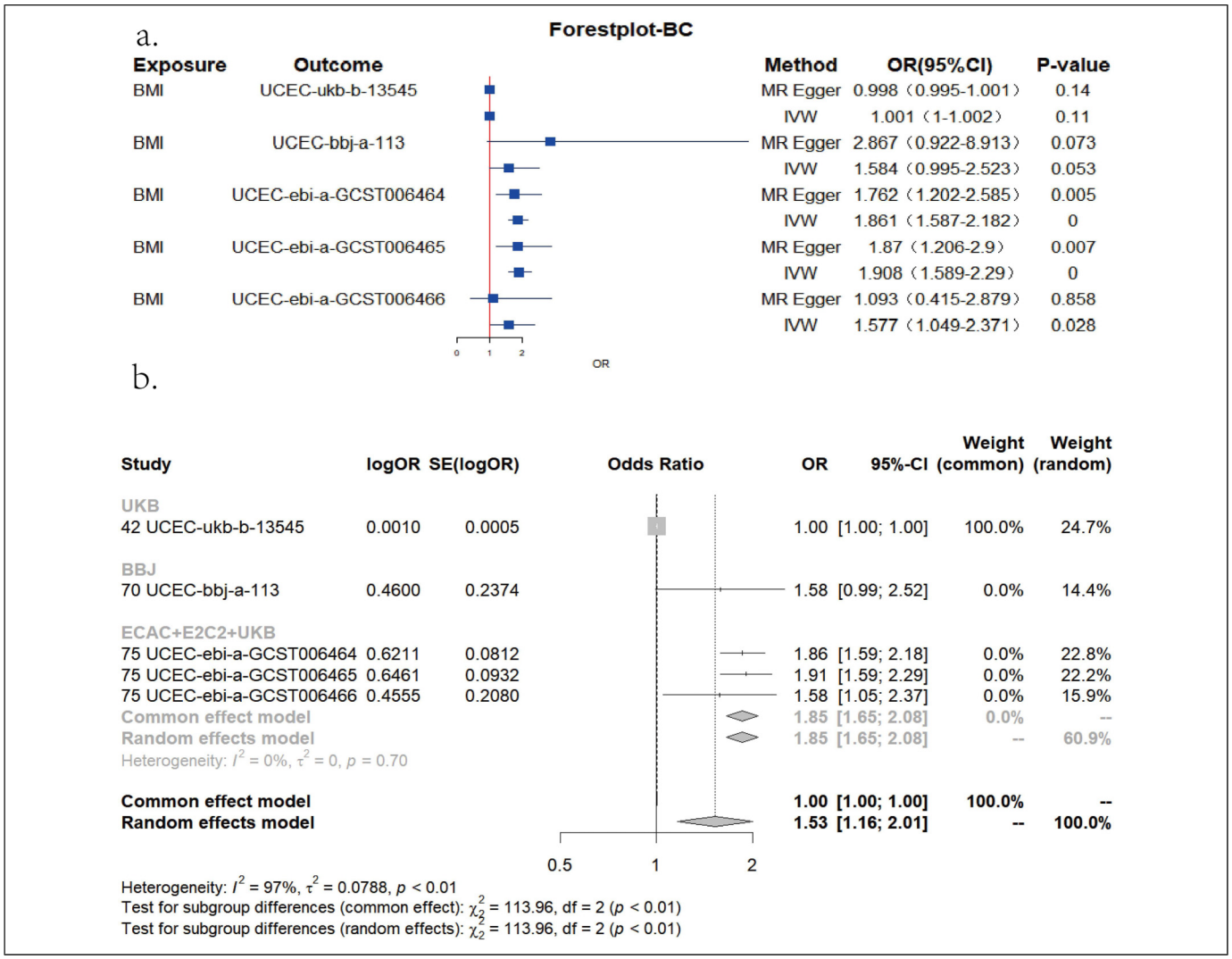

Figure 3. A. Forest plot of the causal relationship between body mass index and the risk of endometrial cancer and its subtypes. B. Risk-related meta-analysis results of BMI and endometrial cancer, endometrial cancer (endometrioid), endometrial cancer (not endometrioid), by study population classification(Random effect model).

and its precancerous lesions. The meta-analysis of different subgroups according to the pathological types (Figure 4B) showed no clear causal relationship between BMI and cervical cancer and its precancerous lesions (CC, OR: 1, 95% CI:1.00-1.00; CIN:OR:1, 95% CI: 1.00-1.00).

Ovarian Cancer and its Related Subtypes. TSMR correlation analysis between BMI and ovarian cancer and its subtypes using the IVW method showed no clear association between BMI and ovarian cancer, but a consistent positive association between BMI and the risk of serous ovarian cancer and endometrioid ovarian cancer (OR > 1, P < 0.05). All the remaining studies were not significant (P > 0.05; Figure 5A).The MR method for studying the risk associations of ovarian cancer and its subtypes under BMI exposure also showed similar estimates of directionality, although some methods lacked statistical significance (Supplementary Table 8). We pooled the relative risk and 95% confidence intervals for ovarian cancer and its subtypes associated with BMI using a random- and fixed-effect model. Meta analysis showed heterogeneity of ovarian cancer and their subtypes (heterogeneity: $I^2 = 70\%$, $t^2 = 0.0116$, $P < 0.01$). We further examined the source of heterogeneity of the study and showed that heterogeneity was mainly associated with pathological subtypes, therefore, we conducted a subgroup analysis of the samples according to the pathological differences of the study individuals. There was no heterogeneity within each subgroup (Figure 5B). The meta-analysis of MR studies using different ovarian cancer subtype datasets showed that increased BMI was positively associated with increased risk of high- and low-grade serous ovarian cancer (SOCH: OR: 1.25, 95% CI: 1.01-1.43; SOCH + L: OR: 1.22, 95% CI: 1.07-1.38; SOC: OR: 1.40, 95% CI: 1.15-1.70). It was also positively associated with the risk of endometrioid ovarian cancer (SOCH: OR: 1.5, 95% CI: 1.01-1.53). Additionally, had no significant causal relationship between elevated BMI, and mucinous and clear cell-like ovarian cancer (P < 0.05).

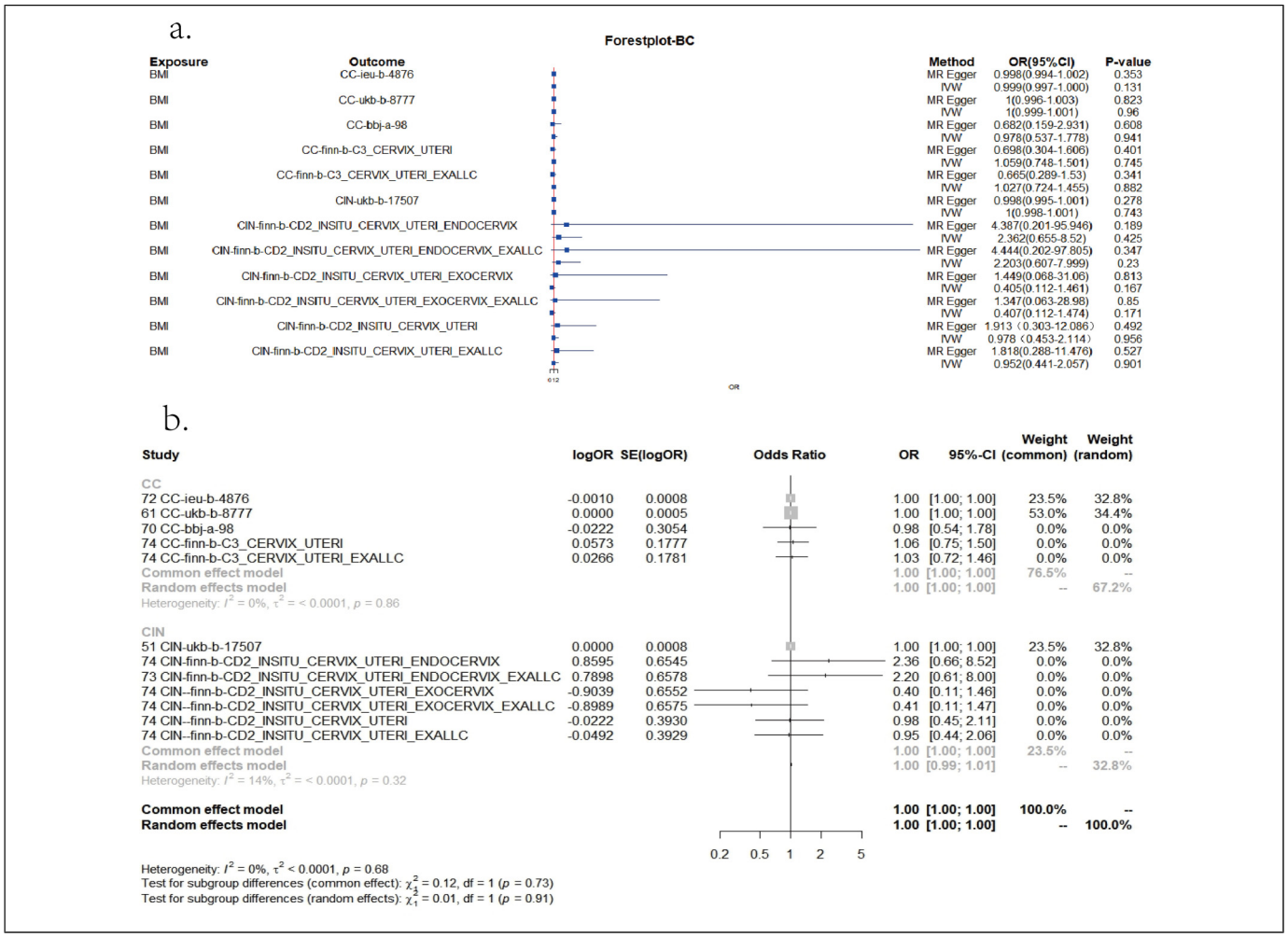

Figure 4. A. Forest plot of the causal relationship between body mass index and the risk of cervical carcinoma subtypes and CIN. B. Results of a meta-analysis of BMI and the risk of cervical cancer and precancerous lesions in women.

Leiomyoma of Uterus. In total, seven GWAS datasets from different databases were included as outcome variables. TSMR correlations between BMI and uterine fibroids was performed using the IVW method. The results showed no clear association of BMI with risk of uterine fibroids (P > 0.05; Figure 6A). Other MR methods for examining associations of uterine fibroid risk under BMI exposure also showed similar directional estimates, although some lacked statistical significance (Supplementary Table 9).We pooled the relative risk and 95% CIs for uterine fibroids associated with BMI using random- and fixed-effect models. The results of the meta-analysis showed that there was no heterogeneity when all the uterine fibroids data were included (heterogeneity: $I^2 = 35\%$, $t^2 = 0.00016$, $P = 0.16$; Figure 6B).

Disussion

Principal Findings

This study conducted the first comprehensive TSMR and meta-analysis exploring the potential causal association between BMI and female reproductive system tumors across various databases. Our findings strongly suggest a causal link between BMI and BC (both ER + and ER-), endometrial cancer (endometrioid and non-endometrioid), and ovarian cancer (high- and low-grade serous, as well as endometrioid ovarian cancer). However, no clear causal association was found between BMI and the risk of cervical cancer, cervical precancerous, mucinous ovarian cancer, clear cell-like ovarian cancer, and uterine fibroids.

Comparisons with Other Studies

A large meta-analysis of 20 datasets was used to demonstrate that premenopausal BC risk is reduced by approximately 8% per 5 kg/m^2 BMI increase (RR, 0.92; 95% CI, 0.88–0.97 [P = 0.001]).[41] Observed BMI was inversely associated with breast cancer risk.[41] The results of our meta-analysis of TSMR also support a causal effect of BMI on BC risk (OR, 0.83; 95% CI, 0.78-0.88 [P < 0.001]). Furthermore, we found a strong positive association with increased BMI on endometrial cancer risk

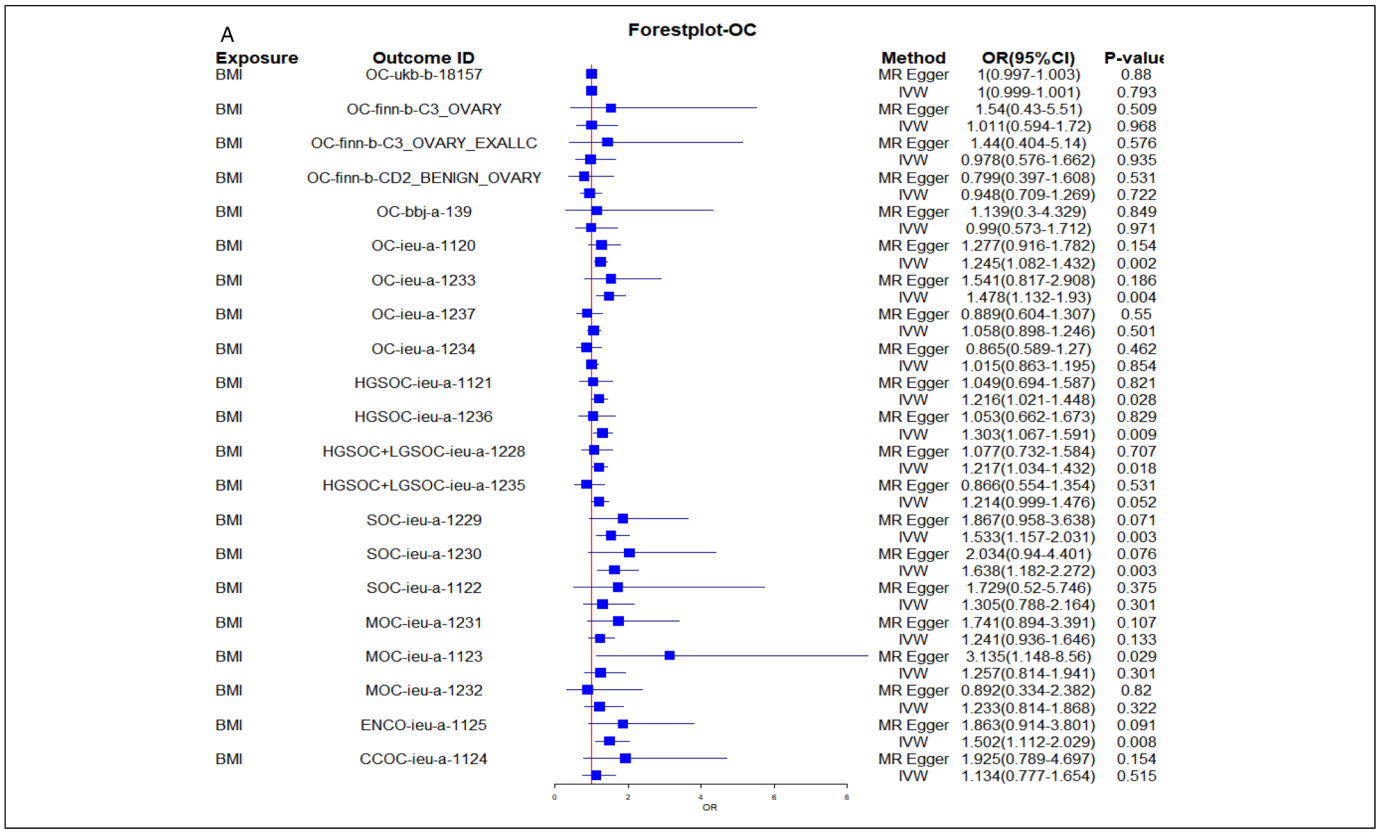

Figure 5. A. Forest plot of body mass index causal risk of ovarian cancer. B. Results of a meta-analysis of BMI by pathological type and risk of ovarian cancer disease in women. (continued)

(OR, 1.53; 95% CI, 1.16-2.01 [P < 0.001]).[42] and stronger evidence for the effect of BMI on endometrial cancer risk and endometrioid has been established.[43] Studies on the relationship between BMI and risk of cervical cancer and its precancerous lesions are limited.The results of a meta-analysis of nine different types of studies showed no clear causal association between BMI and the risk of cervical cancer.[44] Moreover, previous studies found the data on causal relationship between BMI and risk of CIN inconclusive, which is consistent with our TSMR findings (OR,1.53; 95% CI:1.16-2.01[P < 0.001]). However, a small number of studies suggest that increased BMI increases the risk of precancerous cervical cancer lesions.[45] The association between BMI and the risk of ovarian cancer has been controversial. The results of a meta-analysis of cohort and case-control studies showed that both overweight and obesity had an increased risk of ovarian cancer compared with premenopausal and postmenopausal women with normal weight.[46] However, according to our results, this does not apply to all ovarian cancer subtypes. TSMR results showed an increased risk of serous ovarian cancer and endometrioid ovarian cancer in women with high BMI, and also suggested that there was no clear causal relationship between elevated BMI and the risk of mucinous and clear cell-like ovarian cancer. There is no consensus on the association between obesity and the risk of uterine fibroids. While studies have suggested a potential link between that may be related to overweight and central obesity in black women and the prevalence of uterine fibroids[47] this association appears to be specific to the risk of maternal uterine fibroids. However, our results indicate that high BMI does not show a definitive association with the risk of uterine fibroids in European women.

Potential Mechanisms

Obesity is a condition in which a person has a high BMI resulting from excessive amount of adipose tissue. Uncontrolled obesity can lead to metabolic disorders, altered production of steroid hormones, and chronic inflammation, which is be linked to tumor development and progression.Obesity-associated metabolic syndrome and insulin resistance is also caused by obesity-associated inflammation, underscoring the potential importance of inflammation as a key factor in obesity-driven cancer progression.[48] There is also increasing evidence supporting a link between obesity-associated inflammation and endometrial cancer incidence and progression. In addition, obesity significantly impacts body immunity, as recent literature highlights various immune alterations associated with obesity. These include changes in adaptive and innate immunity, including increased Th 1 cell responses, and $CD8^+$ cytotoxic T cell responses.[49] Disruption of many tissue-specific and systemic physiological processes in obesity creates and sustains an altered local

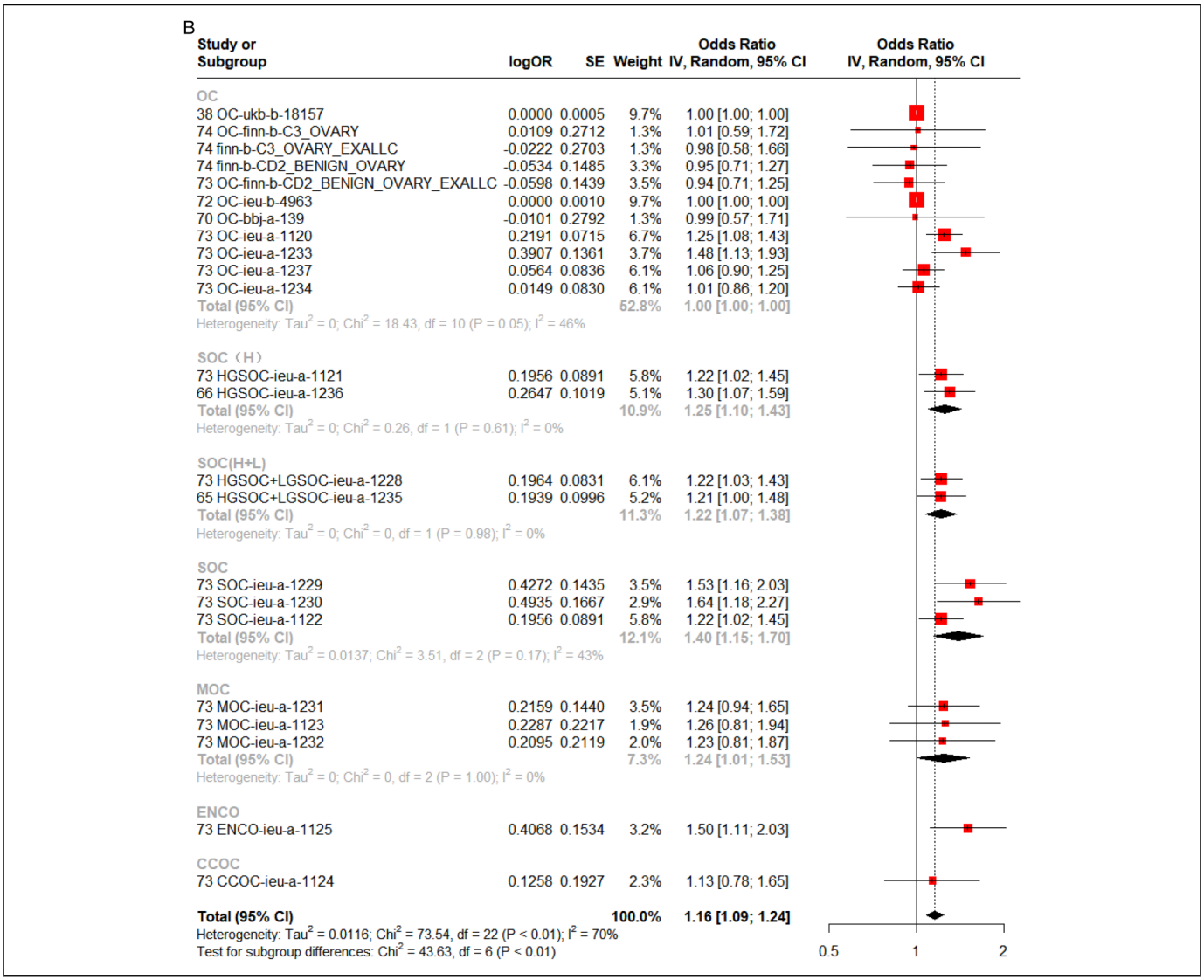

Figure 5. Continued.

environment that facilitates tumor development and growth. Another study indicated that obesity-induced dysfunctional B cell responses, similar to those occurring during aging, can be ameliorated by weight loss in some individuals with obesity through weight loss.[50]

Strengths and Limitations

Our study covers several aspects. First, the TSMR method used excludes confounding factors and reverse causality, unlike the traditional observational design. Second, a meta-analysis of multisource TSMR data was conducted. Compared to the traditional RCT with limited evidence and a small sample size, our study has a sufficient sample size and more relevant results. Finally, despite the existing research on the association between BMI and tumor risk, there is still a lack of research on subtype risk. This study provides new insights into the relationship between BMI and five tumor subtype risks of women. However, our study also has some limitations. The MR results only reflect the changes in tumor risk in women due to the genetic susceptibility status of BMI, while the impact of BMI changes in the short term is unknown and the association needs further confirmation by future clinical studies. Additionally, estimates may be biased when using UK Biobank, as genetic associations of genetic predictors of different tumor subtypes with BMI may come from the same study. However, causal associations were similar when we used datasets from the Finn database whose participants do not overlap with those in the UK Biobank.[51] Furthermore, BMI reflects overall fat content, not just abdominal fat, potentially biasing the causal relationship. Additionally, although the data includes Asians, it is primarily based on European women. Therefore, the results may not apply to other ethnicities, and future studies with larger samples are necessary.

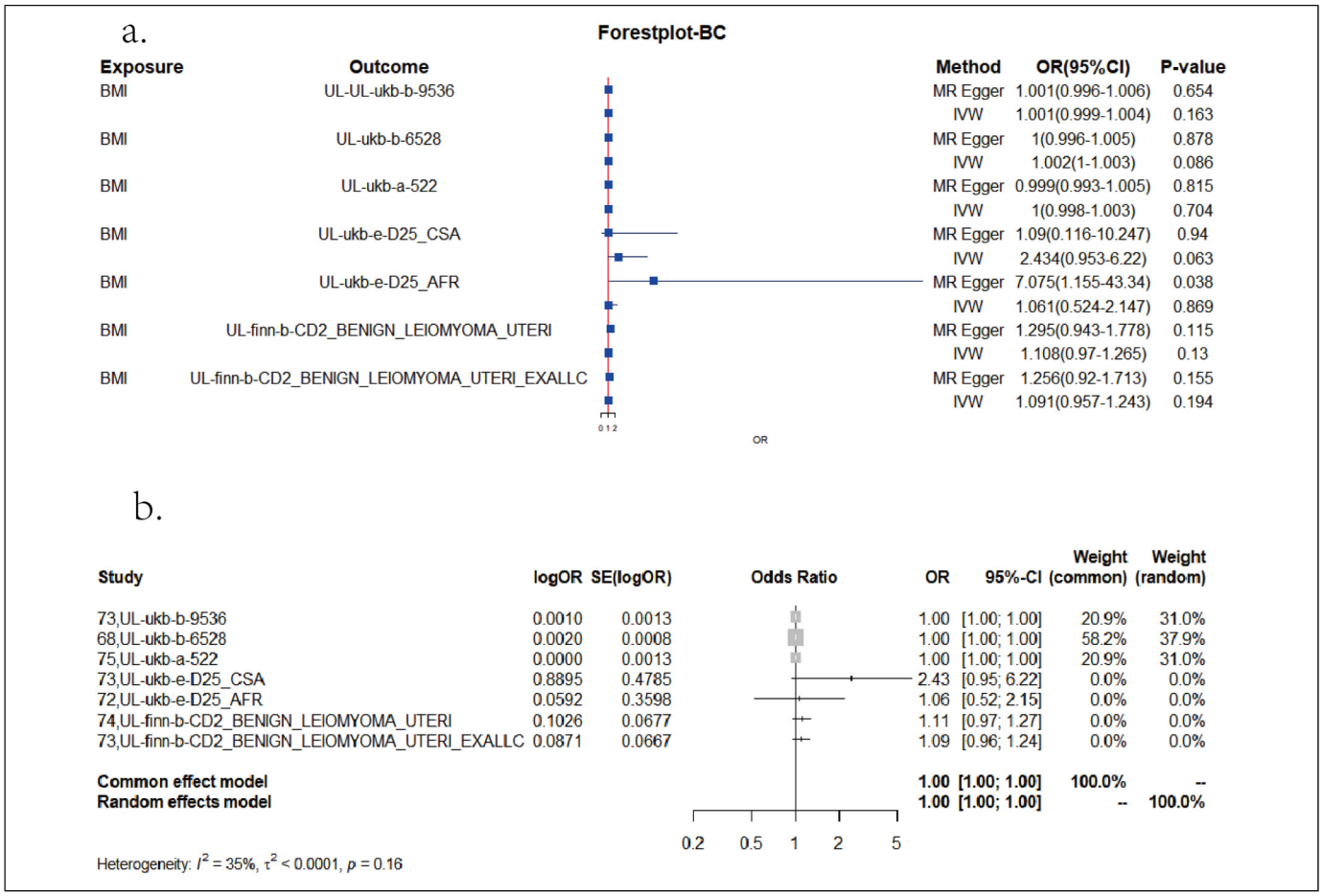

Figure 6. **A.** Forest plot of body mass index causal risk of Leiomyoma of uterus. **B.** Results of a meta-analysis of BMI and risk of Leiomyoma of uterus in women.

Conclusions

Our TSMR results provide genetic evidence in support of causal association differences between BMI and female predisposition to tumors and its multiple subtypes. Our findings highlight that BMI leads to different risk profiles in different tumor subtypes, implying that BMI may be related to the risk of cancers of specific pathological tissue origin in women rather than anatomical sites, and also provide new ideas for tumor prevention in women.

Authors' Contributions

Xi-Ya Jiang: funding acquisition, investigation,writing-original draft, conceived and designed the study. Shu-Guang Zhou: funding acquisition,conceptualization, project administration, Min Xiong: writing-review & editing. Lan Zhen: investigation and methodology.Sen-Lin Wang : investigation, supervision and methodology. Qin-Qin Jin: conceptualization, formal analysis. Yin-Ting Yang: conceptualization, project administration.Ya-Xing Fang: methodology,Lin Hong&Jie Mei:data acquisition and processing.

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Data Availability Statement

The main text and Supplemental materials have included all the data generated in the present study. The sources of the GWAS statistics used in this study could be found in the original GWAS.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics Approval

In the present study, we only utilized publicly available summary data, and the Ethics approval and consent to participants could be obtained in the original GWAS.

Ethics Statement

This article does not contain any studies involving humans or animals, so no ethical statement is required.

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Supplemental Material

Supplemental material for this article is available online.

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