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Association between gynecological cancers and female infertility: insights from bidirectional Mendelian randomization analysis

Jifeng Li[1], Yifei Zeng[1] and Dongxiao Zhang[1*]

Abstract

Purpose In recent years, research interest in the potential link between female infertility (FI) and gynecological cancer (GC), including ovarian cancer (OC), endometrial cancer (EC), cervical cancer (CC), and breast cancer (BC), has grown, yet findings remain inconclusive. This study aims to explore the causal relationship between FI and GC using bidirectional two-sample Mendelian randomization (MR) analyses, thereby informing future strategies for FI and GC prevention.

Methods We utilized SNPs identified from genome-wide association studies (GWAS) on FI and GC. The inverse variance weighted (IVW) method served as the primary approach to assess the causal association between FI and GC. Additionally, five other MR methods—Weighted median, Weighted mode, MR-Egger, Simple mode, and Robust-Adjusted Profile Score—were employed to enhance result robustness and credibility.

Results In the forward MR analysis, our IVW results indicated no significant association between FI and GC (FI-BC: OR = 0.95, 95% CI: 0.83–1.09, *P* = 0.47, P-FDR = 0.775; FI-OC: OR = 1.01, 95% CI: 0.84–1.24, *P* = 0.789, P-FDR = 0.896; FI-CC: OR = 0.80, 95% CI: 0.61–1.06, *P* = 0.118, P-FDR = 0.775; FI-EC: OR = 1.07, 95% CI: 0.88–1.30, *P* = 0.490, P-FDR = 0.775).In the reverse MR analysis, we found a marginal association between BC and FI. However, after adjusting for multiple testing using the FDR method, no significant causal relationship was found between BC and FI, suggesting a marginal association (OR = 1.054, 95% CI: 1.001–1.108, *P* = 0.043, P-FDR = 0.331). For other cancers, no significant causal relationships were observed between OC, CC and EC with FI(OC-FI: OR = 1.043, 95% CI: 0.999–1.087, *P* = 0.051, P-FDR = 0.331;CC-FI: OR = 0.992, 95% CI: 0.956–1.028, *P* = 0.654, P-FDR = 0.836; EC-FI: OR = 1.006, 95% CI: 0.956–1.055, *P* = 0.809, P-FDR = 0.885).

Conclusions Our study found no significant causal relationship between FI and GC. However, a potential marginal association between BC and FI was observed. These findings underscore the need for further research to confirm this association and emphasize the importance of reproductive protection for young breast cancer patients to preserve fertility.

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Introduction

Infertility presents a significant global health challenge, affecting 10–15% of couples worldwide who experience difficulties conceiving [1]. Despite extensive research from genetic [2–3], biological [4], and epidemiological perspectives [5], conclusive outcomes have remained elusive.

Gynecologic cancers encompass ovarian cancer (OC), endometrial cancer (EC), cervical cancer (CC), and breast cancer (BC), primarily influenced by hormonal and reproductive factors [6]. We selected gynecologic cancers due to their high incidence rates in women and their relevance to reproductive health. Additionally, these cancers are influenced by hormonal and reproductive factors, which may intersect with female infertility (FI). The relationship between FI and these cancers remains contentious, motivating further exploration in this study. Recently, the increasing incidence of FI has drawn attention to its potential role in gynecologic cancers. Numerous studies have explored the association between FI and these cancers, yielding varied and conflicting results [6–9]. Challenges such as confounding variables and observational biases, including potential reverse causality, complicate interpretation [10–12].

Given the unresolved debate on the causal link between FI and GC risk, we employed Mendelian randomization (MR) analysis. MR utilizes genetic variants as instrumental variables to infer causality, leveraging Mendelian inheritance principles [13–14]. This approach offers a robust framework for exploring causal relationships in epidemiological research.

This study aimed to elucidate the causal relationship between infertility and gynecologic cancers through comprehensive two-sample MR analysis. By applying MR, we sought to provide clarity amidst the existing uncertainties and contribute to the understanding of these complex relationships in women's health research.

Materials and methods

The design and reporting of this study followed STROBE-MR guidelines to ensure transparency and integrity of Mendelian randomization studies (Supplementary Material 1).

Research design

Three hypotheses must be met in this MR Study: (1) there is a strong association between genetic variants and FI/GC. (2) Genetic variation could not influence the occurrence of FI/GC by confounding factors. (3) Genetic variation can only affect the occurrence of GC through FI (or only affect the occurrence of FI through GC). The MR Research design is shown in Fig. 1.

Data sources and information

In this study, we explored a bidirectional causal relationship between FI and GC, which were used as exposure and outcome variables respectively for MR Analysis. Single nucleotide polymorphisms (SNPS) for female infertility, obtained from the FinnGen database (https://r10.finngen.fi.). SNPS for gynecological cancers (breast, endometrial, ovarian and cervical) were obtained from the source MRC IEU OpenGWAS (MR-base) database (website: https:/gwas.mrcieu.ac.uk). The above specific data information is shown in Table 1. All demographics are European females.

To ensure the independence of exposure (FI) and outcome (GC), we selected SNPs from distinct GWAS sources for each condition. The samples used for FI and GC were separate, minimizing the risk of overlapping that could potentially introduce bias.

SNPs screening process

First, the single nucleotide polymorphisms (SNPs) selected by FI and GC must be genome-wide and strongly associated with the exposed disease ($P < 5 \times 10^{-8}$) by linkage disequilibrium (LD) criteria ($R^2 < 0.001$, LD distance > 10,000 kb) to obtain SNPs. However, in this MR, we find that when using this *p*-value, FI, EC, CC and OC get 3, 3, 0 and 1 SNPs respectively. So, for these four diseases, we properly enlarge the *P* value, choose $P < 5 \times 10^{-6}$. Next, we addressed potential confounding factors and the impact of palindromic sequences. Through a literature review, we identified several confounders for female infertility (FI), including smoking, high-fat diet, alcohol consumption, high BMI, lifestyle factors, family history of infertility, and contraceptive drug use [15–16]. For gynecological cancers (GC), the identified confounders included cigarette smoking, high BMI, high-fat diet, mood disorders, age at menstruation or menopause, and diabetes [17–18]. After identifying the confounders associated with FI and GC, we examined the SNPs included in this study using PhenoScanner. SNPs that were linked to any of the FI/GC risk factors were excluded from the analysis. The exclusion criteria were based on a stringent *P*-value threshold of $P < 5 \times 10^{-8}$.

Palindromic sequences are excluded by R packages "TwoSampleMR" and "MedelianRandomization". Furthermore, SNPs with missing data in the dataset will also be removed. At the same time, when FI and GC were exposed, respectively, we used the variance (R2) and F

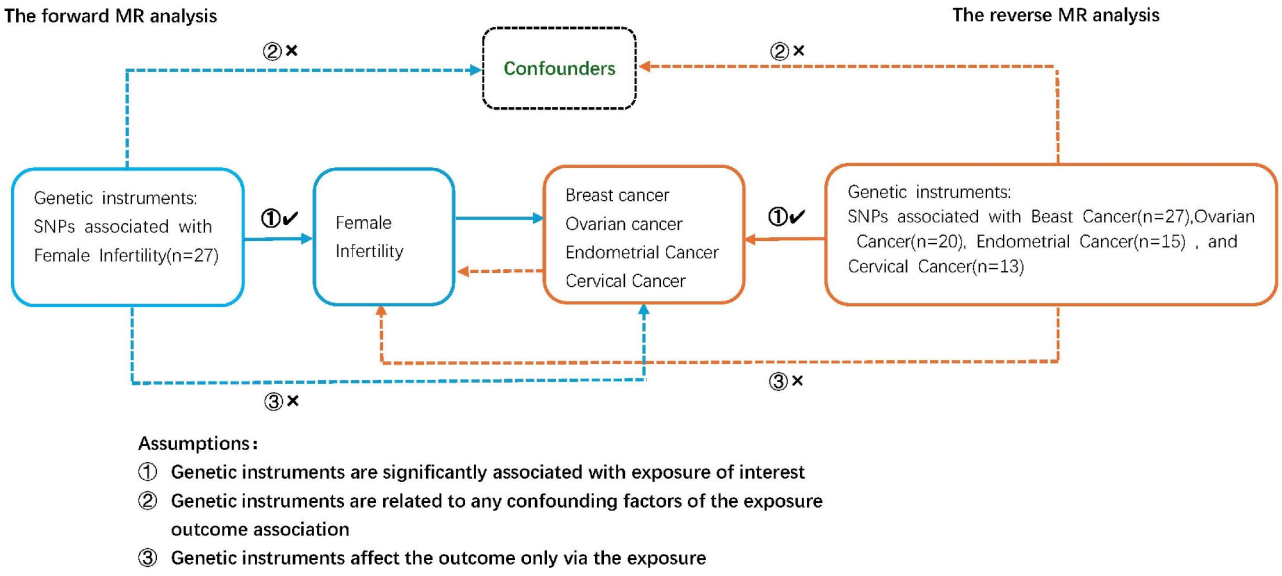

Fig. 1 Schematic representation of the bidirectional Mendelian randomization (MR) analysis framework used in this study. The diagram illustrates the genetic instruments for gynecological cancers and female infertility, along with their respective causal pathways. Arrows indicate the hypothesized causal relationships explored between these two traits

Table 1 Data information on female infertility and gynecological cancer

Diseases	Databases	GWAS ID	Year	Number of SNPs	ncase	ncontrol
FI	FinnGen	N14_FEMALEINFERT	2021	21,215,092	14,759	111,583
BC	BCAC	ieu-a-1131	2017	10,680,257	14,910	17,588
EC	IEU OpenGWAS	ebi-a-GCST90018838	2021	24,135,295	2,188	237,839
OC	IEU OpenGWAS	ebi-a-GCST90018888	2021	24,137,758	188	244,932
CC	IEU OpenGWAS	ebi-a-GCST90018817	2021	24,138,337	909	238,249

FI: female infertility, BC: breast cancer, EC: endometrial cancer, OC: ovarian cancer, CC: cervical cancer, ncase: Number of Cases, ncontrol: Number of control, BCAC: Breast Cancer Association Consortium

statistics to assess the statistical power of their genetic instrumental variables. In order to reduce potential weak instrumental bias, instrumental variables with $F > 10$ were selected for MR Analysis [19]. Finally, we get the SNPs needed for MR Research.

Statistical analysis

Bidirectional MR analysis was performed for FI-GC, with the Inverse Variance Weighted (IVW) method as the primary analysis approach [20]. In addition, five supplementary methods were applied, including Weighted Mode, MR-Egger, Weighted Median, Simple Mode, and Robust Adjusted Profile Score (RAPS) [21]. Cochran's Q test and funnel plot were used to evaluate heterogeneity of SNPs. In cases of heterogeneity, the IVW random effects model was employed to address or exclude abnormal SNPs. To assess the potential for pleiotropy and confounding, additional sensitivity analyses, including MR-Egger and leave-one-out analysis, were conducted. Furthermore, *p*-values were adjusted for multiple comparisons using the False Discovery Rate (FDR) method (Benjamini-Hochberg), with *p*-values (P-FDR) < 0.05 considered significant for causality. These analyses ensured that our findings were not influenced by confounding effects or overlapping samples. Horizontal pleiotropy in the SNPs was further explored using the MR-Pleiotropy RESidual Sum and Outlier (MR-PRESSO) test and the MR-Egger Intercept test [22]. All statistical analyses were performed using the R packages 'TwoSampleMR' and 'MRPRESSO' (R version 4.3.2).

Results

SNPs included in MR analysis

During the SNP selection process, we identified 18–20 SNPs ($F > 10$) as instrumental variables for FI in the forward MR analysis (Supplementary Table 1). For the reverse MR analysis, 12–15 SNPs ($F > 10$) were selected as instrumental variables for gynecological cancers (Supplementary Table 2). Importantly, none of the SNPs associated with FI or GC were found to be correlated with potential confounders related to these conditions. To ensure the robustness of our findings, we assessed the statistical power of our analysis. Specifically, we utilized the F-statistic to evaluate the strength of the instrumental variables, selecting those with an F-statistic greater than 10 to minimize the risk of weak instrument bias.

The analysis demonstrated sufficient statistical power to reliably detect significant causal relationships.

Forward MR between FI and GC

The IVW method showed that there may be no causal relationship between FI and GC (FI-BC: OR:0.95,95%CI 0.83–1.09, $P=0.47$, P-FDR = 0.775; FI-OC: OR: 1.01, 95%CI: 0.84–1.24, $P=0.789$, P-FDR = 0.896;FI-CC: OR: 0.80, 95%CI: 0.61–1.06, $P=0.118$, P-FDR = 0.775; FI-EC: OR: 1.07, 95%CI: 0.88–1.30, $P=0.490$, P-FDR = 0.775). There was no statistical significance in the four complementary methods of FI and GC (Weighted mode, MR-Egger, Weighted median and Simple mode) ($P>0.05$). The scatter plot also verified that there was no causal relationship between FI and GC (Supplementary Fig. 1). Finally, in this study, the RAPS method revealed no causal relationship between FI and BC, OC, or EC ($P>0.05$). However, a marginal causal association between FI and CC was observed ($P=0.049$) (Fig. 2 presents the forest plot of the results from all six methods; Supplementary Table 3). While the RAPS methods suggest a possible link between FI and CC, the evidence remains insufficient to establish a definitive causal relationship. Further investigation through additional studies is warranted to confirm

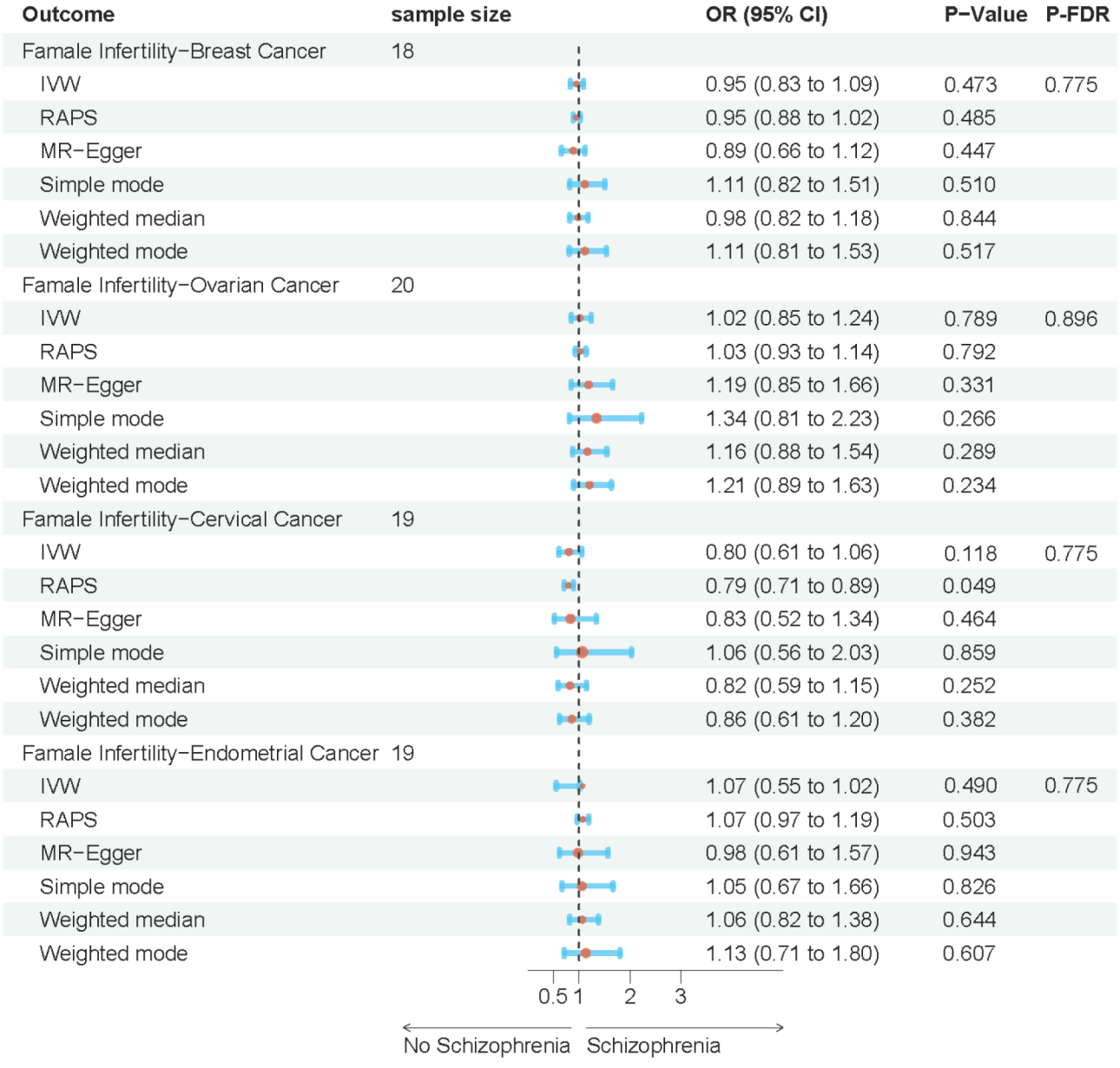

Fig. 2 Forest plot showing the causal effects of gynecological cancers on female infertility based on the Mendelian randomization analysis. Each point represents the effect estimate (odds ratio), with horizontal lines indicating the 95% confidence intervals. The plot includes results from the inverse variance weighted (IVW) method, MR-Egger regression, and weighted median analysis

this finding. The leave-one-out method verifies the consistency of the results (Supplementary Fig. 2). Cochran's Q test showed that there was no significant heterogeneity between FI and BC, OC and EC ($P > 0.05$), while there was heterogeneity between FI and CC ($P < 0.05$, Supplementary Table 4). No abnormal SNPs were found in the funnel plot results (Supplementary Fig. 3). Therefore, we have adopted the random effects model of IVW to deal with the heterogeneity between FI and CC. Both the MR-PRESSO and MR-Egger Intercept methods showed that there was no significant horizontal pleiotropy ($P > 0.05$, Supplementary Tables 5 and 6).

Reverse MR between FI and GC

According to the results of the IVW method, there is a positive causal relationship between BC and FI. However, after adjusting for multiple testing using the FDR method, no significant causal relationship was found between BC and FI, suggesting a marginal association between the two (OR = 1.054, 95% CI: 1.001–1.108, $P = 0.043$, P-FDR = 0.331).In this study, no significant causal relationship was observed between OC, CC, and EC with FI(OC-FI: OR = 1.043, 95% CI: 0.999–1.087,$P = 0.051$,P-FDR = 0.331;CC-FI: OR = 0.992, 95% CI:0.956–1.028,$P = 0.654$, P-FDR = 0.836;EC-FI: OR = 1.006, 95% CI: 0.956–1.055, $P = 0.809$, P-FDR = 0.885).

In the weighted model, MR-Egger model, weighted median model, and simple mode, no significant causal relationship between FI and GC was observed ($P > 0.05$). However, the scatter plot results indicated that the slope direction between GC and FI was consistent, providing further validation for the causal relationship between GC and FI and enhancing the reliability of the study's findings (Supplementary Fig. 4). Moreover, the RAPS method further supported the potential marginal association between BC and FI ($P = 0.044$), rather than a direct causal relationship. The results from the RAPS method further strengthened the reliability of the IVW method (the forest plot for all six methods is shown in Fig. 3, Supplementary Table 7). Through the leave-one-out method and funnel plot analysis, no outlier SNPs were detected (Supplementary Figs. 5 and 6), which further confirmed the stability and reliability of the results. Additionally, Cochran's Q test indicated no significant heterogeneity between GC and FI ($P > 0.05$, Supplementary Table 8). Finally, MR-PRESSO and MR-Egger Intercept methods did not detect significant horizontal pleiotropy ($P > 0.05$, Supplementary Tables 9 and 10), further validating the conclusions of this study.

Discussion

As global attention to women's health has increased, observational studies investigating the relationship between FI and GC have proliferated; However, their findings remain inconsistent. Some studies suggest that FI may [7, 6–23] or may not [6] influence the incidence of GC, while others indicate that GC may [9] or may not [24] elevate the risk of FI. These conflicting results from epidemiological studies fail to provide clear evidence of a causal relationship between FI and GC. To address this issue, we utilized bidirectional MR analysis, which helps to avoid confounding biases and reverse causality typically associated with traditional observational studies. Our bidirectional MR Found no causal relationship between GC and FI, but there may be a marginal association between BC and FI.

Our study aimed to explore the causal relationship between FI and GC using bidirectional MR analysis. The results of the forward MR analysis showed no significant causal relationship between FI and any of the gynecological cancers, including BC, OC, CC and EC. Specifically, the IVW method yielded ORs close to 1 for each pair, with no statistically significant findings ($P > 0.05$). Similarly, the results from the four complementary MR methods—Weighted mode, MR-Egger, Weighted median, and Simple mode—also showed no evidence of a causal relationship between FI and GC ($P > 0.05$). The scatter plot further corroborated these findings, showing no consistent causal direction between FI and GC (Supplementary Fig. 1). Additionally, the RAPS method did not detect any causal relationships between FI and BC, OC, or EC ($P > 0.05$). However, a marginal causal association between FI and CC was observed ($P = 0.049$), suggesting a potential link, but the evidence remains insufficient to establish a definitive causal relationship.

In the reverse MR analysis, which tested the causal effect of GC on FI, a positive association between BC and FI was observed. Although this result did not reach statistical significance after adjusting for multiple comparisons using the FDR method (P-FDR = 0.331), the odds ratio (OR = 1.054, 95% CI: 1.001–1.108, $P = 0.043$) suggests a marginal relationship between BC and FI. This finding implies that an additional unit of breast cancer cases could be associated with a slight increase in the odds of developing infertility. While this result did not meet statistical significance after multiple testing corrections, it provides preliminary evidence for a marginal association that warrants further exploration.

Several potential factors may explain the observed marginal relationship between BC and FI. First, hormonal changes associated with breast cancer, particularly elevated estrogen and progesterone levels, may negatively affect ovarian function and contribute to infertility. Hormone receptor-positive breast cancers are often linked to disruptions in ovarian function, which can impair ovulation and fertility [25–26]. Second, chronic inflammation, commonly seen in breast cancer, may adversely affect reproductive organs, leading to infertility [27–28]. Third,

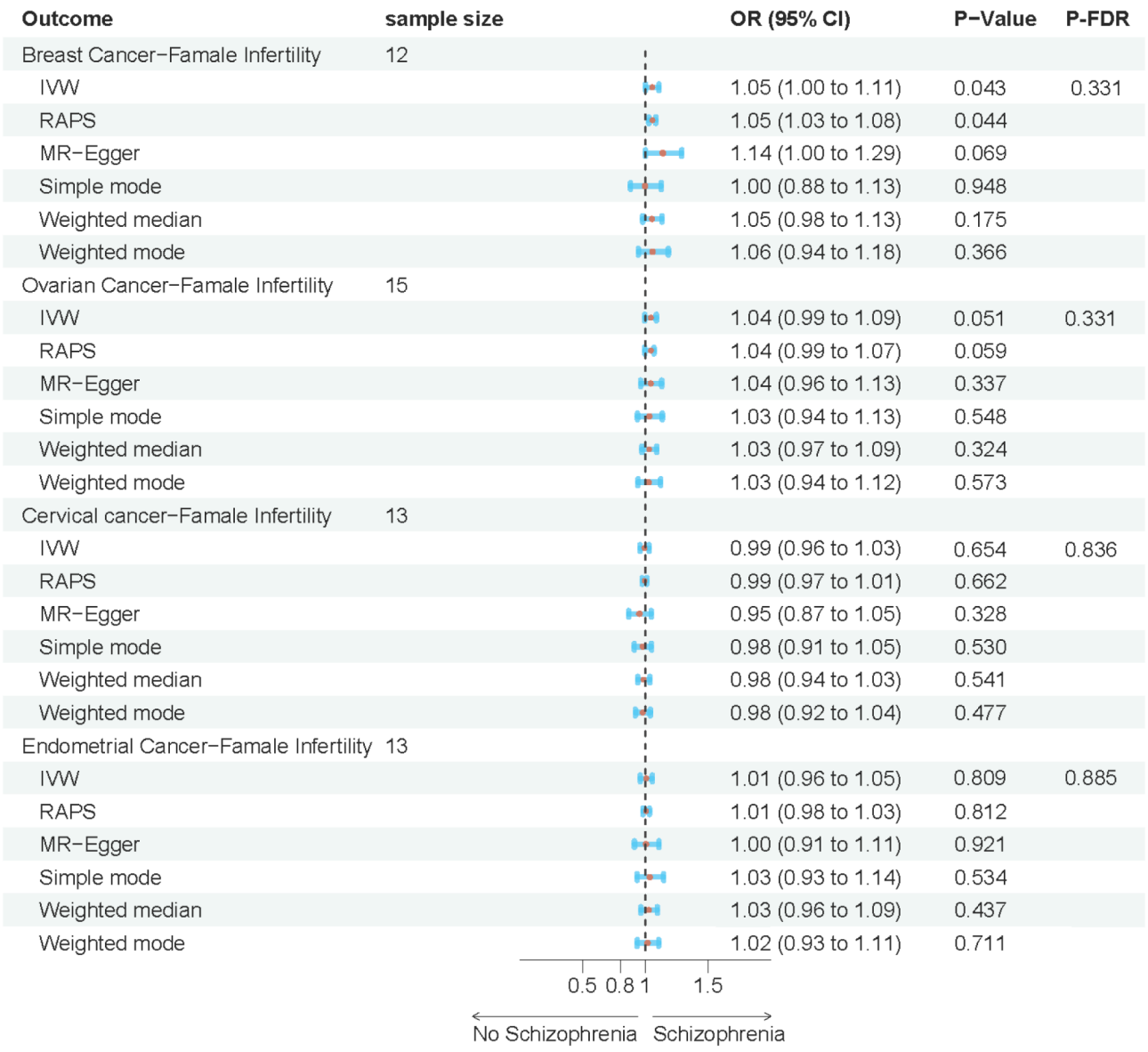

Fig. 3 Forest plot showing the causal effects of female infertility on the risk of gynecological cancers using the bidirectional Mendelian randomization approach. Odds ratios are displayed for each gynecological cancer subtype, with 95% confidence intervals depicted by horizontal lines. Multiple MR methods, including inverse variance weighted (IVW), MR-Egger, and weighted median, are used to provide robust effect estimates

cancer treatments, such as chemotherapy, radiotherapy, and endocrine therapies, are known to impair reproductive health, potentially resulting in infertility [29]. While our study provides evidence for a marginal association, further research is needed to explore the underlying mechanisms and confirm this relationship.

Our findings align with previous MR studies, which similarly found no causal relationship between FI and other cancers, such as EC [30]. This supports the robustness of our methodology and reinforces the utility of bidirectional MR analysis in minimizing confounding and reverse causality. The large sample size, which included 14,759 cases and 11,583 controls, enhances the statistical power of our study, and the exclusive focus on European women reduces racial bias. Additionally, the consistency between our main IVW results and those from complementary MR methods, such as Weighted Median, MR-Egger, Weighted Mode, and RAPS, strengthens the robustness of our findings. However, minor discrepancies between methods may arise due to their varying sensitivity to horizontal pleiotropy, heterogeneity, and invalid instruments. For instance, MR-Egger is more flexible in handling directional pleiotropy but tends to have lower statistical power, whereas Weighted Median can provide valid estimates even when up to 50% of instruments are invalid. Therefore, employing multiple MR approaches

offers a comprehensive evaluation, increasing the reliability and validity of our conclusions.

However, our study has some limitations. First, it relied on a single database, which may limit the generalizability of our findings. Future studies should aim to integrate data from multiple databases to provide a more comprehensive analysis and validate these results. Second, survival bias may have influenced our findings, particularly in the reverse MR analysis. Women who have experienced breast cancer may undergo more frequent cancer screenings, potentially affecting the detection rates of infertility. This could have biased our results, especially regarding the association between BC and an increased risk of FI. Third, our study was restricted to a single population of European women, which limits the generalizability of our findings to other ethnic groups.

Therefore, we recommend that clinicians consider offering fertility preservation options, such as egg or embryo freezing, to young breast cancer patients, especially those with significant fertility concerns. Additionally, healthcare providers should be proactive in discussing potential fertility risks and available reproductive interventions as part of the overall cancer care plan. Future research should also focus on developing guidelines for reproductive health management in breast cancer survivors, aiming to mitigate the long-term impact of cancer treatments on fertility.

In conclusion, while our study suggests a marginal association between breast cancer and female infertility, the evidence remains inconclusive due to the lack of statistical significance after multiple testing corrections. Further research, including basic experiments and randomized controlled trials, is essential to establish a more definitive understanding of this relationship. Importantly, our findings highlight the need for protective interventions to preserve fertility in young women diagnosed with breast cancer, particularly for those with significant fertility concerns. Such interventions could help mitigate the reproductive consequences of cancer treatments.

Conclusions

Our bidirectional Mendelian randomization analysis found no significant causal relationship between female infertility FI and GC. However, a marginal association between BC and FI was observed, suggesting a potential link, though the evidence remains inconclusive after multiple testing corrections.

These findings highlight the need for further research to explore the mechanisms behind the potential relationship between BC and infertility. Additionally, our study emphasizes the importance of fertility preservation strategies for young breast cancer patients.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12905-025-03729-9.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Supplementary Material 8

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Author contributions

The study was conceived and designed by JFL, and DXZ. DXZ, and YFZ coordinated the study. JFL and YFZ contributed to data collection. JFL performed the statistical analysis and prepared the first draft of the manuscript. DXZ revised the paper and helped to write the final draft of the manuscript. All authors gave final approval of the version to be published.

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethical approval and consent to participate

This study is based on publicly available summarized data. The protocol and data collection were approved by the ethics committee of each genome-wide association study. Written informed consent was obtained from each participant of previously published GWASs before data collection.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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