DOI: 10.1002/imo2.70032

CORRESPONDENCE

iMetaOmics WILEY

Leveraging genetic data for female breast cancer prevention and therapy: Perspectives from Mendelian randomization

To the editor,

Female breast cancer is a complex disease influenced by a combination of genetic factors and environmental factors, both of which contribute to carcinogenesis and progression [1]. In the past decade, remarkable advancements in the large-scale genome-wide association studies (GWAS) have enabled comprehensive analyses of millions of genetic variants linked to lifestyle factors, molecular biomarkers, and health outcomes, which have promoted the development of Mendelian randomization (MR) analysis. MR analysis leverages these abundant genetic variants as instrumental variables (IVs) to infer the causal relationships between exposures and health outcomes [2]. Here, we aim to introduce the application of MR analysis in the prevention and therapy of female breast cancer, as well as to discuss emerging opportunities to advance the field.

1 | OVERVIEW OF THE MR ANALYSIS

MR is an application of IV analysis that aims to infer the causal relationships between exposures and health outcomes by leveraging genetic variants as IVs, such as single nucleotide polymorphisms (SNPs) [2]. An exposure could be a clinical risk factor, a plasma metabolite or protein, or a gut bacterial species, and an outcome could refer to a disease or any complex human trait. The principle of MR analysis is based on Mendel's second law, which states that alleles segregate independently when DNA is passed from parents to offspring during gamete formation [2]. This biological principle ensures that genetic variants are randomly distributed among individuals, which is similar to the randomly assigned interventions in a randomized controlled trial (RCT) [2]. Therefore, MR acts as a "natural RCT," providing a natural experiment for causal inference and significantly reducing biases from confounding factors and reverse causality in traditional observational studies [2]. For example, differences in risk of disease between two gene allele subgroups (e.g., allele A and allele T in *rs1229984* in *ADH1B*) can indicate the potential causal associations between risk factors (e.g., alcohol intake) and health outcomes (e.g., female breast cancer) (Figure S1). To obtain valid and reliable results from MR analysis, genetic variants should meet three core assumptions (Figure S2): (1) relevance: genetic variants must exhibit strong associations with the exposure of interest (e.g., *rs1229984* in *ADH1B* for alcohol intake); (2) independence: genetic variants should not be associated with potential confounders (e.g., *rs1229984* not associated with smoking status); (3) exclusion restriction: genetic variants must influence the outcome exclusively through the exposure (e.g., *rs1229984* affects the incidence risk of female breast cancer only through alcohol intake). MR can be conducted using either individual-level genetic data or summary statistics from the GWAS. Given the widespread availability of GWAS summary data and the lower costs compared to experimental approaches, MR has become a widely used and powerful tool in the field of female breast cancer research (Figure S3).

2 | APPLICATION OF MR ANALYSIS IN FEMALE BREAST CANCER

MR has been utilized to explore the potential causal associations between various risk factors and female breast cancer, predict the efficacy and adverse effects of pre-existing and new-onset drugs, and evaluate opportunities of drug repurposing for the therapy of female breast cancer.

2.1 | Identifying genetically predicted risk factors

We conducted a systematic search across three databases (PubMed, Embase, and Web of Science) to identify all studies published from the inception of the databases to August 1, 2024. The eligible studies reported the potential causal relationships between any type of exposure and the occurrence of female breast cancer using any design of MR analysis. The search strategy is detailed in Table S1, and comprehensive methods can be found in the Supplementary Information. The initial literature search yielded 3783 potentially relevant studies, with 174 eligible studies retained after the systematic screening process (Figure 1A). The genetically predicted risk factors of female breast cancer were classified into seven categories: lifestyle factors, nutrients, obesity and lipid metabolism, sex hormones and reproductive factors, inflammatory biomarkers, pathological conditions and related biomarkers, and social structure factors. The effect estimates for the principal genetically predicted risk factors from MR studies with the maximum sample

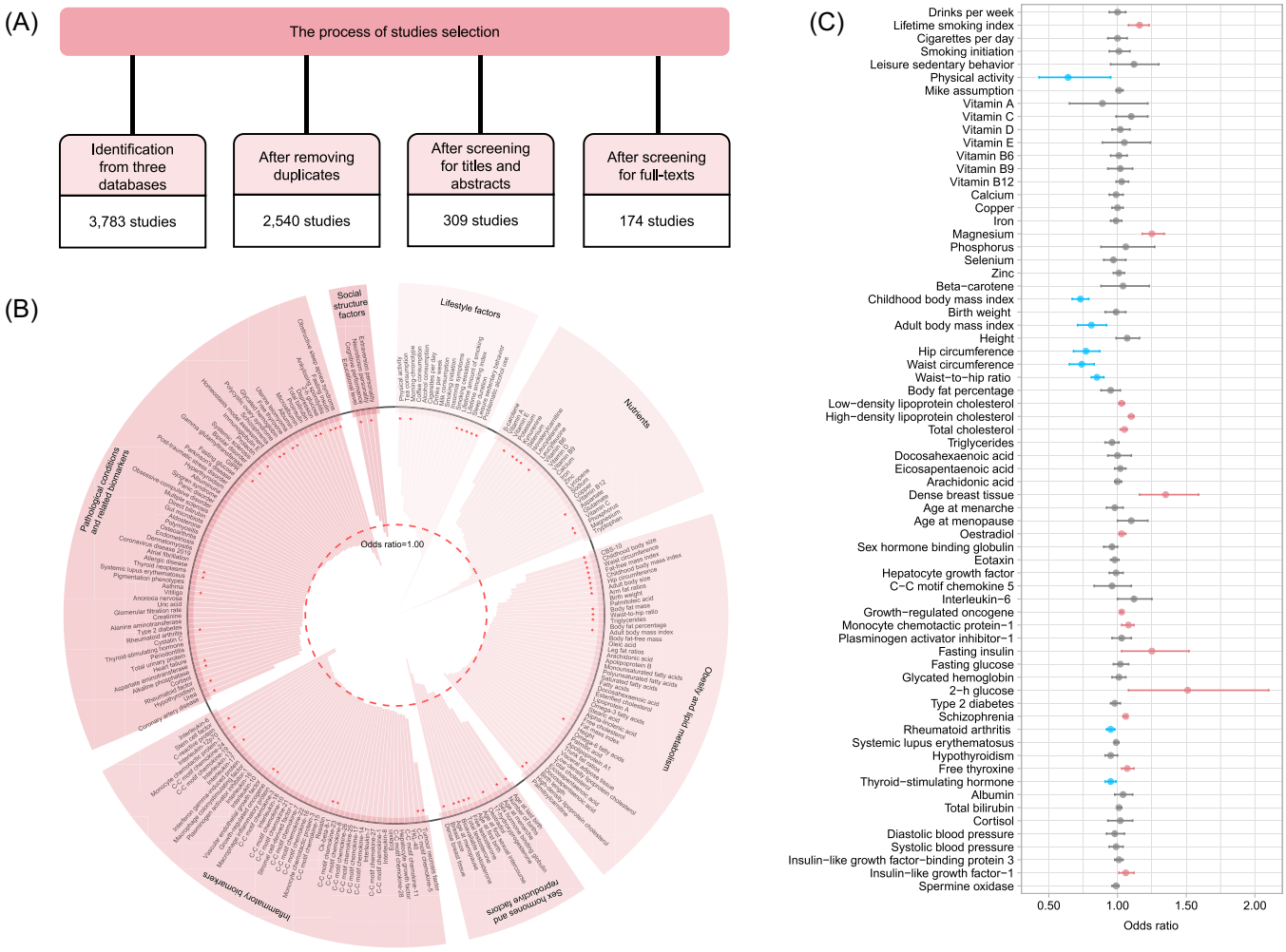

FIGURE 1 Overview of the genetically predicted risk factors of female breast cancer. (A) We conducted a systematic search across three databases (PubMed, Embase, and Web of Science) to identify all studies published from the inception of the databases to August 1, 2024. The initial literature search yielded 3783 potentially relevant studies, with 174 eligible studies retained after the systematic screening process. (B) The genetically predicted risk factors of female breast cancer were classified into seven categories: lifestyle factors, nutrients, obesity and lipid metabolism, sex hormones and reproductive factors, inflammatory biomarkers, pathological conditions and related biomarkers, and social structure factors. The length of the column represents the estimate of odds ratio (OR), and a column longer than the red circle corresponds to an OR > 1. Significance (*$p < 0.05$) and direction of associations were determined by the inverse variance weighted methods in Mendelian randomization studies with the largest sample size. (C) We identified a total of 14 risk factors and eight protective factors significantly associated with the occurrence risk of female breast cancer based on the pooled estimates. The red represents risk factors, the blue represents protective factors, and the gray represents nonsignificant factors for female breast cancer. CBS-10, comparative body size at age 10; GIPR, glucose-dependent insulinotropic polypeptide receptor.

size were presented in Figure 1B. More detailed information regarding the characteristics of the included studies and the systematic review results can be found in Tables S2 and S3, respectively.

To enhance causal inference, we further conducted a quantitative synthesis of MR evidence and compared these results with findings from the recently published meta-analysis on the traditional epidemiological studies. We identified a total of 14 risk factors and eight protective factors significantly associated with the occurrence risk of female breast cancer based on the pooled estimates (Figure 1C). Detailed meta-analysis results are available in Table S4. Our comparative analysis suggested that long-term smoking behavior, lack of physical activity, low body mass index (BMI) in childhood, dense breast tissue, high level of circulating oestradiol, schizophrenia, and insulin-like growth factor (IGF-1) might play a potentially causal role in the development of female breast cancer (Figure S4).

Several two-sample MR studies have demonstrated significant associations between genetically determined lifetime smoking patterns, problematic alcohol consumption, and an increased risk of female breast cancer [3, 4]. These studies further identified potential epigenetic mechanisms, indicating that DNA methylation at specific CpG sites might play a critical role in the carcinogenesis of female breast cancer. These CpG sites were potential intervention targets for the prevention of female breast cancer, such as epigenetic modifications at *cg07932199* (*ATXN2*) related to smoking traits, as well as *cg03260624* (*CDC7*), *cg10816169* (*ZNF318*), *cg03345232* (*RIN3*), and *cg26312998* (*RP11-867G23.13*) associated with drinking behavior [3, 4]. Additionally, a two-sample MR study demonstrated that improving the residential environmental quality, especially by reducing noise and air pollution exposure, might significantly decrease the risk of female breast cancer [5]. This highlights the correlation between environmental changes and the risk of female breast cancer.

Using data from metabolomics and lipidomics, MR has enabled systematic investigations into how genetically determined differences in vitamins, minerals, and lipoprotein profiles may contribute to the occurrence of female breast cancer. For instance, a comprehensive two-sample MR study examined the associations between 112 unique blood metabolites and female breast cancer [6]. The study found that high-density lipoprotein cholesterol and acetate might act as the causal mediators in the development of female breast cancer [6]. Additionally, a large-scale MR study explored the effects of lipoprotein subclasses on the occurrence of female breast cancer, considering factors such as particle size, particle number, and lipid composition [7]. It revealed the heterogeneous effect of high-density lipoprotein subclasses, in which small high-density lipoprotein traits were associated with a decreased risk of female breast cancer, while non-small high-density lipoprotein traits were associated with an increased risk of female breast cancer [7].

In contrast to traditional epidemiological studies, multivariable MR analyses revealed a direct protective effect of early-life obesity on female breast cancer with an odds ratio (OR) of 0.59 (95% confidence interval [CI], 0.50 to 0.71) after adjusting for adult body size [8]. This contradictory finding might be attributed to temporal heterogeneity in the relationship between genetic variants and obesity traits across the life course [8]. One longitudinal study demonstrated that the association between a 97-variant genetic risk score and adult BMI diminished with age [9]. Notably, other studies found that the associations between genetic variants and early-life body size remained robust throughout the lifespan, suggesting that the influence of genetically determined childhood body size might persist into adulthood, regardless of subsequent weight changes or other confounding factors [8, 10]. Consequently, the association between adult body size and breast cancer risk became nonsignificant after adjustment for genetically predicted early-life obesity [8].

Current clinical guidelines recognize breast mammographic density (BMD) as an effective factor for identifying high-risk populations for female breast cancer [11]. MR studies indicated that breast cancer risk for women with dense breast tissue increased by 39%, while for those with non-dense tissue decreased by 35% [12]. Additionally, BMD is dynamic throughout a woman's lifetime and can be influenced by several modifiable factors, such as tobacco and alcohol consumption, physical activity, dietary patterns, and levels of circulating oestradiol [13]. Therefore, BMD might serve as a promising biomarker not only for predicting risk but also for evaluating the effectiveness of breast cancer prevention efforts [13]. It is recommended to counsel high-risk individuals on modifying these risk factors to reduce their BMD and lower their lifetime risk of developing breast cancer.

MR methods have been increasingly utilized to clarify the causal relationships between various pathological conditions and breast cancer risk. These conditions included metabolic disorders, immune-mediated diseases, neurological and psychiatric disorders, reproductive system diseases, cardiovascular conditions, endocrine abnormalities, hepatopancreatobiliary disorders, gastrointestinal diseases, skin and musculoskeletal diseases, and other pathological conditions (Figure 2). The complex interactions between these pathological conditions and their related biomarkers and female breast cancer risk highlighted that multimorbidity and comorbidity patterns are considerable issues to provide valuable insights into the targeted early detection of high-risk populations.

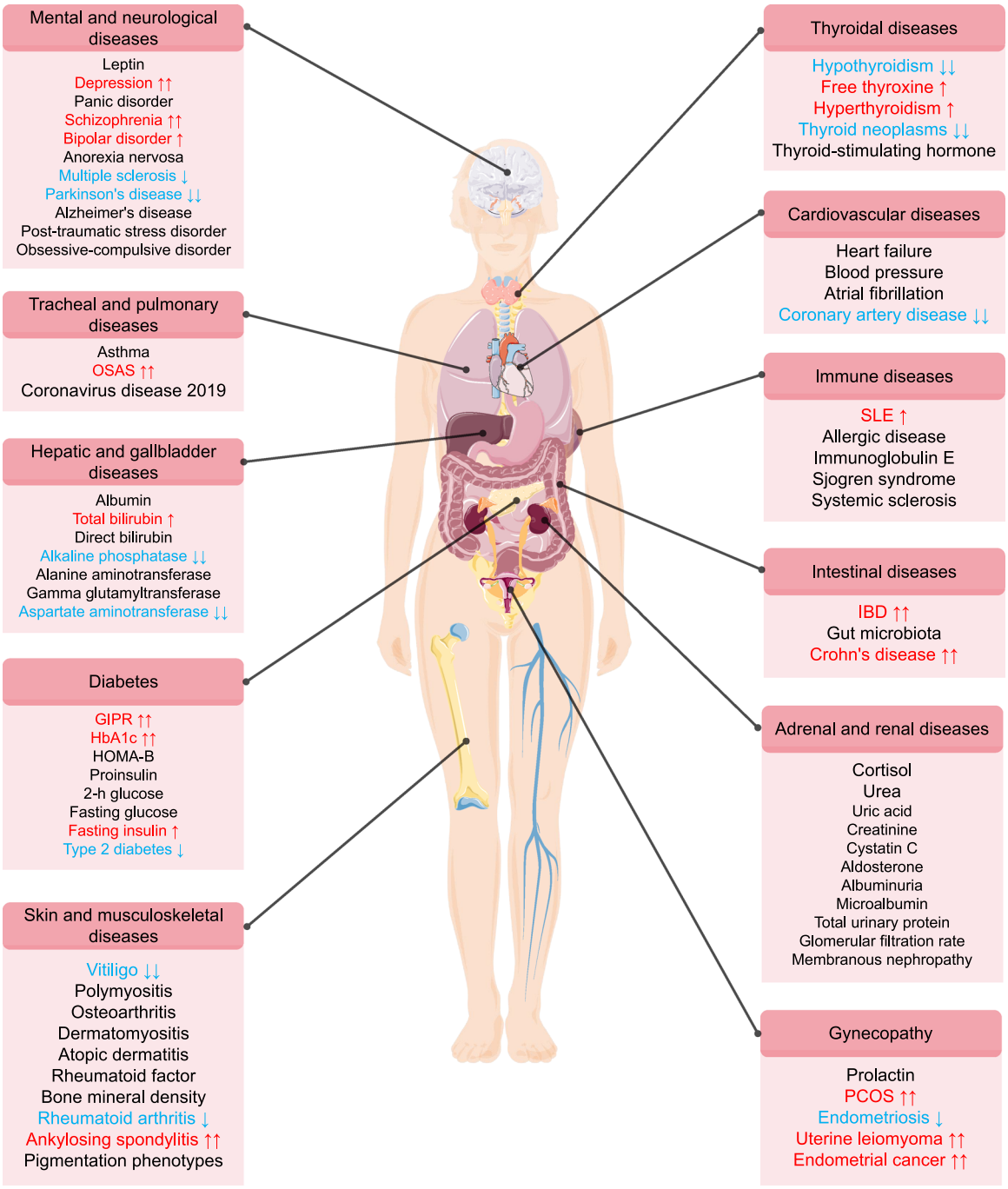

FIGURE 2 A summary of genetically predicted associations between pathological conditions and related biomarkers and the occurrence of female breast cancer. The red with two upward arrows represents a strong positive association, the red with one upward arrow represents a modest positive association, the blue with two upward arrows represents a strong inverse association, the blue with one upward arrow represents a modest inverse association, and the black represents a nonsignificant association. Abbreviations: GIPR, glucose-dependent insulinotropic polypeptide receptor; HbA1c, glycated hemoglobin; HOMA-B, homeostasis model assessment-beta; IBD, inflammatory bowel disease; OSAS, obstructive sleep apnea syndrome; PCOS, polycystic ovary syndrome; SLE, systemic lupus erythematosus.

In terms of social structure factors, a two-step MR analysis found that each standard deviation increase in educational attainment was associated with a 9% reduction in the risk of female breast cancer, with particularly strong protective effects observed for estrogen receptor (ER)-negative breast cancer [14]. Several behavioral mediators might contribute to this association, including moderate physical activities (mediation proportion,

2.66%), walking for pleasure (12.17%), other exercise (15.19%), ever smoking (10.44%), and BMI (6.05%) [14]. These findings suggest that population-based educational interventions may represent an effective strategy for the prevention of female breast cancer, primarily through enhancing health literacy, promoting healthy lifestyle behaviors, and improving participation in screening programs [15].

2.2 | Predicting drug efficacy and adverse effects

Drug development is essential to the advancement of female breast cancer therapies. However, the process of drug development is slow, expensive, and at high risk throughout all development phases. MR is a promising strategy that can accelerate this process and enhance the probability of success. By leveraging naturally randomized genetic variations, MR can identify the causal relationships between drug targets and diseases as well as predict the efficacy and adverse effects of both pre-existing and new-onset drugs [16]. Additionally, genetic associations can provide valuable insights into the lifelong effects of genetic perturbations of drug targets [16]. Notably, circulating proteins are significant indicators of oncogenic pathways and potential therapeutic targets. Recent MR studies evaluated the relationships between blood protein concentrations and breast cancer risk, based on cis-protein quantitative trait loci (cis-pQTL) SNPs [17, 18]. These studies identified several novel potential drug targets and biomarkers for breast cancer, such as *AOC2*, *SPN1*, *CD160*, and *RALB* [17, 18].

2.3 | Evaluating the drug repurposing

MR methods have emerged as a powerful tool to evaluate the potential of drug repurposing, which offers a cost-effective strategy to identify new therapeutic applications for existing medications in the treatment of female breast cancer. As an example, a large-scale MR study utilized genetic instruments for 1406 actionable targets of approved non-oncological drugs based on gene expression, DNA methylation, and protein expression quantitative trait loci (eQTL, mQTL, and pQTL, respectively) [19]. This study identified six significant MR associations with gene expression levels (*TUBB*, *MDM2*, *CSK*, *ULK3*, *MC1R*, and *KCNN4*) and two significant associations with gene methylation levels across 21 CpG islands (*RPS23* and *MAPT*), suggesting the promising targets for existing drugs in breast cancer therapy.

3 | FUTURE PERSPECTIVES

Nowadays, MR analysis has become a useful tool in providing valuable insights into the prevention and therapy of female breast cancer, including identifying genetically predicted risk factors, predicting drug efficacy and adverse effects, and evaluating the potential of drug repurposing. The development of female breast cancer is a multifaceted process driven by the dynamic interactions between external and internal exposures including enviromental change, behavior, infectious, and metabolic factors. With the advancement of biological technologies, the number of large-scale multi-omics data is increasing, such as genomics, transcriptomics, proteomics, metabolomics, and environmental exposome. Despite the expanding applications of MR analysis in the exploration of biological mechanisms, there are a few studies that systematically integrate MR methodologies with these multi-omics data [20]. The development of female breast cancer involves complex molecular components that interact through intricate biological networks. In the future, a combination of innovative MR methodologies and various multi-omics data can offer unprecedented potential to reveal the causal networks for risk factors and drug targets, as well as to improve our understanding of the biological mechanisms underlying female breast cancer etiology [20].

4 | METHODS

Detailed methods for the meta-analysis can be found in the Supporting Information.

AUTHOR CONTRIBUTIONS

Danqi Huang: Software; validation; formal analysis; data curation; writing—original draft; visualization. **Jingbo Zhai**: Validation; data curation; writing—review and editing. **Min Yang**: Validation; writing—review and editing; data curation. **Wei Xiong**: Methodology; validation; writing—review and editing. **Huilin Wang**: Methodology; validation; writing—review and editing. **Yang Bai**: Methodology; validation; writing—review and editing. **Jinqiu Yuan**: Methodology; validation; writing—review and editing. **Quan Wang**: Methodology; validation; writing—review and editing. **Bobo Zheng**: Methodology; validation; writing—review and editing. **Jingyi Liu**: Methodology; validation; writing—review and editing. **Shengling Qin**: Methodology; validation; writing—review and editing. **Rui Sun**: Methodology; validation; writing—review and editing. **Jinhui Tian**: Methodology; validation; writing—review and editing. **Wenbo Meng**: Conceptualization; investigation;

writing—review and editing; resources; supervision; project administration; methodology. **Jianping Huang**: Conceptualization; investigation; writing—review and editing; project administration; supervision; resources; methodology. **Jiang Li**: Project administration; supervision; resources; writing—review and editing; conceptualization; investigation; methodology.

ACKNOWLEDGMENTS

Graphical abstract and Figure 2 were partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license. We apologize for not being able to cite additional work owing to space limitations.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article. This study does not generate any new data. Supporting information materials (methods, figures, tables, graphical abstract, slides, videos, Chinese translated version and update materials) may be found in the online DOI or iMeta Science http://www.imeta.science/imetaomics/.

ETHICS STATEMENT

No animals or humans were involved in this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Figure S1. Comparison of Mendelian randomization studies and randomized controlled trial.

Figure S2. Canonical causal diagram for instrument variable assumptions in Mendelian randomization studies.

Figure S3. Number of Mendelian randomization studies on female breast cancer published by year.

Figure S4. Comparative analysis of the meta-analysis results from Mendelian randomization and traditional epidemiological studies.

Table S1. Search strategy.

Table S2. Summary of the characteristics of the included studies.

Table S3. Systematic review results for Mendelian randomization studies on female breast cancer.

Table S4. Meta-analysis results.