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Original Research

A Mendelian Randomization Analysis of Obesity-Metabolite Pathways in Endometrial Cancer, Ovarian Cancer, Endometriosis, and Polycystic Ovary Syndrome

Lingfang Ye[1,*,†], Qianya Lin[1,†], Meng Cen[1], Beilei Chen[1], Haizan Yu[1]

[1]Department of Gynaecology, Women and Children's Hospital of Ningbo University, 315012 Ningbo, Zhejiang, China
*Correspondence: xuelian_12345@163.com; feyyyelingfang@nbu.edu.cn (Lingfang Ye)
[†]These authors contributed equally.

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Abstract

Background: This study aimed to investigate the causal pathways that link obesity to the risk of gynecological diseases through specific circulating plasma metabolites. The diseases examined were endometrial cancer (EC), ovarian cancer (OC), endometriosis, and polycystic ovary syndrome (PCOS). A Mendelian randomization (MR) framework was used to identify and quantify the mediating role of metabolites. **Methods:** A three-stage, two-sample MR and mediation analysis was conducted. First, we estimated the causal effects of genetically predicted body mass index (BMI) and waist-hip ratio (WHR) on plasma metabolites. Second, we assessed the causal effects of the identified obesity-driven metabolites on four gynecological diseases. Finally, mediation analyses were performed to quantify the proportion of the obesity effect mediated by significant metabolites. Genetic instruments were derived from the largest available genome-wide association studies of European ancestry. The primary analytical method was inverse variance weighted (IVW), supplemented by sensitivity analyses. **Results:** Genetically predicted higher BMI showed evidence of causal effects for increased risks of EC, PCOS, and OC, whereas WHR showed no significant associations. BMI and WHR were associated with 218 and 172 plasma metabolites, respectively, with several metabolites identified as potential risk factors for gynecological diseases. For EC, these included androsterone sulfate and lipids within very low-density lipoprotein (VLDL), whereas for endometriosis, they included triglycerides within small VLDL and serum total triglycerides. Mediation analysis revealed that androsterone sulfate mediated 34.89% of the effect of BMI on EC risk, while serum total triglycerides mediated 22.41% of this effect. **Conclusions:** This study provides genetic evidence that general adiposity influences the risk of several gynecological diseases in part through specific metabolic pathways. Androgen and lipid metabolism emerged as candidate intermediate traits that explain a significant proportion of the effect of obesity on EC risk. These findings identify potential targets for risk stratification and preventive strategies.

Keywords: obesity; Mendelian randomization; androgen metabolism; lipid metabolism; endometrial cancer

1. Introduction

Obesity profoundly reshapes systemic physiology, predisposing individuals to a wide spectrum of chronic diseases such as cardiovascular disorders and multiple cancers [1,2]. Excess adiposity among women imposes a particularly high burden on reproductive health. Endometrial cancer (EC), ovarian cancer (OC), endometriosis, and polycystic ovary syndrome (PCOS) are all strongly linked to obesity, yet the underlying mechanisms remain incompletely understood. Biologically, adiposity is known to drive a pro-inflammatory and insulin-resistant milieu that disrupts endocrine homeostasis [3,4]. Inflammatory cytokines such as tumor necrosis factor-α (TNF-α) reduce the level of sex hormone-binding globulin (SHBG), thereby enhancing estrogen bioavailability and endometrial proliferation [5]. Likewise, obesity aggravates the metabolic and immune dysregulation intrinsic to PCOS and endometriosis [4,6,7]. Despite these observations, the precise molecular mechanisms through which obesity translates into gynecological pathology remain unresolved.

The identification of definitive causal pathways from observational data is challenging due to residual confounding from lifestyle, environmental factors, and the potential for reverse causation. A powerful approach to elucidating the mechanistic underpinnings of obesity-related disease risk is to identify circulating metabolites that mediate its effects. Metabolites serve as direct molecular signatures of physiological and pathological processes, positioning them as ideal candidates for mediating the systemic impact of obesity on distal organ sites [8,9]. While both obesity and risk of gynecological disease have been associated with alterations in the plasma metabolome [10,11], these observational associations are susceptible to the same biases, leaving the causal role of specific metabolites unresolved.

Mendelian randomization (MR) is an analytical method that uses genetic variants as instrumental variables to infer causal relationships between an exposure and an outcome. As genetic alleles are randomly assigned at conception and fixed throughout life, MR studies are largely in-

sulated from confounding and reverse causation, provided key assumptions are met [12]. In the present study, we employed a comprehensive two-sample MR framework to systematically investigate the role of plasma metabolites as mediators of obesity on the risk of four obesity-related gynecological diseases: EC, endometriosis, PCOS, and OC. By leveraging large-scale genome-wide association study (GWAS) data for body mass index (BMI), waist-hip ratio (WHR), and plasma metabolites, we first identified obesity-driven metabolites. We then assessed the causal effect of these metabolites on the risk of the aforementioned gynecological diseases. Finally, we performed mediation analyses to quantify the proportion of the obesity effect mediated through specific metabolic pathways. The aim of our study was to uncover novel biological insights into the etiology of obesity-driven gynecological disease, with the potential to identify new targets for risk stratification and preventive strategies.

2. Methods

2.1 Study Design

The analytical framework for this study is summarized in Fig. 1. We implemented a three-stage MR design to delineate the metabolic pathways linking obesity to gynecological disease risk. First, we estimated the causal effect of BMI and WHR on plasma metabolites using two-sample MR. Next, we estimated the causal effect of the identified obesity-driven metabolites on the risk of four obesity-related gynecological diseases: EC, endometriosis, PCOS, and OC. Finally, for statistically significant associations, we performed mediation analyses to quantify the proportion of the effect of obesity on the disease risk mediated by each metabolite. The dataset used in this study is publicly accessible on the database website, and therefore, no additional ethical approval or informed consent was required.

2.2 Sources of Information on Exposure, Mediators, and Outcome

Genetic instruments for the exposure, mediators, and outcome were derived from the largest available genome-wide association studies (GWAS) of European ancestry individuals to minimize weak instrument bias. Summary statistics for BMI and WHR were obtained from a meta-analysis of the GIANT consortium and the UK Biobank (BMI, n = 681,275; WHR, n = 697,734) [13,14]. The UK Biobank samples used in both GWAS are substantially overlapping (~450,000 individuals), while the GIANT components show minimal overlap, as confirmed by bivariate linkage disequilibrium (LD) score regression in the original publications. This overlapping structure enhances the comparability of genetic instruments across the two adiposity traits by minimizing differences in population stratification. The genetic association of plasma metabolites is derived from the research of Shin et al. [15] and Kettunen et al. [16]. Summary-level data for gynecological disease outcomes were obtained from publicly available GWAS databases (https://opengwas.io/datasets/). Specifically, genetic associations for OC were acquired from the Ovarian Cancer Association Consortium (OCAC) [17]. Data for PCOS were sourced from Tyrmi et al. [18] (797 cases and 140,558 controls), for endometriosis from Sakaue et al. [19] (4511 cases and 227,260 controls), and for EC data from a study comprising 10,296 cases and 108,979 controls [20]. Detailed sample sizes for each gynecological disease are presented in Table 1 (Ref. [17,18,19,20]).

Table 1. Detailed sample sizes for each gynecological disease.

Diseases	Ancestry	PubMed ID
Endometrial Cancer	European	30093612 [20]
endometriosis	European	34594039 [19]
PCOS	European	34791234 [18]
Ovarian cancer	European	28346442 [17]

PCOS, polycystic ovary syndrome.

2.3 SNP Selection and Statistical Analysis

MR was performed to estimate the causal effect of BMI and WHR on each plasma metabolite. Independent instrumental variables (IVs) for BMI and WHR were selected at the genome-wide significance threshold ($p < 5 \times 10^{-8}$), clumped based on LD ($r^2 < 0.01$) within a 1000-kb window, and referenced to the 1000 Genomes Project European panel [21]. SNPs within the major histocompatibility complex region were excluded due to complex LD and pleiotropy. Instrument strength was assessed using the F-statistic, calculated as $F = (R^2 / 1 - R^2) \times ((N - k - 1) / k)$, where R^2 represents the proportion of variance in the exposure explained by the instruments, N is the GWAS sample size, and k is the number of instruments. Variants with F >10 were indicated as a low risk of weak instrument bias [22]. Detailed information on the instrumental variables for body mass index and waist-hip ratio has been summarized in **Supplementary Table 1**. The inverse variance weighted (IVW) method was primarily employed for causal inference, complemented by four supplementary approaches (MR-Egger, Weighted Median, Simple Mode, and Weighted Mode) to assess robustness [23,24]. Effect estimates were presented as odds ratios (ORs) with 95% confidence intervals (CIs) for binary outcomes. IVW results were adjusted using the false discovery rate (FDR). Associations with $p_{IVW} < 0.05$ were considered robust evidence of a significant causal effect [25]. The robustness of our findings was evaluated through sensitivity analyses examining potential pleiotropy and heterogeneity, with $p > 0.05$ considered to support the absence of these biases. We first calculated the total effect of BMI/WHR on gynecological diseases, the influence of BMI/WHR on metabolites (β1), and the influence of metabolites on gynecological diseases (β2). Subsequently, we calculated the mediating effect (β1*β2),

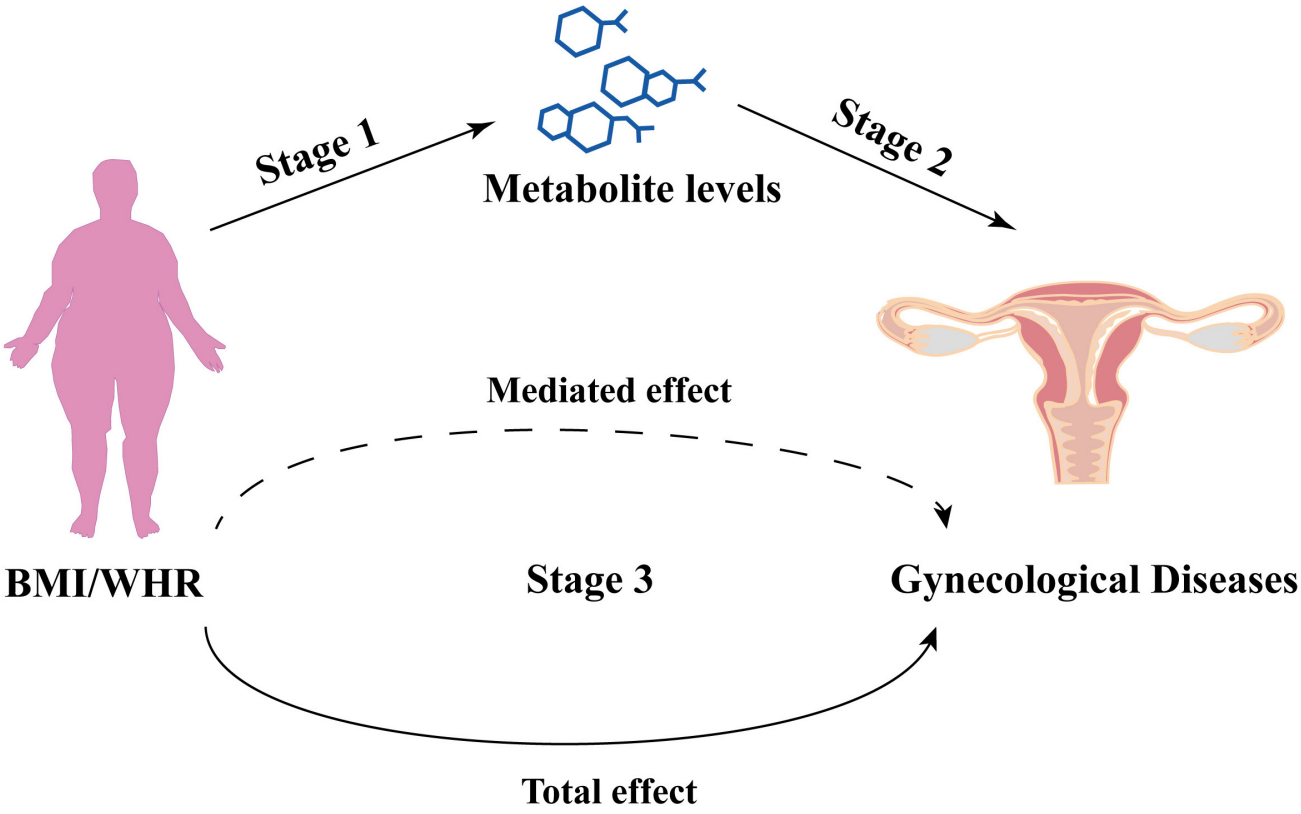

Fig. 1. Methodology flow chart. BMI, body mass index; WHR, waist-hip ratio.

with the direct effect being the total effect minus the mediating effect [26]. All analyses were conducted using R software (version 4.4.1; Vienna, Austria).

3. Results

3.1 Genetic Causality Between BMI/WHR and Gynecological Diseases

Using MR analysis under the significance threshold of $p_{IVW} < 0.05$, we identified potential associations between female adiposity traits and several gynecological diseases. After considering the standard of $p_{FDR} < 0.05$, robust evidence was found supporting the causal effects of BMI on multiple gynecological conditions. Specifically, genetically-predicted higher BMI was associated with significantly increased risks of EC (OR = 1.758, 95% CI: 1.570–1.968, $p_{IVW} = 1.305 \times 10^{-22}$, $p_{FDR} = 1.566 \times 10^{-21}$), PCOS (OR = 1.431, 95% CI: 1.195–1.714, $p_{IVW} = 9.905 \times 10^{-5}$, $p_{FDR} = 5.942 \times 10^{-4}$), and OC (OR = 1.191, 95% CI: 1.080–1.312, $p_{IVW} = 4.449 \times 10^{-4}$, $p_{FDR} = 1.779 \times 10^{-3}$), but not endometriosis (OR = 0.962, 95% CI: 0.837–1.107, $p_{IVW} = 0.591$, $p_{FDR} = 0.645$). In contrast, WHR showed no significant causal associations with any of the four diseases: EC (OR = 0.936, 95% CI: 0.84–1.044, $p_{IVW} = 0.234$, $p_{FDR} = 0.329$), PCOS (OR = 1.162, 95% CI: 0.993–1.359, $p_{IVW} = 0.061$, $p_{FDR} = 0.144$), endometriosis (OR = 1.072, 95% CI: 0.947–1.213, $p_{IVW} = 0.274$, $p_{FDR} = 0.329$) and OC (OR = 0.993, 95% CI: 0.904–1.091, $p_{IVW} = 0.884$, $p_{FDR} = 0.884$). All WHR-disease associations had p_{FDR} values exceeding 0.1, with point estimates suggesting null or weakly positive effects that lacked statistical precision. No associations for WHR were observed with EC or OC. All results are shown in Fig. 2. Pleiotropy and heterogeneity tests both confirmed the robustness of the MR results (**Supplementary Tables 2,3**). These findings suggest that general adiposity, as measured by BMI, may exert significant effects on the risk of several major gynecological conditions, particularly EC and PCOS. In contrast, central adiposity, as measured by WHR, shows no significant independent association with these diseases.

3.2 Genetic Causality Between Metabolites and Gynecological Diseases

We next investigated the potential causal effects of circulating metabolites on gynecological diseases using univariable MR analysis. Under the significance threshold of $p_{IVW} < 0.05$ and $p_{FDR} < 0.1$, we identified significant associations between specific metabolites and both EC and endometriosis (Fig. 3). For EC, the strongest risk-increasing effects were observed for X-18601 (OR = 2.940, 95% CI: 1.573–5.495, $p_{IVW} = 0.001$), androsterone sulfate (OR = 2.018, 95% CI: 1.389–2.931, $p_{IVW} = 2.290 \times 10^{-4}$), serum total triglycerides (OR = 1.717, 95% CI: 1.256–2.348, $p_{IVW} = 7.110 \times 10^{-4}$), and X-13429 (OR = 1.517, 95% CI: 1.195–1.926, $p_{IVW} = 6.200 \times 10^{-4}$). Conversely, two lipid components exhibited protective effects: free cholesterol in

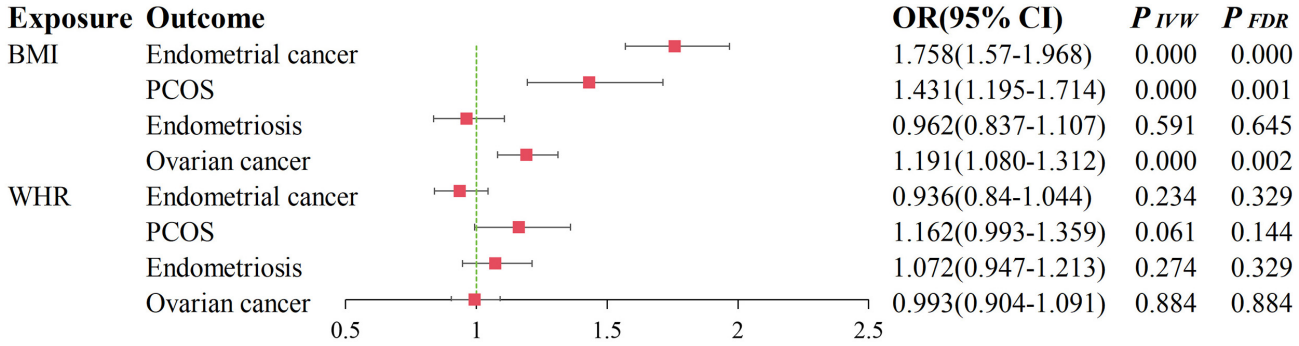

Fig. 2. MR analysis of obesity and gynecological diseases. MR, Mendelian randomization.

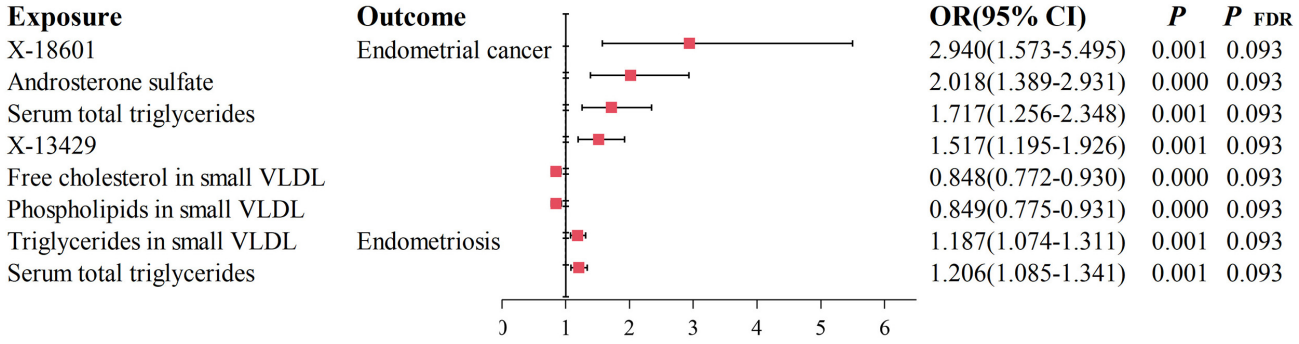

Fig. 3. MR analysis of metabolites and gynecological diseases. VLDL, very low-density lipoprotein.

small VLDL (OR = 0.848, 95% CI: 0.772–0.930, p_{IVW} = 4.960 × 10^{-4}) and phospholipids in small VLDL (OR= 0.849, 95% CI: 0.775–0.931, p_{IVW} = 4.960 × 10^{-4}). For endometriosis, two triglyceride-related metabolites showed significant risk-enhancing effects (p_{FDR} = 0.093): triglycerides in small VLDL (OR = 1.187, 95% CI: 1.074–1.311, p_{IVW} = 7.727 × 10^{-4}) and serum total triglycerides (OR = 1.206, 95% CI = 1.085–1.341, p_{IVW} = 5.277 × 10^{-4}). No heterogeneity or pleiotropy was found in the sensitivity analyses (**Supplementary Tables 4,5**). These findings suggest that specific metabolites, including androgen derivatives and VLDL lipid components, may play a role in the pathogenesis of gynecological diseases, providing mechanistic insights for future investigations into the metabolic basis of these conditions.

3.3 Genetic Causality Between BMI/WHR and Metabolites

Under the conditions of p_{IVW} < 0.05 and p_{FDR} < 0.1, we conducted MR analysis to determine potential associations between BMI and 218 metabolites, and WHR and 172 metabolites. The *F*-statistic for the instrumental variables ranged between 19.5 and 7807.8 for WHR and 19.5 and 8500.2 for BMI, indicating minimal weak instrument bias. These associations encompassed diverse metabolite classes, including amino acids, lipids, carbohydrates, and organic acids. Among the 58 metabolites associated with both adiposity traits, the majority showed directionally consistent effects with metabolites positively associated with both BMI and WHR. For instance, elevated genetically-predicted WHR was associated with increased levels of isoleucine (OR = 1.230, 95% CI: 1.155–1.310, p_{IVW} = 1.490 × 10^{-10}, p_{FDR} = 9.667 × 10^{-9}) and glutamate (OR = 1.043, 95% CI: 1.022–1.066, p_{IVW} = 7.431 × 10^{-5}, p_{FDR} = 0.001), and inversely associated with glycine (OR = 0.969, 95% CI: 0.954–0.985, p_{IVW} = 1.400 × 10^{-4}, p_{FDR} = 0.004) and palmitoleate (16:1n7) (OR = 0.952, 95% CI: 0.931–0.974, p_{IVW} = 1.846 × 10^{-5}, p_{FDR} = 1.900 × 10^{-4}). Similarly, higher genetically-predicted BMI was associated with elevated isoleucine (OR = 1.017, 95% CI: 1.007–1.027, p_{IVW} = 7.215 × 10^{-4}, p_{FDR} = 7.133 × 10^{-9}) and glutamate (OR = 1.054, 95% CI: 1.030–1.078, p_{IVW} = 7.904 × 10^{-6}, p_{FDR} = 8.401 × 10^{-6}). Notably, palmitoleate (16:1n7) showed a positive association with BMI (OR = 1.028, 95% CI: 1.003–1.054, p_{IVW} = 0.026, p_{FDR} = 0.087), contrasting with its inverse relationship with WHR. The above results are shown in Fig. 4. The detailed results can be found in **Supplementary Table 6**. Among the 58 metabolites that showed significant causal associations with both BMI and WHR (p_{FDR} < 0.1), we observed predominantly concordant effect directions. For instance, isoleucine and glutamate were positively associated with both adiposity traits. However, notable instances of opposing trends were also identified. Palmitoleate (16:1n7) demonstrated a clear bidirectional pattern: genetically predicted BMI was associated with increased levels of this lipid, whereas genetically predicted WHR was associated with decreased levels. Such divergence suggests the metabolic consequences of general adiposity and central adiposity are not always directionally concordant, reflect-

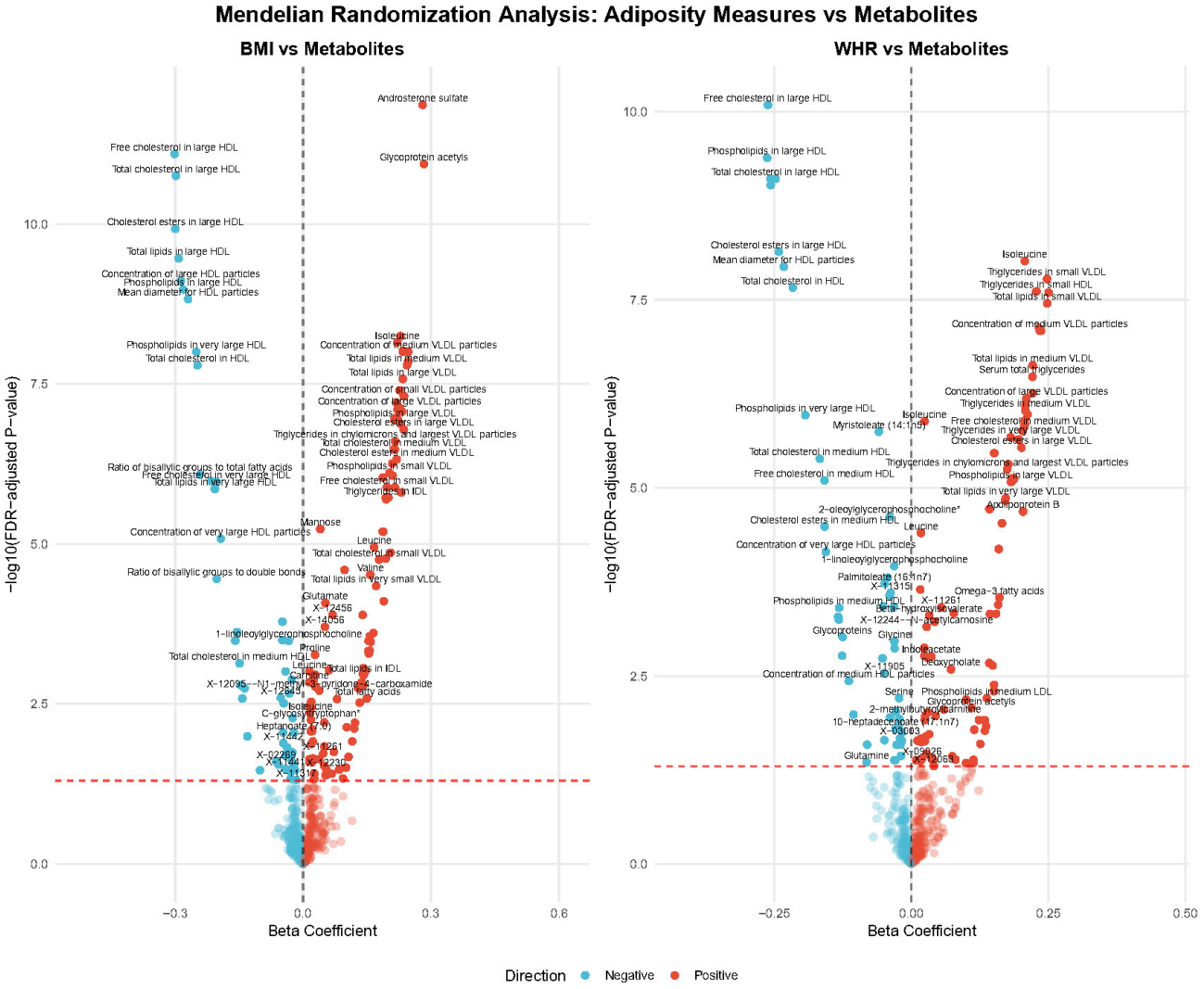

Fig. 4. MR analysis of obesity and metabolite. MR analyses revealed 58 metabolites significantly associated with both BMI and WHR, with most effects directionally consistent. Notably, palmitoleate (16:1n7) showed opposite directions: positive with BMI but negative with WHR, highlighting divergent metabolic impacts of general versus central adiposity. HDL, high-density lipoprotein.

ing distinct underlying biological mechanisms. No heterogeneity or pleiotropy was found in the sensitivity analyses (**Supplementary Tables 7,8**). These findings highlight the distinct and shared causal effects of central and general adiposity on the human plasma metabolome, implicating specific amino acids and fatty acids as potential mediators in adiposity-related metabolic dysregulation.

3.4 Mediation Analysis

The leave-one-out analysis of the key intermediate pathways is shown in **Supplementary Fig. 1**. To quantify the mediating effects of specific metabolites in various obesity-gynecological disease pathways, we conducted formal mediation analyses using the product of coefficients method. This successfully quantified the pathways from obesity to EC. Specifically, BMI increased the risk of EC through two major avenues. Androsterone sulfate showed evidence consistent with partial mediation of the genetically-predicted BMI-EC association, with an estimated mediation proportion of 34.89% (indirect effect: OR = 1.218, 95% CI: 1.085–1.366, $p = 0.001$; direct effect: OR = 1.444, 95% CI: 1.229–1.697; total effect: OR = 1.758, 95% CI: 1.570–1.968). These results suggest that a non-trivial fraction of the genetic association between BMI and EC risk may be statistically attributable to variation in circulating androsterone sulfate levels. Serum total triglycerides also served as a significant mediator, accounting for 22.41% of the total effect (indirect effect: OR = 1.135, 95% CI: 1.045–1.233, $p = 0.003$; direct effect: OR = 1.549, 95% CI: 1.347–1.782; total effect: OR = 1.758, 95% CI: 1.570–1.968). Serum triglycerides showed evidence consistent with partial mediation and may partly contribute to the observed BMI-EC relationship. The above results highlight the importance of steroid hormone metabolism and lipid dysregulation as mechanistic links between adiposity and endometrial carcinogenesis.

4. Discussion

This study used MR and mediation analysis frameworks to comprehensively investigate the causal pathways connecting adiposity to the risk of gynecological disease through specific metabolic mediators. Our findings provide three fundamental advances in understanding obesity-related gynecological pathology. First, we found that genetically-predicted BMI was associated with an increased risk of several gynecological conditions, whereas genetically-predicted WHR showed limited evidence of independent effects in this dataset. Second, we identified metabolites whose genetically predicted levels in MR analyses were consistent with causal effects on disease risk, thus highlighting candidate metabolic pathways that warrant functional validation. Third, through formal mediation analysis, we quantified substantial mediating effects of androsterone sulfate (34.89%) and serum triglycerides (22.41%) in the BMI-EC relationship. Collectively, these findings refine epidemiological associations by providing a genetics-informed framework that identifies and prioritizes specific circulating metabolites as potential mechanistic links between adiposity and gynecologic disease.

Obesity-induced low-grade chronic inflammation drives extensive metabolic reprogramming that connects peripheral adipose tissue with reproductive organs. Adipocytes and infiltrating macrophages release cytokines, including interleukin 6 and TNF-α, which activate nuclear factor kappa B signaling and promote hepatic production of acute phase proteins [27,28]. These systemic inflammatory responses modify glucose and lipid metabolism, enhance oxidative stress, and shift circulating metabolite profiles toward a pro-tumorigenic state [6].

The contrasting causal effects between BMI and WHR highlight the complex relationship between the distribution of adiposity and the risk of gynecological disease. Although both BMI and WHR represent obesity measures, our results indicate that general adiposity rather than central fat distribution serves as the primary driver of gynecological pathology. This observation aligns with the current understanding of systemic metabolic dysfunction, where the overall adipose tissue burden rather than specific fat depots is thought to be the predominant influence over endocrine homeostasis and inflammatory signaling. The particularly strong causal effect of BMI on EC risk reinforces the established connection between obesity and endometrial carcinogenesis, likely operating through both estrogen-dependent and -independent pathways [29]. The observation of opposing effects of BMI and WHR on specific metabolites, most notably palmitoleate, provides additional nuance to our understanding of adiposity-related metabolic dysregulation. Palmitoleate (16:1n7) is a well-characterized lipokine secreted from adipose tissue that exerts insulin-sensitizing and anti-inflammatory effects [30]. Its positive association with BMI may represent a homeostatic feedback mechanism in which expanded adipose tissue upregulates secretion of this protective lipid to counteract systemic insulin resistance. Conversely, the negative association with WHR suggests that dysfunction of visceral adipose tissue—characterized by adipocyte hypertrophy, hypoxia, and inflammatory infiltration—may impair this adaptive response [31,32]. This dissociation reinforces the notion that "obesity" is not a monolithic exposure; rather, the total adiposity burden and fat distribution pattern exert qualitatively distinct effects on systemic metabolism. Our findings underscore the importance of disaggregating adiposity phenotypes in future metabolomic studies.

The present study found that androsterone sulfate was a significant mediator, accounting for 34.89% of the BMI effect on EC risk. This provides compelling genetic evidence for the involvement of androgen metabolism in obesity-driven endometrial pathogenesis. Androsterone sulfate is a major circulating androgen metabolite and may promote neoplastic transformation through multiple mechanisms, including direct androgen receptor activation, conversion to biologically active androgens in peripheral tissues, and modulation of estrogen receptor signaling [33]. Specifically, androsterone sulfate can be taken up by endometrial cells and desulfated via steroid sulfatase to generate androsterone, which then binds to androgen receptors expressed on the endometrial epithelium. Activation of the androgen receptor has been shown to stimulate the proliferation of EC cells and is associated with a worse prognosis. In addition, androgens can serve as substrates for aromatase in the conversion to estrogens, thereby amplifying estrogen receptor signaling, which is a well-established driver of endometrial proliferation [34,35]. This dual pathway positions androsterone sulfate not merely as a biomarker, but also as an active participant in a steroid metabolic network linking systemic adiposity to local endometrial pathology.

The significant mediating role of serum triglycerides emphasizes the importance of lipid metabolism in EC development. Hypertriglyceridemia, a hallmark of obesity-related metabolic syndrome, may contribute to carcinogenesis through various mechanisms, including the provision of essential lipid substrates for membrane synthesis in rapidly proliferating cells, the generation of pro-inflammatory lipid mediators, and the induction of endoplasmic reticulum stress responses [36]. Beyond fueling tumor energetics, triglyceride-rich lipoproteins may influence the immune landscape of the OC microenvironment. Excess fatty acids released from intermediate density lipoproteins can enter tumor cells through CD36-mediated uptake and undergo oxidation via carnitine palmitoyltransferase-dependent pathways to support anabolic growth [37,38,39]. Concurrently, these lipids can reprogram tumor-associated macrophages toward an immunosuppressive phenotype, thereby reducing antitumor immunity [40,41]. Through these metabolic and immunologic effects, dysregulated lipoprotein turnover may connect systemic obesity to local immune evasion and tumor progression.

Emerging evidence suggests that obesity orchestrates cross-organ metabolic signaling through a gut-liver reproductive axis. Adipose-derived hormones, including leptin and adiponectin, together with inflammatory mediators, can modulate hepatic lipid synthesis and systemic metabolite flux [42,43]. These signals may reach reproductive tissues through the circulation, altering their cellular energy balance, steroidogenesis, and immune cell infiltration [44,45]. Such inter-organ communication implies that gynecologic cancers represent not only local hormonal disorders, but may also be downstream manifestations of whole-body metabolic dysregulation.

Limitations

Several limitations warrant consideration when interpreting our findings. First, despite comprehensive sensitivity analyses, residual pleiotropy cannot be entirely excluded in MR studies. Second, the metabolic data primarily reflect circulating levels, which may not fully capture tissue-specific metabolic alterations relevant to gynecological pathology. Third, our focus on populations of European ancestry limits the generalizability of our findings to other ethnic groups. Finally, the unknown identities of several significant metabolites underscore the need for continued metabolite annotation efforts in this field.

5. Conclusions

In conclusion, our study provides genetic evidence consistent with adiposity influencing the risk of gynecological disease. Moreover, it identified circulating metabolites that may represent candidate intermediate traits linking adiposity to endometrial cancer. These findings prioritize certain androgen-related and lipid-related metabolites for future mechanistic and translational validation studies.

Abbreviations

BMI, body mass index; CIs, confidence intervals; FDR, false discovery rate; GWAS, genome-wide association studies; IVW, inverse variance weighted; LD, linkage disequilibrium; MR, Mmendelian randomization; OCAC, Cancer Association Consortium; OR, odds ratio; PCOS, polycystic ovary syndrome; WHR, waist-hip ratio; EC, endometrial cancer; OC, ovarian cancer; VLDL, very low-density lipoprotein; SHBG, sex hormone-binding globulin; GWAS, genome-wide association study.

Availability of Data and Materials

Summary GWAS BMI/WHR data are available from https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files. Summary GWAS metabolite data are available from https://www.omicspred.org/. The data of endometrial cancer (ID: ebi-a-GCST006464), ovarian cancer (ID: ieu-a-1120), endometriosis (ID: ebi-a-GCST90018839), polycystic ovary syndrome (ID: ebi-a-GCST90044902) can be obtained from https://gwas.mrcieu.ac.uk/.

Author Contributions

The study was conceived and designed by LY and QL. BC, MC and HY were responsible for data acquisition. LY, QL and MC conducted the statistical analyses. The results were interpreted by LY and QL. The initial manuscript was drafted by LY and QYL. All authors contributed to critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT-3.5 in order to check spelling and grammar. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/CEOG49198.

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