International Journal of Women's Health

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

The Impact of Age at First Sexual Intercourse on Female Reproductive Disorders: A Mendelian Randomized Study

Xin Xin[1,2], Lu Guan[3], Jiaxi Li[4], Jinfu Zhang[1,5], Haicui Wu[6]

[1]Guanghua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, 200052, People's Republic of China; [2]Shanghai University of Traditional Chinese Medicine, Shanghai, 201203, People's Republic of China; [3]Shandong University of Traditional Chinese Medicine, Jinan, 250011, People's Republic of China; [4]Shandong Wendeng Osteopathic Hospital, Wendeng, Shandong, 264400, People's Republic of China; [5]Shanghai University of Traditional Chinese Medicine, Shenzhen Hospital, Shenzhen, Guangdong, 518001, People's Republic of China; [6]Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, 250014, People's Republic of China

Correspondence: Jinfu Zhang, Guanghua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, 200052, People's Republic of China, Email zhangjinfu@tongji.edu.cn; Haicui Wu, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, 250014, People's Republic of China, Email haicui_w@163.com

Background: Female reproductive disorders (FRDs) are common diseases among women of childbearing age, affecting their reproductive health. Age at first sexual intercourse (AFS) is potentially linked to FRDs, and this study aims to investigate these associations and underlying mechanisms, to offer new insights and guidance for sex education in adolescent women and reproductive health management.

Methods: Mendelian randomization (MR) analysis was performed using summary data from genome-wide association studies (GWASs). The AFS summary data were sourced from 397,338 European participants, and the outcome data were obtained from the FinnGen consortium. Additionally, multivariate MR (MVMR) and mediation analyses were also adopted to explore more detailed association. The MR results were rigorously validated, with the inverse variance weighted (IVW) method employed as the primary approach to assess causal relationships.

Results: There is a significant causal relationship between AFS and ovarian dysfunction (OD), polycystic ovarian syndrome (PCOS), and spontaneous abortion (0.45 [0.25–0.81], p=0.008; 0.35 [0.17–0.74], p=0.006; 0.76 [0.63–0.92], p=0.006). Among them, the genetic association between AFS and spontaneous abortion remained significant even after adjusting for more confounding variables (0.73 [0.55–0.95], p=0.020; 0.76 [0.61–0.95], p=0.015), and Body mass index (BMI) may be an important mediating factor in the association between AFS and PCOS (38.41%, p=7.17e-6) or OD (35.64%, p= 1.51e-6).

Conclusion: Our research suggested that early AFS is closely associated with a higher risk of reproductive disorders, and timely interventions targeting BMI may partially alleviate the adverse effects of early sexual activity on reproductive health. The analysis based on genetic data emphasizes the importance of early sex education for adolescents, while weight management can to some extent avoid the occurrence of reproductive disorders during childbearing age, which also provide scientific basis for understanding the pathogenesis of FRDs and formulating appropriate reproductive health education strategies.

Keywords: female reproductive disorders, spontaneous abortion, age at first sexual intercourse, body mass index, Mendelian randomization, mediation effect

Introduction

Female fertility is essential for conception and successful delivery. Evaluating fertility involves assessing factors such as ovarian reserve, follicle maturation, and embryo development in Female Reproductive Disorders (FRDs), including ovarian dysfunction (OD), Polycystic Ovary Syndrome (PCOS), endometriosis, primary ovarian failure (POF), and spontaneous abortion.[1,2] These disorders present various fertility and health challenges, and their etiology is complex with considerable phenotypic variability. While numerous studies have identified potential mechanisms and biomarkers associated with these

Received: 21 May 2025
Accepted: 27 August 2025
Published: 2 September 2025

diseases,[3] the specific genetic mechanisms underlying FRDs remain poorly understood. Research indicates that FRDs may be influenced by an array of factors. Adverse health conditions, such as fluctuations in body mass index (BMI),[4] cardiovascular diseases,[5,6] diabetes,[7] and depressive states[8] that arise prior to the onset of FRDs, may act as mediating or confounding influences. Moreover, recent studies have established correlations between lifestyle choices—such as smoking, alcohol consumption, sleep duration, and dietary habits—and the incidence of reproductive diseases.[9,10]

Age at first sexual intercourse (AFS) has been linked to various health outcomes and serves as a predictive marker for longevity when combined with genetic variants identified through genome-wide association studies (GWASs).[11] Liu et al found that AFS is a risk factor for severe depression,[12] highlighting its potential investigational significance in understanding future physical and mental health conditions. AFS also plays a crucial role in female sexual development with implications for reproductive health and human evolution.[13] Claire Prince et al revealed a complex bidirectional relationship between reproductive traits, including AFS, and female body shape across the lifespan,[14] emphasizing the strong connection between AFS and overall female health status. Additionally, studies have suggested a relationship between AFS and epigenetic aging, indicating that a woman's developmental experiences may influence the onset of age-related reproductive diseases.[15] However, the exact causal relationship between AFS and more reproductive diseases is still unclear, and previous research methods cannot avoid the influence of confounding factors. It is crucial to have a broader and deeper understanding of the pathogenesis of reproductive diseases and develop effective prevention strategies.

Conducting prospective and cohort studies to examine the association between AFS and FRDs on a large scale is an essential method. However, the research process is complicated by various exposures and confounding factors, which makes establishing precise associations challenging. Mendelian randomization (MR) is a genetic epidemiological approach that utilizes single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) to assess relationships between exposures and outcomes. MR studies can minimize the impact of environmental confounders and reduce reverse causal relationships.[16] Multivariate MR (MVMR) can further investigate the independent effects of various exposures on outcomes by simultaneously adjusting for multiple confounding factors.

In this study, we conducted in-depth exploration of the genetic association and potential mediating factors between AFS and FRDs through two sample MR, MVMR, and two-step MR analysis, with the aim of minimizing the interference and impact of BMI, depression, cardiovascular disease, diabetes, and other lifestyle confounders. The relevant results will provide evidence for the importance of sex education for adolescent women and long-term weight management in reproductive health, and broaden the understanding of clinical doctors and researchers on the mechanisms and treatment strategies of reproductive disorders.

Methods

Research Design

This study utilized a two-sample MR analysis with extensive publicly available GWAS data to investigate the causal relationship between AFS and FRDs including OD, PCOS, Endometriosis, POF, and spontaneous abortion. Additionally, the MVMR model was applied to control for genetic variations linked to potential confounders such as BMI, depression, cardiovascular diseases, and diabetes, aiming to determine if AFS exerts an independent causal effect on FRDs beyond these confounding factors. Subsequent two-step MR analyses were conducted on identified mediators from the MVMR outcomes to explore underlying mechanisms. By adjusting for lifestyle factors, the study revealed a causal association between AFS and FRDs.

The methodology of this study is outlined in Figure 1. To ensure the effectiveness of MR analysis,[7] three key assumptions must be satisfied. Assumption 1: the IVs utilized to estimate causal effects should exhibit a strong association with AFS. Assumption 2: the IVs should be independent of any potential factors that could influence the relationship between AFS and FRDs. Assumption 3: the IVs should directly impact FRDs through AFS rather than through alternative pathways.[17] Assumption 4: the IVs employed for MVMR must be linked to at least one exposure, in accordance with the fulfillment of the aforementioned three assumptions.[18]

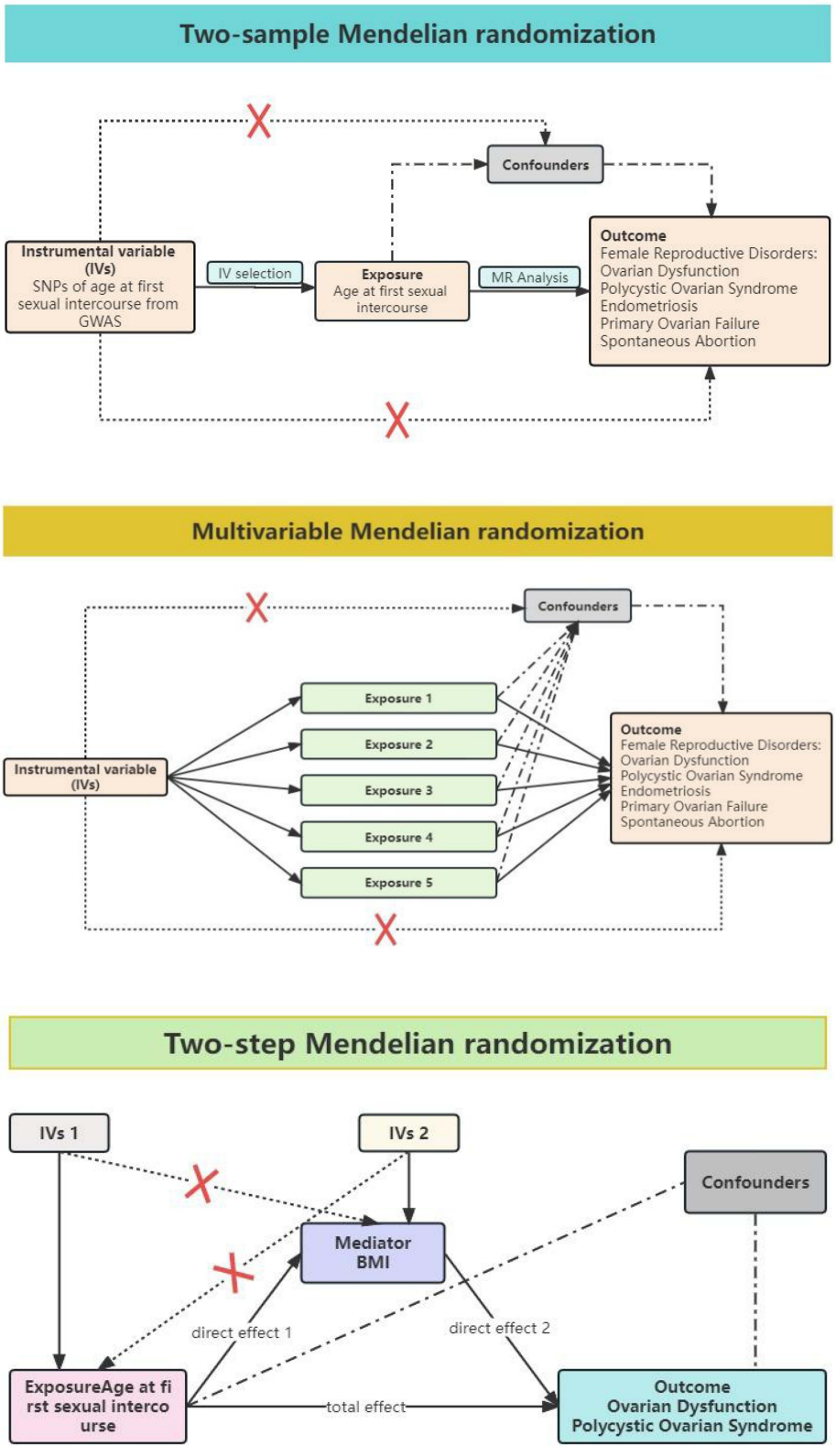

Figure 1 Design of Two-sample MR, Multivariate MR, and Two-step MR studies.
Abbreviations: IVs, Instrumental variables; BMI, Body mass index.

https://doi.org/10.2147/IJWH.S534178

Data Sources

We obtained data on exposure and outcomes from the International Oncology Unit (IEU) OpenGWAS and GWAS directories. The summary statistical data for the exposure factor AFS were derived from a meta-analysis of 36 cohort studies, representing the largest AFS GWAS to date (ID: ebi-a-GCST90000047). The measurement method of AFS is carried out by asking questions. Women were asked, "What was your age when you first had sexual intercourse? (Sexual intercourse includes vaginal, oral or anal intercourse)", collected from all individuals except those who indicated they had sexual intercourse under the age of 12 or never had sexual intercourse. Responses to this question were used to derive AFS data, resulting in a total of 397,338 European subjects.[5]

Depression data were sourced from the PGC Alliance (170,756 cases and 329,443 controls, ID: ieu-b-102),[19] while ischemic heart disease (IHD) data were obtained from the Neale laboratory (20,857 cases and 340,337 controls, ID: ukb-d-I9_IHD). Data on BMI, diabetes, alcohol intake, and coffee intake were retrieved from the MRC-IEU alliance (461,460 subjects, ID: ukb-19953; 18,228 cases and 444,705 controls, ID: ukb-b-12948; 462,346 cases and 9,851,867 controls, ID: ukb-b-5779; 428,860 cases and 9,851,867 controls, ID: ukb-b-5237). Smoking data were sourced from the GSCAN Alliance (249,752 cases and 12,003,613 controls, ID: ieu-b-142).[20] Furthermore, IVs for insomnia were extracted from GWAS data with the ID ebi-a-GCST90018869, comprising 1402 cases and 485,225 controls.[21]

All outcome factors, including OD (942 patients and 118,228 controls, ID: finn-b-E4-OVARDYS), POF (254 patients and 118,228 controls, ID: finn-b-E4-OVARFAIL), PCOS (642 patients and 118,228 controls, ID: finn-b-E4-POCS), Endometriosis (8288 patients and 68,969 controls, ID: finn-b-N14 ENDOMETRIOSIS), and spontaneous abortion (9113 patients and 89,340 controls, ID: finn-b-O15_ABORT SPONTAN), were obtained from the FinnGen Alliance.[22] Furthermore, all GWAS data utilized in this study originated from European population samples, ensuring no overlap between exposure and outcome samples, as data for exposure and outcome were derived from distinct cohorts.

Statistical Analysis

Relevant SNPs that met the genome-wide significance threshold of $p < 5e\text{-}8$ were extracted from the GWAS data. To ensure independence, SNPs with $LDr^2>0.001$ within a 10,000 kb window were excluded to eliminate SNPs in a state of linkage disequilibrium. The strength of the IVs was assessed using variance (R^2) and F-statistic values to mitigate weak instrumental bias, with F-statistic values exceeding 10 indicating a robust correlation. Pleiotropy testing was conducted to statistically evaluate the secondary phenotype of the selected SNPs and to eliminate potential pleiotropy effects. The "harmonise_data" function was employed to align the allele directions of exposure and outcome-sharing SNPs and to exclude incompatible and unidentifiable palindromic SNPs according to their effect allele frequency (EAF), simultaneously removing SNPs strongly correlated with the outcome. The remaining SNPs were then subjected to further analysis. A significance level of $p < 0.05$ was considered indicative of a causal relationship, with SNPs serving as IVs. All analyses were conducted using R software (version 4.3.2).

MR Analysis

The MR analysis used inverse variance weighted (IVW) analysis, weighted median (WM) analysis, MR-Egger regression, a weighted model, and a simple model to evaluate the causal relationship. IVW analysis was the main statistical analysis method used,[23,24] and $P < 0.05$ was considered statistically significant. The intercept test of the MR–Egger method was adopted to analyze whether the IVs had a pleiotropic effect on the results and provided estimates of causal effects independent of direct effects under weak assumptions.[25] Weighted and simple model methods have also been used for sensitivity. The weighted model clusters the SNPs on the basis of similarity and statistics of the inverse variance weighting of the SNPs of each cluster. A causal estimate was derived on the basis of the maximum weighting.

Scatter, forest, and funnel plots were used to visualize the MR results. Additionally, we used the Mendelian randomization-pleiotropy residual sum and outlier (MR-PRESSO) method to test all the SNPs globally.[26] When SNPs with heterogeneity were identified, the IVW random effects model was applied,[27] and a P value < 0.05 was considered statistically significant. The MR-Egger intercept and weighted median analysis were used to evaluate horizontal pleiotropy. Finally, "leave-one-out" analysis was conducted to test the sensitivity of the SNP's influence on the outcome.

The combined effect of the remaining SNPs was calculated by removing a single SNP to confirm that no causality was driven by a single SNP, thus reducing bias. Meanwhile, utilizing bioinformatics databases to understand the function of SNPs to further exclude the possibility of influencing outcomes through other pathways. We did not correct for multiple testing in this exploratory study to discover more potential positive indicators.[28]

Multivariate MR

We employed MVMR analysis to investigate the potential impact of AFS on the development of FRDs while considering BMI, depression, heart disease, and diabetes as control variables to address potential confounding factors. Additionally, MVMR aimed to establish an independent causal link between AFS and FRDs. In cases where outcome variables exhibited significant causal associations, we adjusted for genetic predisposition to correlated unhealthy lifestyle behaviors and re-conducted MVMR analysis following the potential factors about lifestyle mentioned above.

Two-Step MR

We performed a two-step MR analysis on the exposure and potential mediators to investigate the mediating effect (Figure 1). The coefficient product method was employed to illustrate the significance of mediating effects. Due to the limited number of significant SNPs, we assessed the correlation between IVs in the OD and PCOS cohorts, setting a p value threshold of <5e-6 for analytical convenience.[29]

Results

IVs

According to the requirements of MR analysis that the effect alleles of exposure and outcome are consistent, we removed 1 SNP with incompatible alleles and 37 palindrome SNPs exhibiting moderate allele frequencies to avoid estimating causal effects that may lead to bias. Subsequently, 154 conditionally independent SNPs were selected as instrumental variables for the MR analysis of FRDs. Information regarding the F-statistic and R^2 values was presented in Appendix Table 1. The F-statistics for all SNPs fell within the range of 27 to 171, suggesting a minimal risk of weak instrumental bias.

Potential Causal Effects of AFS on FRDs—Two-Sample MR

The forest plot (Figure 2) illustrated the MR estimates of the causal relationship between AFS and FRD risk using various methods. The IVW analysis results, employing the random effects method, indicated a potential negative association between earlier AFS and the incidence of OD, PCOS, or spontaneous abortion, with no significant correlation found for POF and Endometriosis. Specifically, later AFS might be associated with reduction in OD risk (Odds Ratio (OR)=0.45, 95% CI [0.25–0.81]), and linked to low risk of PCOS (OR=0.35, 95% CI [0.17–0.74]) and spontaneous abortion (OR=0.76, 95% CI [0.63–0.92]). Notably, a similar correlation was observed between AFS using the weighted median method and the IVW method (OR=0.38, 95% CI [0.16–0.88]). Heterogeneity tests conducted with MR–Egger, IVW, and MR-PRESSO revealed heterogeneity in the effects of AFS on PCOS and Endometriosis, indicating the necessity for further investigation into the potential causal relationship between later AFS and these conditions. However, multiplicity tests did not show any multiplicative effects of AFS on the outcome variables, including PCOS and Endometriosis (Appendix Table 2). Scatter plots in Appendix Figure 1 depicted the relationship between AFS and FRDs, while leave-one-out plots for AFS and OD, PCOS, and spontaneous abortion, displayed in Appendix Figures 2–4, confirmed the robustness of our findings by excluding the influence of individual SNPs on causal estimates.

Evaluation of the Potential Causal Correlation Between AFS and FRDs Using MVMR

We utilized MVMR-IVM analysis to control confounding factors BMI, depression, diabetes, and ischemic heart disease statuses, evaluating the direct impact of AFS on FRDs, including OD, PCOS, POF, Endometriosis, or spontaneous abortion. Results from Appendix Table 3 revealed that after adjusting for potential confounding factors (ischemic heart disease, and diabetes), the causal effect of AFS on OD and PCOS remained the same ($p<0.05$). Conversely, adjusting for BMI or depression attenuated the protective effect of later AFS on PCOS or OD incidence ($p>0.05$), suggesting the

A

Outcome	Method	nSNP	OR(95%CI)	p−value
OD	MR Egger	154	0.30(0.02 to 3.90)	0.356
	Weighted median	154	0.38(0.16 to 0.88)	0.024*
	Inverse variance weighted	154	0.45(0.25 to 0.81)	0.008*
	Simple mode	154	0.15(0.01 to 2.10)	0.163
	Weighted mode	154	0.21(0.02 to 2.45)	0.215
PCOS	MR Egger	154	0.71(0.03 to 18.26)	0.834
	Weighted median	154	0.62(0.23 to 1.69)	0.349
	Inverse variance weighted	154	0.35(0.17 to 0.74)	0.006*
	Simple mode	154	0.96(0.05 to 17.79)	0.979
	Weighted mode	154	1.03(0.09 to 12.46)	0.979
POF	MR Egger	154	0.03(0.00 to 3.19)	0.139
	Weighted median	154	0.41(0.09 to 1.94)	0.264
	Inverse variance weighted	154	0.71(0.23 to 2.15)	0.543
	Simple mode	154	0.24(0.00 to 19.78)	0.525
	Weighted mode	154	0.24(0.00 to 13.27)	0.485
EMs	MR Egger	154	1.22(0.44 to 3.40)	0.702
	Weighted median	154	0.92(0.69 to 1.24)	0.593
	Inverse variance weighted	154	0.90(0.71 to 1.14)	0.371
	Simple mode	154	0.93(0.42 to 2.07)	0.868
	Weighted mode	154	1.02(0.51 to 2.01)	0.961
SA	MR Egger	154	0.52(0.23 to 1.20)	0.126
	Weighted median	154	0.76(0.57 to 1.00)	0.051
	Inverse variance weighted	154	0.76(0.63 to 0.92)	0.006*
	Simple mode	154	1.12(0.49 to 2.54)	0.784
	Weighted mode	154	0.93(0.41 to 2.08)	0.853

B

Outcome	SNPs	OR(95%CI)	p−value
Ovarian dysfunction	154	0.45(0.25 to 0.81)	0.008*
Polycystic Ovarian Syndrome	154	0.35(0.17 to 0.74)	0.006*
Primary ovarian failure	154	0.71(0.23 to 2.15)	0.543
Endometriosis	154	0.90(0.71 to 1.14)	0.371
Spontaneous abortion	154	0.76(0.63 to 0.92)	0.006*

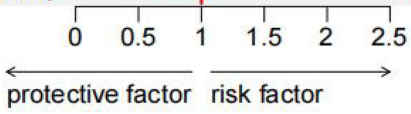

Figure 2 Two-sample MR of AFS on FRDs. (**A**) Risk association between age of first sexual intercourse and reproductive disorders; (**B**) IVW results between age of first sexual intercourse and reproductive disorders. *indicates significant differences in association.
Abbreviations: OD, Ovarian dysfunction; PCOS, Polycystic Ovarian Syndrome; POF, Primary ovarian failure; EMs, Endometriosis; SA, Spontaneous abortion.

significant impact of BMI and depression on ovarian function. It is worth noting that after controlling the influence of single or all mixed factors such as BMI, depression, diabetes and ischemic heart disease, the significant causal relationship between AFS and the incidence rate of spontaneous abortion still exists (p=0.020, or=0.72, 95% CI [0.55 to 0.95]). Late AFS is an independent causal factor against the risk of spontaneous abortion: every 1-year increase in the age of first sexual activity, the risk of spontaneous abortion decreases by 29% (Figure 3A).

The Mediating Effects of BMI on PCOS and OD

The MVMR results, considering confounding factors like BMI, depression, diabetes status, and heart disease status, revealed a significant influence of BMI on the causal associations between later AFS and PCOS, as well as OD, following pairwise and full confounding adjustments in the analysis, suggesting its potential mediating role. In the two-step MR analysis involving BMI. In the first step, BMI IV was used to estimate the causal effect of AFS on potential mediator variables, and it was found that BMI levels were associated with a decrease in AFS (p<0.001, OR = 0.65, 95% CI [0.60 to 0.71]). Furthermore, BMI was causally linked to an elevated OD risk (p<0.001, OR = 1.99, 95% CI [1.47 to 2.68]). The causal effect of AFS mediated BMI on OD was calculated to be 38.41%. Similarly, a potential correlation was found between BMI and PCOS occurrence (p<0.001, OR = 2.37, 95% CI [1.67 to 3.37]), and found that BMI mediates the effect of AFS on PCOS, with a mediating effect of up to 35.64% (Table 1). Additional results are available in Appendix Table 4.

MVMR Analysis of the Correlation Between AFS, Unhealthy Lifestyle Habits, and Spontaneous Abortion Risk

Considering that even after controlling the confounding factors including BMI, depression, ischemic heart disease and diabetes, AFS still shows an independent causal relationship with spontaneous abortion, in order to more rigorously and deeply explore whether lifestyle is a potential confounding factor, drawing from recent literature,[30,31] we incorporated

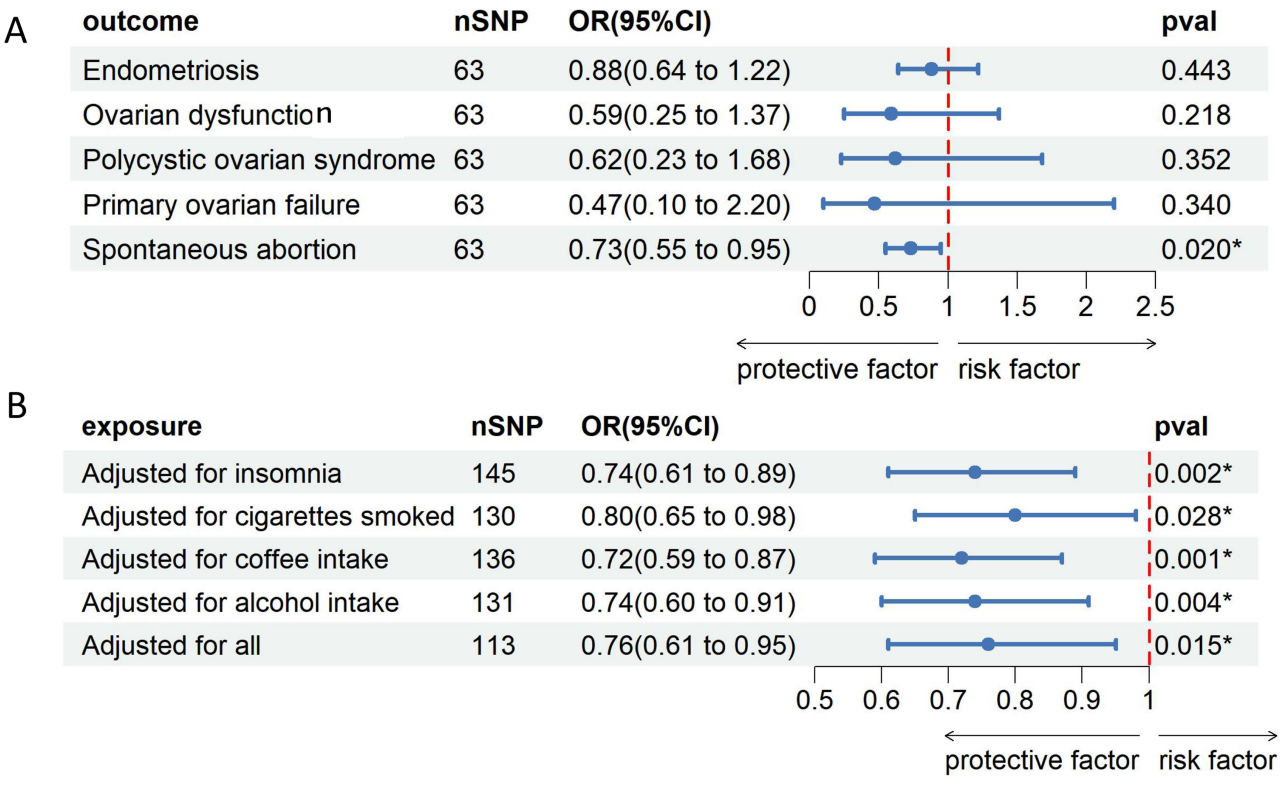

Figure 3 MVMR analysis. (**A**) MVMR-IVW analysis of the genetic causal effect of age of first sexual intercourse on reproductive disorders after adjusting BMI, depression, diabetes, and heart disease. (**B**) MVMR-IVW analysis of the genetic causal effects of age of first sexual intercourse on reproductive disorders after adjusting for smoking, alcohol consumption, coffee intake, and insomnia. * indicates significant differences.

https://doi.org/10.2147/IJWH.S534178

Table 1 Mediating Role of BMI in the Association Between AFS and OD/PCOS

Exposure	Mediator	Outcome	Total effect			Direct effect 1		
			Beta	SE	p	Beta	SE	p
AFS	BMI	OD PCOS	−0.77 −1.04	0.31 0.38	1.21E-02 6.25E-03	−0.43	0.04	2.12E-24
Exposure	**Mediator**	**Outcome**	**Direct effect 2**			**Mediation effect**		
			Beta	**SE**	**p**	**Effect size (95% CI)**	**Proportion (95% CI)**	
AFS	BMI	OD PCOS	0.69 0.86	0.15 0.18	7.17E-06 1.51E-06	−0.29 (−0.50~-0.09) −0.37 (−0.68~-0.07)	38.41 (11.25–65.58) 35.64 (6.33–64.95)	

Abbreviations: AFS, age of first sexual intercourse; FRDs, female reproductive disorders.

smoking (ID: ieu-b-142), alcohol consumption (ID: ukb-b-5779), coffee intake (ID: ukb-b-5237), and insomnia (ID: ebi-a-GCST90018869) as confounding variables in the MVMR analysis of AFS and spontaneous abortion. Following adjustments for each confounding factor of lifestyles independently and collectively, a robust causal link between AFS and spontaneous abortion was always identified, illustrated in Figure 3B. The relevant results further strongly emphasized the independent causal relationship between AFS and spontaneous abortion.

Discussion

FRDs pose significant challenges for reproductive healthcare providers and women of childbearing age. Currently, the treatment of FRDs focuses on alleviating clinical symptoms and assisting with conception; however, a comprehensive understanding of the underlying mechanisms remains elusive. Advances in genomics have made it possible to identify links between disease development and genetic factors. The intricate interplay between genetic and environmental influences has long attracted researchers' interest. Although the complex etiology of these diseases may relate to individual variables, the combined effects of genetic variations and environmental factors frequently determine certain populations' susceptibility to specific diseases,[32] which emphasizes the importance of MR analysis, aiming to avoid interference from environmental, reverse causality, and confounding factors as much as possible. This study reveals a significant potential causal relationship between AFS and reproductive system diseases. Engaging in first sexual activity at a later age is an important factor in reducing the risk of OD, PCOS, and spontaneous abortion, particularly for spontaneous abortion, where it demonstrates a strong and stable independent protective effect. This association may be partly mediated by lower BMI. The relevant findings underscore the importance of weight management in regulating female reproductive health, bridging a critical gap in understanding the interaction mechanisms between sexual development characteristics and reproductive disorders while providing a new perspective on FRDs and their related mechanisms.

A large-scale health survey of the Ghanaian population indicated that early sexual behavior is associated with long-term health consequences, particularly an increased risk of obesity over time, highlighting the key role of early sexual behavior throughout life.[33] This finding aligns with our mediation MR analysis results and, combined with biological data from European and African populations, further confirms the association between early sexual behavior and long-term weight. Relevant mechanisms may involve complex physiological responses due to changes in reproductive hormones at various stages of a woman's life cycle. Inappropriate sexual activity at a young age can disrupt normal body composition changes associated with puberty.[34] Furthermore, previous studies have shown that early sexual activity increases the likelihood of unintended pregnancy and sexually transmitted infections in women.[35] Early pregnancies and postpartum weight management become critical factors influencing long-term weight.[36] Additionally, research in Japan has established a link between childhood experiences and unintended pregnancies, with impaired social interactions and emotional deficits being potential contributing factors.[37] Unhealthy diets resulting from emotional disorders further exacerbate the risk of overweight or obesity, especially following involuntary early sexual activity.[38]

AFS, as a reproductive behavioral characteristic, plays a crucial role in female sexual development and future reproductive health. Early sexual activity may be perceived as a negative experience during adolescence, affecting the

reproductive health of women of childbearing age by impacting mental health and potentially contributing to the development of reproductive system diseases. Our multivariate MVMR results support this assertion, suggesting that BMI and depression may mediate the genetic association between AFS and OD or PCOS. It is known that the occurrence of OD and PCOS is associated with ovarian dysfunction due to reproductive hormone disorders, characterized by impaired follicle growth and maturation, abnormal follicle release, and hormonal imbalances—common factors that influence female fertility and contribute to cases of infertility, anxiety, and depression. Among these factors, BMI is strongly correlated with the onset of PCOS; its biological mechanisms may involve complex interactions among androgens, insulin resistance, and fat, along with excessive oxidative stress, inflammation, and cellular iron death.[39] OD often manifests in women after menopause, where low estrogen levels significantly affect obesity and mental health.[40] A retrospective study suggests a potential relationship between the regulation of reproductive hormones in the pituitary and ovary and body fat distribution, particularly regarding abdominal fat thickness.[41] This suggests that BMI may participate in the mechanisms of reproductive-related diseases by influencing hormone release. Losing weight may become one of the important strategies to avoid the high risk of OD and PCOS caused by early first sexual activity.

A multicenter cohort study revealed that women who experience premature menopause before the age of 40 have a higher obesity rate compared to those who menopause after 40.[42] Laboratory experiments have indicated that low expression of fat mass and obesity-related genes can improve premature ovarian failure through specific molecular pathways, potentially reversing excessive apoptosis of granulosa cells and enhancing oocyte quality.[43] However, after controlling for multiple confounding factors, our study did not find a significant genetic association between early AFS and POF. This may be due to biases stemming from the limited POF-related data available in the GWAS database. Future research with larger samples will be essential for understanding the pathogenesis and treatment of POF. Likewise, after adjusting for confounding factors, the genetic association between AFS and EMs weakened. Nonetheless, we noted cross-sectional evidence that early compulsive sexual behavior contributes to the occurrence of EMs.[44] In summary, previous studies have demonstrated differences in lipid levels between girls with precocious puberty and those with normal development, underscoring the importance of early sex education and weight intervention for these girls to prevent reproductive disorders.[45]

An increasing body of evidence highlights the significant impact of lifestyle factors on the occurrence and progression of diseases. Population cohort studies have shown that obesity-inducing diets are risk factors for previous miscarriages and non-live births, correlating with adverse pregnancy outcomes.[46] A systematic review and dose-response meta-analysis have also found an association between coffee and caffeine intake and the risk of spontaneous abortion.[47] Similarly, secondary analyses of population data reveal that pre-pregnancy alcohol abuse is a significant risk factor for miscarriage,[48] mirroring findings from cohort studies.[49] Therefore, in this study, we analyzed the genetic association between AFS and spontaneous abortion while controlling for confounding lifestyle factors. However, even after factoring in additional lifestyle influences, early AFS consistently exhibited a causal relationship with spontaneous abortion—indicating that it remains an independent risk factor, regardless of ultrasound findings, obesity, depression, or other comorbidities and adverse lifestyle factors.

MR analysis provided genetic evidence linking AFS to frailty,[50] suggesting that early AFS may exert complex effects on muscle, nervous, endocrine, and immune system dysregulation, which may also contribute to the high risk of spontaneous abortion. Additionally, depletion of the vaginal microbiome during early pregnancy is a recognized risk factor for miscarriage.[51] Premature sexual behaviors resulting from inadequate sex education may lead to reproductive tract infections due to unintended pregnancies and induced abortions.[52] The resultant disruption of vaginal and uterine microbiota could be a potential cause of an increased risk of long-term spontaneous miscarriages. Furthermore, it remains unclear whether early AFS leads to spontaneous abortion at the genetic level or simply augments fertility and abortion procedures, as participants were not queried about the number of pregnancies or subsequent sexual activities related to early or late AFS. More rigorous clinical observations and detailed data analyses are necessary to clarify these correlations. However, the relevant results still emphasize the importance of adolescent sex education.

The MR analysis method mitigates biases inherent in observational studies; however, several limitations must be acknowledged. Firstly, the GWAS database from which the FRDs-related outcome variables in this study were sourced lacks sufficient data; including a small number of patients may result in bias. Additionally, there may be a risk of false positives

in the results of uncorrected multiple comparison analyses; Besides, due to the limited number of significant loci in PCOS or OD analyses, the significance threshold has been set below the standard threshold, which may lower analytical intensity or introduce bias, rendering the results potentially unreliable. Large-scale prospective studies based on broader populations are still needed for further validation. The data on exposure and outcome variables in this study were solely obtained from the European population, which may limit the generalizability of the findings to other races and populations. Therefore, conducting more extensive and comprehensive longitudinal studies and analyses, across diverse races and populations is imperative for drawing reliable conclusions. Finally, We only considered the influence of limited confounding factors, and we will continue to explore and discover more important mediators besides BMI in future research.

Conclusions

In summary, we have identified a preliminary genetic association between early sexual activity and the occurrence of reproductive diseases in women. Early sexual activity may serve as an independent risk factor for spontaneous abortion, while BMI may partially mediate the relationship between early sexual activity and the development of OD and PCOS. These findings underscore the importance of providing sex education and reproductive health information to adolescent girls to prevent certain reproductive disorders. Furthermore, subsequent weight management may be a key strategy for reducing the risk of these conditions. In the future, we will conduct large-scale, longitudinal studies that include diverse racial and ethnic populations and address additional confounding factors to provide more reliable insights into the mechanisms underlying FRDs and strategies for protecting female fertility.

Abbreviations

AFS, age at first sexual intercourse; FRDs, female reproductive disorders; MR, mendelian randomization; GWASs, genome-wide association studies; MVMR, multivariate MR; OD, ovarian dysfunction; BMI, body mass index; PCOS, polycystic ovarian syndrome; IVW, inverse variance weighted; POF, primary ovarian failure; SNPs, single nucleotide polymorphisms; IVs, instrumental variables.

Data Sharing Statement

The data from the UK Biobank can be accessed at (https://www.ukbiobank.ac.uk). The summary statistics data are publicly available on the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/). The original contributed data are fully included in our article and supplementary materials. Contact the corresponding author to obtain further inquiries.

Ethics Approval and Consent to Participate

This study is exempt from approval according to Article 32 (1) and (2) of the "Ethical Review Measures for Research Involving Human Life Sciences and Medical Sciences" issued by China on February 18, 2023. The data used in this study comes from publicly available and free sources that comply with local legislation and institutional requirements. All GWAS data are sourced from ethically approved original studies. All participants provided informed consent forms, which can be obtained from their articles. This study would not cause harm to the human body, and did not involve sensitive personal information or commercial interests.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas: took part in drafting, revising or critically reviewing the article, gave final approval of the version to be published, agreed on the journal to which the article has been submitted and agreed to be accountable for all aspects of the work.

Funding

This research was funded by National Natural Science Foundation of China (No. 82274573, 81703958), Natural Science Foundation of Shandong Province (No. ZR2021MH255) and the Special Fund of "Taishan Scholars" of Shandong Province (No. rc2021001-01).

Disclosure

The authors declare that they have no conflicts of interest in this work.

References

1. Liu M, Wu K, Wu Y. The emerging role of ferroptosis in female reproductive disorders. *Biomed Pharmacother*. 2023;166:115415. doi:10.1016/j.biopha.2023.115415
2. Huttler A, Murugappan G, Stentz NC, Cedars MI. Reproduction as a window to future health in women. *Fertil Steril*. 2023;120(3 Pt 1):421–428. doi:10.1016/j.fertnstert.2023.01.005
3. Tong C, Wu Y, Zhuang Z, Wang Z, Yu Y. Combining proteomic markers to construct a logistic regression model for polycystic ovary syndrome. *Front Endocrinol*. 2023;14:1227252. doi:10.3389/fendo.2023.1227252
4. Liu Q, Tang B, Zhu Z, et al. A genome-wide cross-trait analysis identifies shared loci and causal relationships of type 2 diabetes and glycaemic traits with polycystic ovary syndrome. *Diabetologia*. 2022;65(9):1483–1494. doi:10.1007/s00125-022-05746-x
5. Murugappan G, Li S, Lathi RB, Baker VL, Eisenberg ML. Increased risk of incident chronic medical conditions in infertile women: analysis of US claims data [published correction appears in Am J Obstet Gynecol. 2020 Nov;223(5):757]. *Am J Obstet Gynecol*. 2019;220(5):473.e1–473.e14. doi:10.1016/j.ajog.2019.01.214
6. Gleason JL, Shenassa ED, Thoma ME. Self-reported infertility, metabolic dysfunction, and cardiovascular events: a cross-sectional analysis among U.S. women. *Fertil Steril*. 2019;111(1):138–146. doi:10.1016/j.fertnstert.2018.10.009
7. Vaduva P, Laouali N, Fagherazzi G, Gelot A, Bonnet F, Kvaskoff M. Association between endometriosis and risk of type 2 diabetes: results from the prospective E3N cohort. *Maturitas*. 2023;177:107805. doi:10.1016/j.maturitas.2023.107805
8. Tay CT, Loxton D, Bahri Khomami M, Teede H, Harrison CL, Joham AE. High prevalence of medical conditions and unhealthy lifestyle behaviours in women with PCOS during preconception: findings from the Australian longitudinal study on women's health. *Hum Reprod*. 2023;dead190. doi:10.1093/humrep/dead190
9. Wang Q, Liu F, Tuo Y, Ma L, Feng X. Associations between obesity, smoking behaviors, reproductive traits and spontaneous abortion: a univariable and multivariable Mendelian randomization study. *Front Endocrinol*. 2023;14:1193995. doi:10.3389/fendo.2023.1193995
10. Cirillo M, Argento FR, Becatti M, Fiorillo C, Coccia ME, Fatini C. Mediterranean diet and oxidative stress: a relationship with pain perception in endometriosis. *Int J Mol Sci*. 2023;24(19):14601. doi:10.3390/ijms241914601
11. eQTLGen Consortium; Mills MC, Tropf FC, Brazel DM, et al. Identification of 371 genetic variants for age at first sex and birth linked to externalising behaviour. *Nat Hum Behav*. 2021;5(12):1717–1730. doi:10.1038/s41562-021-01135-3
12. Lu Z, Sun Y, Liao Y, et al. Identifying causal associations between early sexual intercourse or number of sexual partners and major depressive disorders: a bidirectional two-sample Mendelian randomization analysis. *J Affect Disord*. 2023;333:121–129. doi:10.1016/j.jad.2023.04.079
13. Perez-Fernandez J, Arroyo-Velasco DO, Huaman MR, et al. Association between early sexual initiation and sexually transmitted infections among Peruvian reproductive-age women. *Front Public Health*. 2023;11:1191722. doi:10.3389/fpubh.2023.1191722
14. Prince C, Howe LD, Sharp GC, Fraser A, Richmond RC. Establishing the relationships between adiposity and reproductive factors: a multivariable Mendelian randomization analysis. *BMC Med*. 2023;21(1):350. doi:10.1186/s12916-023-03051-x
15. Zhang B, Yuan Q, Luan Y, Xia J. Effect of women's fertility and sexual development on epigenetic clock: mendelian randomization study. *Clin Clin Epigenet*. 2023;15(1):154. doi:10.1186/s13148-023-01572-z
16. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ*. 2018;362:k601. doi:10.1136/bmj.k601
17. Thanassoulis G, O'Donnell CJ. Mendelian randomization: nature's randomized trial in the post-genome era. *JAMA*. 2009;301(22):2386–2388. doi:10.1001/jama.2009.812
18. Burgess S, Thompson SG. Multivariable Mendelian randomization: the use of pleiotropic genetic variants to estimate causal effects. *Am J Epidemiol*. 2015;181(4):251–260. doi:10.1093/aje/kwu283
19. Howard DM, Adams MJ, Clarke TK, et al. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nat Neurosci*. 2019;22(3):343–352. doi:10.1038/s41593-018-0326-7
20. Liu M, Jiang Y, Wedow R, et al. Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. *Nat Genet*. 2019;51(2):237–244. doi:10.1038/s41588-018-0307-5
21. Sakaue S, Kanai M, Tanigawa Y, et al. A cross-population atlas of genetic associations for 220 human phenotypes. *Nat Genet*. 2021;53(10):1415–1424. doi:10.1038/s41588-021-00931-x
22. Kurki MI, Karjalainen J, Palta P, et al. FinnGen provides genetic insights from a well-phenotyped isolated population. *Nature*. 2023;613(7944):508–518. doi:10.1038/s41586-022-05473-8
23. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. *Genet Epidemiol*. 2013;37(7):658–665. doi:10.1002/gepi.21758
24. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol*. 2016;40(4):304–314. doi:10.1002/gepi.21965
25. Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR–Egger method. *Eur J Epidemiol*. 2017;32(5):377–389. Erratum in: Eur J Epidemiol. 2017 May;32(5):391-392. doi: 10.1007/s10654-017-0276-5. doi:10.1007/s10654-017-0255-x
26. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet*. 2018;50(5):693–698. Erratum in: Nat Genet. 2018 Aug;50(8):1196. doi: 10.1038/s41588-018-0164-2. doi:10.1038/s41588-018-0099-7
27. Liu J, Pan R. Causal effects of systemic inflammatory proteins on Guillain-Barre Syndrome: insights from genome-wide Mendelian randomization, single-cell RNA sequencing analysis, and network pharmacology. *Front Immunol*. 2024;15:1456663. doi:10.3389/fimmu.2024.1456663
28. Xiang Y, Zhang C, Wang J, et al. Identification of host gene-microbiome associations in colorectal cancer patients using mendelian randomization. *J Transl Med*. 2023;21(1):535. doi:10.1186/s12967-023-04335-9

29. Wang Q, Shi Q, Wang Z, Lu J, Hou J. Integrating plasma proteomes with genome-wide association data for causal protein identification in multiple myeloma. *BMC Med*. 2023;21(1):377. doi:10.1186/s12916-023-03086-0
30. Yuan S, Liu J, Larsson SC. Smoking, alcohol and coffee consumption and pregnancy loss: a Mendelian randomization investigation. *Fertil Steril*. 2021;116(4):1061–1067. doi:10.1016/j.fertnstert.2021.05.103
31. Yang Q, Borges MC, Sanderson E, et al. Associations between insomnia and pregnancy and perinatal outcomes: evidence from mendelian randomization and multivariable regression analyses. *PLoS Med*. 2022;19(9):e1004090. doi:10.1371/journal.pmed.1004090
32. Dowaidar M. Gene-environment interactions that influence CVD, lipid traits, obesity, diabetes, and hypertension appear to be able to influence gene therapy. *Mol Aspects Med*. 2023;94:101213. doi:10.1016/j.mam.2023.101213
33. Okyere J, Ayebeng C, Dickson KS, Duodu PA. From early sexual debut to later overweight and obesity: a multilevel analysis of Ghanaian women. *Trop Med Health*. 2025;53(1):88. doi:10.1186/s41182-025-00753-1
34. Liu D, Dou C, Ye C, et al. Chain effect of lifecourse reproductive characteristics and body fat and muscle on cardiovascular disease in women: a Mendelian randomization study. *Cardiovasc Diabetol*. 2025;24(1):170. doi:10.1186/s12933-025-02681-0
35. Skinner SR, Robinson M, Smith MA, et al. Childhood behavior problems and age at first sexual intercourse: a prospective birth cohort study. *Pediatrics*. 2015;135(2):255–263. doi:10.1542/peds.2014-1579
36. Siega-Riz AM, Herring AH, Carrier K, Evenson KR, Dole N, Deierlein A. Sociodemographic, perinatal, behavioral, and psychosocial predictors of weight retention at 3 and 12 months postpartum. *Obesity*. 2010;18(10):1996–2003. doi:10.1038/oby.2009.458
37. Kanamori Y, Miyamoto Y, Sawada U, Iida M, Tabuchi T, Nishi D. Association between adverse childhood experience and unintended pregnancy among Japanese women: a large-scale cross-sectional study. *J Psychosom Obstet Gynaecol*. 2023;44(1):2274295. doi:10.1080/0167482X.2023.2274295
38. Smith HA, Markovic N, Danielson ME, et al. Sexual abuse, sexual orientation, and obesity in women. *J Womens Health*. 2010;19(8):1525–1532. doi:10.1089/jwh.2009.1763
39. Hayat N, Akram Z, Khalid N, Ullah NR, Mazhar T. Link between iron-mediated lipid peroxidation and polycystic ovary syndrome (PCOS): exploring the genes underlying iron regulatory mechanism. *J Ovarian Res*. 2025;18(1):48. doi:10.1186/s13048-024-01562-6
40. Meegaswatte H, McKune AJ, Panagiotakos DB, et al. The association between the American heart association life's essential 8 and metabolic syndrome among postmenopausal women: findings from NHANES 2011-2020. *Nutrients*. 2025;17(10):1688. doi:10.3390/nu17101688
41. Guo H, Yang B, Kiryu S, et al. Evaluation of the relations between reproduction-related pituitary and ovarian hormones and abdominal fat area-related variables determined with computed tomography in overweight or obese women who have undergone bariatric surgery: a cross-sectional study. *Quant Imaging Med Surg*. 2023;13(10):7065–7076. doi:10.21037/qims-22-1283
42. Vogt EC, Real FG, Husebye ES, et al. Premature menopause and autoimmune primary ovarian insufficiency in two international multi-center cohorts. *Endocr Connect*. 2022;11(5):e220024. doi:10.1530/EC-22-0024
43. Wang R, Wang W, Wang L, et al. FTO protects human granulosa cells from chemotherapy-induced cytotoxicity. *Reprod Biol Endocrinol*. 2022;20(1):39. doi:10.1186/s12958-022-00911-8
44. Hawks L, Woolhandler S, Himmelstein DU, Bor DH, Gaffney A, McCormick D. Association between forced sexual initiation and health outcomes among US women. *JAMA Intern Med*. 2019;179(11):1551–1558. doi:10.1001/jamainternmed.2019.3500
45. Jiang M, Gao Y, Wang K, Huang L. Lipid profile in girls with precocious puberty: a systematic review and meta-analysis. *BMC Endocr Disord*. 2023;23(1):225. doi:10.1186/s12902-023-01470-8
46. Yang X, Mu F, Zhang J, et al. Reproductive factors and subsequent pregnancy outcomes in patients with prior pregnancy loss. *BMC Pregnancy Childbirth*. 2024;24(1):219. doi:10.1186/s12884-024-06422-1
47. Lyngsø J, Ramlau-Hansen CH, Bay B, Ingerslev HJ, Hulman A, Kesmodel US. Association between coffee or caffeine consumption and fecundity and fertility: a systematic review and dose-response meta-analysis. *Clin Epidemiol*. 2017;9:699–719. doi:10.2147/CLEP.S146496
48. Ayana GM, Raru TB, Deressa A, et al. Association of alcohol consumption with abortion among ever-married reproductive age women in Ethiopia: a multilevel analysis. *Front Glob Womens Health*. 2022;3:1028166. doi:10.3389/fgwh.2022.1028166
49. Magnus MC, Hockey RL, Håberg SE, Mishra GD. Pre-pregnancy lifestyle characteristics and risk of miscarriage: the Australian longitudinal study on women's health. *BMC Pregnancy Childbirth*. 2022;22(1):169. doi:10.1186/s12884-022-04482-9
50. Fan M, Wang D, Wu X, Gao W. Exploring the causal relationship between female reproductive traits and frailty: a two-sample mendelian randomization study. *Front Physiol*. 2024;15:1349952. doi:10.3389/fphys.2024.1349952
51. Eslami M, Naderian R, Ahmadpour A, et al. Microbiome structure in healthy and pregnant women and importance of vaginal dysbiosis in spontaneous abortion. *Front Cell Infect Microbiol*. 2025;14:1401610. doi:10.3389/fcimb.2024.1401610
52. Materu J, Konje ET, Urassa M, Marston M, Boerma T, Todd J. Comparison of survival analysis approaches to modelling age at first sex among youth in Kisesa Tanzania. *PLoS One*. 2023;18(9):e0289942. doi:10.1371/journal.pone.028994