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ORIGINAL RESEARCH

Global Spatiotemporal Trends and Modifiable Risk Factors for Female Infertility: An Age-Period-Cohort Using Global Burden of Disease Study 2021 and Mendelian Randomization Analysis

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Background: This study aims to describe the global burden of female infertility, analyze its spatial and temporal trends, and offer targeted epidemiological insights to support the prevention and management of female infertility.

Methods: Drawing on insights from the GBD 2021 study, we analyzed age-standardized prevalence rates (ASPR) of female infertility (1990–2021) across global regions and Socio-Demographic Index (SDI) categories. We quantified temporal trends using estimated annual percentage change (EAPC) and Age-Period-Cohort analyses across age groups and geographic regions. Furthermore, the causal relationships between 16 modifiable risk factors, 10 serum biomarkers, and female infertility were assessed by two-sample Mendelian randomization (MR) and mediation analysis.

Results: Globally, the ASPR of female infertility exhibited an increasing trend over the study period. Across all SDI regions, infertility prevalence peaked at ages 35–40. MR analysis identified poor general health (IVW OR, 1.94; 95% CI, 1.49–2.52; $P_{FDR} = 1.24\times10^{-5}$), elevated waist-to-hip ratio (WHR) (IVW OR, 1.12; 95% CI, 1.04–1.20; $P_{FDR} = 3.26\times10^{-3}$), and neuroticism (IVW OR, 1.10; 95% CI, 1.04–1.15; $P_{FDR} = 1.25\times10^{-3}$) as significant risk factors, whereas higher educational attainment (IVW OR, 0.95; 95% CI, 0.93–0.97; $P_{FDR} = 3.26\times10^{-4}$), greater body fat percentage (IVW OR, 0.67; 95% CI, 0.52–0.85; $P_{FDR} = 4.10\times10^{-3}$) and napping (IVW OR, 0.63; 95% CI, 0.45–0.89; $P_{FDR} = 1.94\times10^{-2}$) had protective effects. Mediation analysis demonstrated that HbA1c and triglycerides (TG) partially mediated the relationship between WHR and infertility, while TG mediated the effect of educational attainment on female infertility.

Conclusion: Age-Period-Cohort modeling suggests that shifts in reproductive age patterns, environmental exposures, and cohort-specific risk profiles are key contributors to observed disparities. Targeted public health interventions, including educational promotion, lifestyle modifications, and routine metabolic screening, are essential to mitigate the rising infertility burden in the coming decades.

Keywords: female infertility, age-standardized prevalence rate, socio-demographic index, age-period-cohort analysis, Mendelian randomization, modifiable risk factors, global burden of disease

Introduction

Female infertility is clinically defined as the inability of a woman of childbearing age to conceive after 12 months of unprotected, regular sexual intercourse, or after 6 months in women 35 years of age and older.[1,2] Globally, infertility affects approximately 8–12% of couples of childbearing age, placing a significant economic and psychological burden on individuals and families.[3] Beyond personal consequences, infertility has broader demographic implications, contributing to declining population growth, labor shortages, and increased pressure on social welfare systems, thereby posing a threat to the long-term sustainability of national economies. Despite its wide-ranging social and economic impact, female

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infertility remains a relatively underrecognized public health concern, with limited data available on its global distribution and temporal dynamics.

Recent developments in the Global Burden of Disease (GBD) study have enhanced our understanding of infertility epidemiology. Wang et al[4] analyzed trends in female infertility among women aged 20–49 from 1990 to 2019 using the latest GBD data. Liang et al[5] reported a global rise in infertility prevalence among individuals aged 15–49 between 1990 and 2021, with projections suggesting a continued increase through 2040. Feng et al[6] primarily attributed this upward trend to population growth. However, the relationship between female infertility and varying levels of socioeconomic development in different regions, periods, and age groups remains insufficiently explored. The research seeks to fill this void by applying the most recent GBD data to conduct an extensive examination of the worldwide impact of female infertility Employing age-period-cohort modeling and socioeconomic stratification, we seek to elucidate temporal and geographic patterns, thereby informing public health policy and research priorities.

The etiological mechanisms underlying female infertility are multifactorial and complex, encompassing a range of lifestyle, environmental, and biological factors, all of which are modulated by socio-economic dynamics. Traditional observational studies have uncovered a link between female infertility and various modifiable risk factors, including obesity, tobacco and alcohol use, sleep disturbances, and psychological stress.[7–12] However, these studies are often limited by residual confounding, reverse causation, and inconsistent findings across populations. To address these methodological limitations, we employed a Mendelian Randomization (MR) approach, utilizing genetic variants as instrumental variables to infer causal relationships while minimizing bias from confounding and reverse causality. Sixteen modifiable risk factors were selected based on their relevance to public health, potential for clinical intervention, and previously reported associations with reproductive outcomes. In addition, we investigated circulating blood biomarkers such as glucose, lipid profiles, urate, and uric acid levels as potential mediators, given their biological links to lifestyle and psychosocial factors, and their suggested associations with female infertility in existing studies.[13–16]

By integrating these methods, our study aims to delineate causal pathways and identify modifiable targets for the prevention and management of female infertility. We conducted a comprehensive analysis of the global burden of female infertility from 1990 to 2021, utilizing GBD data to assess temporal trends stratified by region, age group, and socio-demographic index (SDI). Age-Period-Cohort modeling was applied to disentangle the independent effects of aging, temporal changes, and birth cohort characteristics across SDI strata. Furthermore, using a two-sample MR framework, we explored the causal impact of modifiable exposures and serum biomarkers on female infertility, while also evaluating the mediating roles of biomarkers in these associations. Collectively, these findings aim to inform targeted, evidence-based public health strategies and guide future research into effective prevention and therapeutic interventions for female infertility across diverse socio-economic landscapes.

Materials and Methods

Overview and Global Data Sources

This study utilized publicly available data from the GBD 2021 dataset, which provides comprehensive epidemiological estimates across 204 countries and 21 global regions. Female infertility is clinically defined as the inability to achieve pregnancy after at least 12 months of regular unprotected intercourse, or after 6 months for women aged 35 years and older. The etiology of female infertility includes a wide spectrum of factors, such as advancing age, physiological and hormonal abnormalities, as well as lifestyle and environmental influences. In the GBD 2021 framework, female infertility was identified using the International Classification of Diseases (ICD) diagnostic codes: ICD-9 codes 628–628.9, V26-V26.49, V26.51, V26.8-V26.9, V59.7-V59.74, and ICD-10 codes N97-N98.9.

To quantify the burden of female infertility, we extracted metrics including total prevalence and age-standardized prevalence rate (ASPR) from 1990 to 2021. Age-standardized rates were computed using the direct standardization method, referencing the world standard population defined in the GBD 2021 methodology. To assess disease burden across varying development levels, we employed SDI, a composite indicator that incorporates average educational attainment in individuals aged ≥ 15 years, the total fertility rate under age 25, and per capita income. Based on SDI quintiles, countries and territories were categorized into five levels: low (0–0.466), low-middle (0.466–0.619), middle

(0.619–0.712), high-middle (0.712–0.810), and high (0.810–1), with higher SDI scores indicating greater socioeconomic development. Furthermore, female infertility burden was assessed across seven reproductive age strata as defined by GBD 2021: 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, and 45–49 years. This stratified approach facilitated the evaluation of age-specific trends over time and across development levels. As this study was based exclusively on secondary data, ethical approval was not required.

GBD Trend Analysis

The ASR of female infertility is expressed per 100,000 individuals, with corresponding 95% uncertainty intervals (UIs) provided to capture the precision of the estimates. To analyze trends in ASR from 1990 to 2021, we calculated the estimated annual percentage change (EAPC) and its 95% confidence intervals (CIs). The EAPC is a widely used metric for quantifying the rate of change in a time series, with a positive EAPC (> 0) indicating an annual increase in ASR, and a negative EAPC (< 0) suggesting a decline. Further statistical methods employed include Joinpoint regression analysis to identify significant changes in trend direction, as well as the Age-Period-Cohort model to assess the independent effects of age, period, and cohort on female infertility prevalence. To explore the relationships between female infertility burden and socio-demographic development, Pearson correlation analysis was performed between disease statistics, the SDI, and the EAPC. The statistical significance of the APC model was assessed using Wald tests. Visualizations and further statistical outputs were generated using the World Health Organization's Health Equity Assessment Toolkit.

Joinpoint Regression

To assess temporal trends in the burden of female infertility across different SDI regions from 1990 to 2021, we employed Joinpoint regression analysis (version 5.3.0.0), which enables the identification of changes in trend patterns over time. This method utilizes segmented regression within a log-linear framework to detect inflection points where significant shifts in the trend occur. The grid search method (GSM) was applied to examine all potential join points, with the optimal number of join points selected based on the minimal mean squared error (MSE). To determine the appropriate number of join points, the Monte Carlo permutation test was utilized, allowing for a maximum of five and a minimum of zero join points. For each SDI region, the final model produced estimates of the annual percentage change (APC) for each segment, the average annual percentage change (AAPC), and their respective 95% confidence intervals (CIs). The AAPC, which weights the APC of each segment by its duration, provides a comprehensive summary of the overall trend, accounting for variations in the trajectory of infertility burden over time.

Age-Period-Cohort Modelling

The Age-Period-Cohort model assessed how age, time period, and birth cohort independently influenced global female infertility rates in five SDI regions. Model construction was performed using the R packages "magrittr" and "dplyr". Within this framework, the age factor accounts for biological aging processes, the period factor captures temporal shifts in environmental and societal influences, and the cohort factor reflects generational differences in exposure to risk factors. All temporal intervals (age, period, and cohort) were analyzed in 5-year increments from 1992 to 2021, with data from 1990 to 1991 excluded due to incomplete intervals. The model's net drift quantified the overall temporal trend, with statistical significance established at $P < 0.05$. Age-specific disease burden patterns were visualized through longitudinal age curves, while rate ratios (RR) for period and cohort effects provided insights into temporal and generational variations in infertility prevalence.

Two-Sample MR and Mediation Analysis

An overview of the MR study is presented in Figure 1. The research process was conducted in accordance with the STROBE-MR checklist,[17] which is provided in Supplementary Material. We employed a two-sample MR approach to examine the associations between modifiable risk factors, blood biomarkers, and female infertility, as illustrated in Figure 1A. Sixteen modifiable risk factors were categorized into five groups: (1) Basic conditions: Overall health rating (OHR) and years of education (EduYears); (2) Physical conditions: Body mass index (BMI), waist-to-hip ratio adjusted for BMI (BMI-adjusted WHR), and body fat percentage (BFP); (3) Lifestyle factors: Smoking status, alcohol

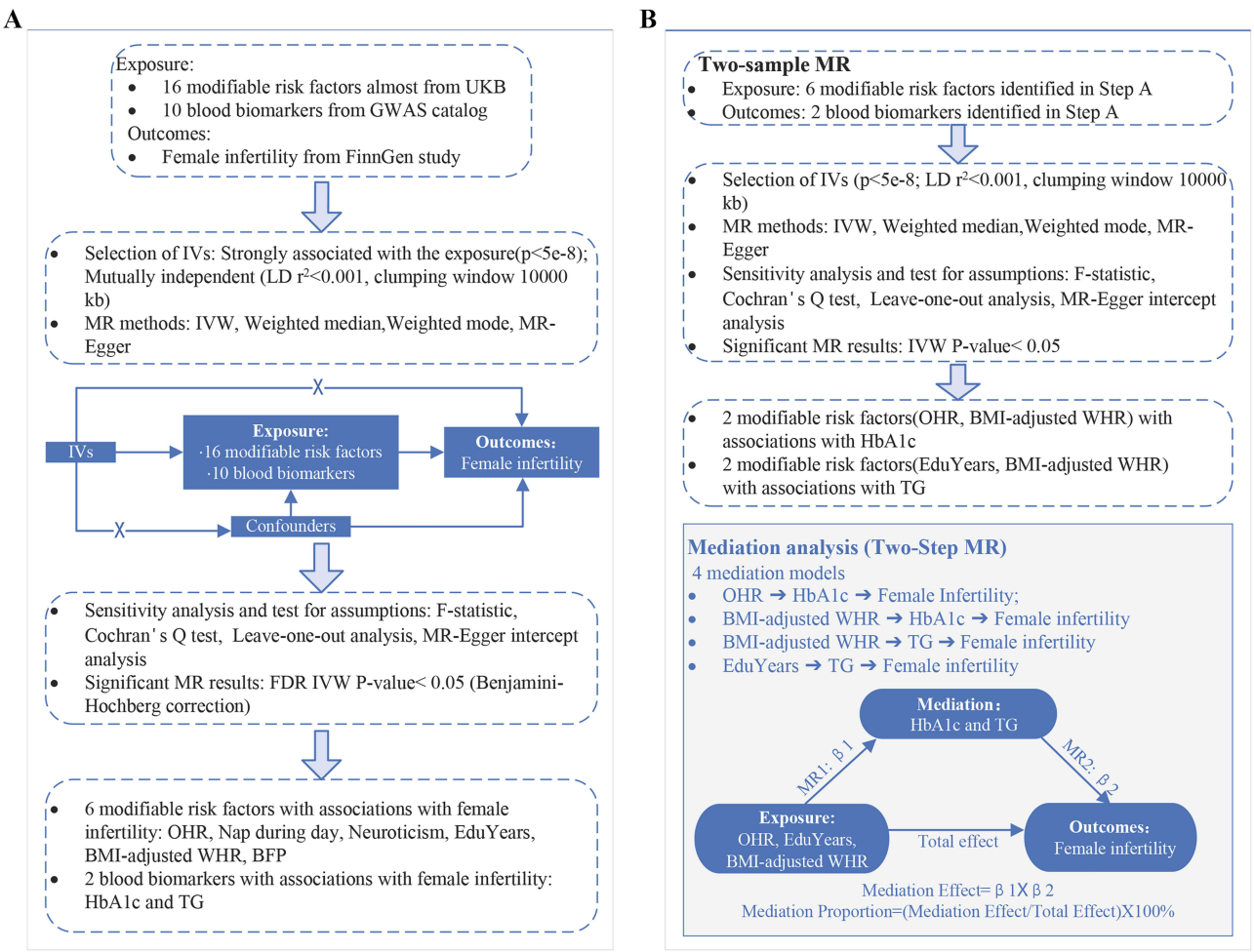

Figure 1 Study workflow of Mendelian Randomization. (**A**) Two-sample MR for the modifiable risk factors and blood biomarkers associated with female infertility; (**B**) The mediation analysis of blood biomarkers between modifiable risk factors and female infertility.

Abbreviations: MR, Mendelian Randomization; UKB, UK Biobank; GWAS, genome-wide association study; IVs, instrumental variables; LD, linkage disequilibrium; IVW, inverse variance-weighted; FDR, false discovery rate; OHR, overall health rating; EduYears, years of education; BMI, Body mass index; BMI-adjusted WHR, waist-to-hip ratio adjusted for BMI; BFP, body fat percentage; HbA1c, glycated hemoglobin; TG, Triglycerides.

consumption (drinks per week), and coffee and tea consumption; (4) Sleep conditions: Daytime napping, insomnia, and snoring; and (5) Emotional factors: Neuroticism, depression, and anxiety. The blood biomarkers examined included indicators of glucose homeostasis (fasting glucose, two-hour glucose, and glycated hemoglobin (HbA1c)), lipid homeostasis (total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides (TG)), and additional measures such as urate and serum uric acid levels. Comprehensive details of the genome-wide association study (GWAS) summary data sources are provided in Supplementary Table S1. To investigate potential mediation pathways, a two-step MR framework was implemented to assess whether blood biomarkers mediated the causal relationship between modifiable risk factors and female infertility, as illustrated in Figure 1B.

Statistical Analysis

Single nucleotide polymorphisms (SNPs) were employed as instrumental variables (IVs) to infer causal relationships. SNPs were selected using a stringent genome-wide significance threshold of $P < 5\times10^{-8}$. To ensure independence among selected variants, linkage disequilibrium (LD) pruning was conducted using a threshold of $r^2 < 0.001$ and a clumping window of 10,000 base pairs. The strength of each SNP as an instrumental variable was assessed using the F statistic, calculated by squaring the SNP-exposure association coefficient and dividing it by the square of its standard error. SNPs with F statistics > 10 were considered sufficiently strong to minimize weak instrument bias. The primary MR analysis

was conducted using the inverse variance-weighted (IVW) method under a multiplicative random-effects model. To evaluate the robustness of IVW estimates, three complementary MR methods were applied: weighted median, weighted mode, and MR-Egger regression. Multiple hypothesis testing was addressed using the false discovery rate (FDR) correction via the Benjamini-Hochberg procedure. Associations with an FDR-adjusted $P < 0.05$ were considered statistically significant. Associations with unadjusted $P < 0.05$ but FDR-adjusted $P > 0.05$ were interpreted as suggestive but inconclusive. For statistically significant results, we assessed horizontal pleiotropy using the MR-Egger intercept test, MR-PRESSO global test, and leave-one-out sensitivity analysis. Heterogeneity among SNP estimates was evaluated using Cochran's Q statistic and the I^2 index. Leave-one-out analyses were further conducted to determine whether individual SNPs disproportionately influenced the overall effect estimates. Statistical analyses were conducted with R software, version 4.4.2, and the following R packages, "TwoSampleMR", "MR-PRESSO", "Coloc", and "Mendelian Randomization", all of which are freely available on the official R website, where *P*-values below 0.05 denote statistical significance.

Results

Global Burden and Prevalence of Female Infertility

In 2021, the estimated global burden of female infertility affected approximately 110.09 million women (95% UI: 58.61–195.03 million), corresponding to an ASPR of 2764.62 per 100,000 population (95% UI: 1476.33–4862.57). Over the 32-year period from 1990 to 2021, the global ASPR demonstrated a consistent upward trajectory, with an overall increase of 21.94%, as reflected by the EAPC of 0.71 (95% CI: 0.60–0.82). At the regional level, East Asia recorded the highest ASPR in 2021 (4102.68; 95% UI: 2124.47–7170.94), whereas Australasia reported the lowest (152.74; 95% UI: 37.22–604.18). Between 1990 and 2021, the greatest increase in ASPR was observed in Andean Latin America (EAPC: 8.46; 95% CI: 7.43–9.50), while the most notable decline occurred in Oceania (EAPC: - 1.32; 95% CI: - 1.52 to - 1.12). At the national level in 2021, the Central African Republic exhibited the highest ASPR (5751.56; 95% UI: 3585.62–9238.57), while Australia reported the lowest (123.31; 95% UI: 34.12–515.39) (Figure 2A and Supplementary Table S2). Over the past three decades, the steepest increase in ASPR occurred in Ecuador (EAPC: 9.31; 95% CI: 7.90–10.74), whereas Malawi exhibited the sharpest decline (EAPC: - 5.71; 95% CI: - 6.09 to - 5.34) (Figure 2B and Supplementary Table S2).

Influence of Sociodemographic Transition on the Prevalence of Female Infertility

This study systematically explored the association between the ASPR of female infertility and the SDI across 204 countries and 21 GBD regions from 1990 to 2021. At the global level, a significant inverse correlation was observed between ASPR and SDI ($R = -0.28$, $P < 0.05$), suggesting that higher levels of socioeconomic development are associated with a reduced burden of female infertility (Figure 3A). In regions classified as high SDI (SDI > 0.8), the ASPR showed a marked decline with increasing SDI, indicating that improvements in education, income, and reproductive health access may mitigate infertility prevalence. Regionally, East Asia consistently exhibited the highest ASPR across the entire study period, whereas South Asia demonstrated trends that closely mirrored the global average. At the country level in 2021, a similar negative association between SDI and ASPR was evident ($R = -0.20$, $P < 0.05$), reinforcing the broader global pattern (Figure 3B). To further investigate the dynamics of fertility burden over time, we examined the relationship between EAPC in ASPR and SDI over the past three decades. Globally, no significant correlation was observed between EAPC and SDI ($R = 0.02$, $P = 0.81$), indicating overall stability in trend patterns regardless of development status (Figure 3C). However, a nonlinear pattern emerged across SDI categories. In low-SDI regions, the EAPC for ASPR was predominantly negative, suggesting a declining trend. As SDI levels increased, particularly in low-middle SDI regions, EAPC values began to shift toward positive, indicating a transition from declining to increasing infertility burden. The most pronounced increases in ASPR were observed in low-middle and middle SDI regions, highlighting the complex interplay between development transitions and reproductive health outcomes.

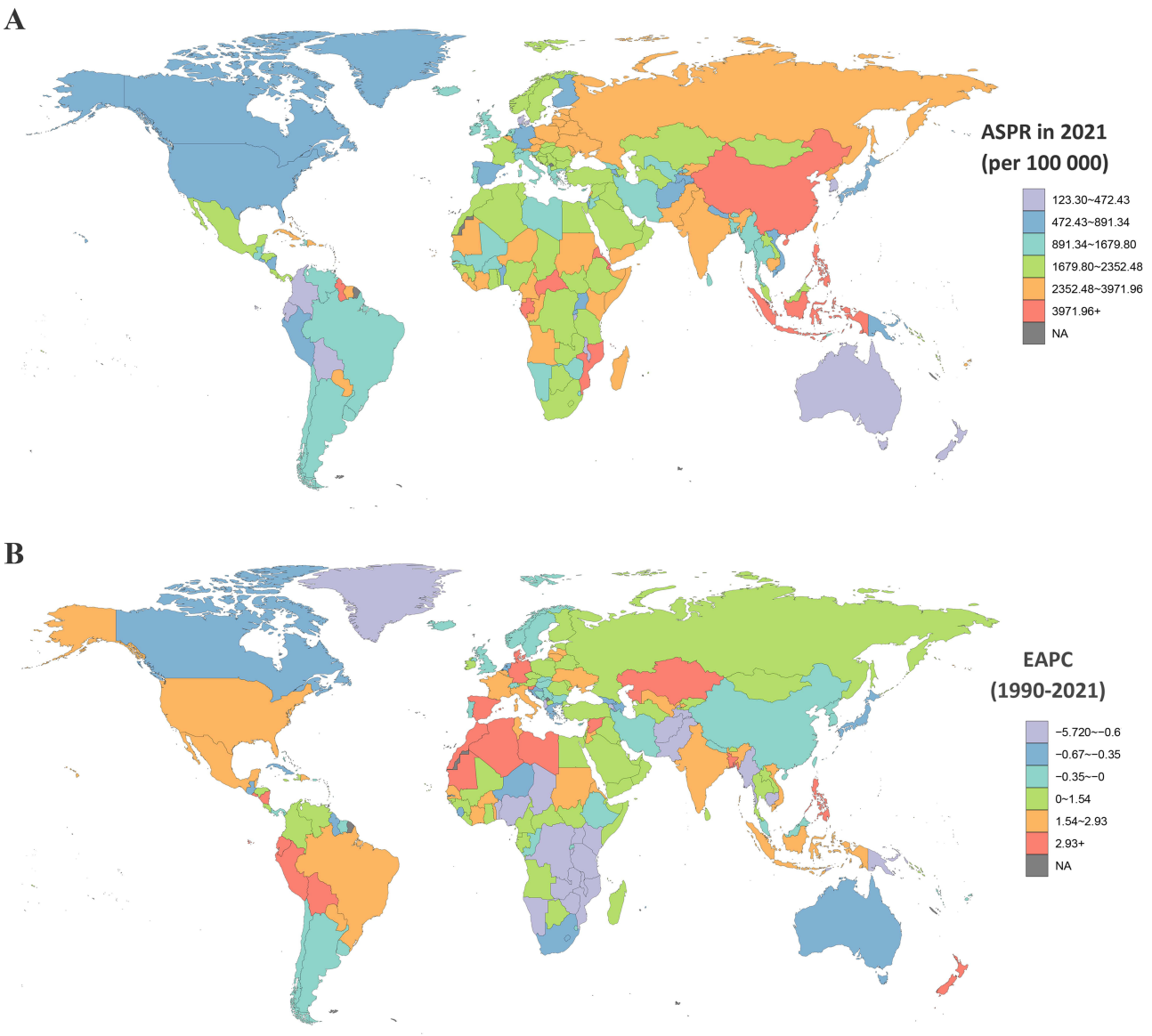

Figure 2 The global burden of female infertility across 204 countries and territories. (**A**) Age-standardised prevalence rates of female infertility in 2021; (**B**) EAPC of age-standardised prevalence rates of female infertility from 1990–2021.
Abbreviations: ASPR, age-standardised prevalence rate; EAPC, estimated annual percentage changes.

Age-Based Analysis of the Global Burden of Female Infertility

Based on data from the GBD 2021 study, the prevalence of female infertility was assessed across the reproductive age spectrum (15–49 years). Globally and across all SDI regions, the ASPR of infertility increased with age, peaking in the 35–39 year age group, and declining thereafter, with the lowest burden observed in women aged 45–49 years. Across age groups 15–39, high SDI regions consistently exhibited the lowest ASPR, reflecting better reproductive healthcare access and preventive interventions. In contrast, the high-middle SDI regions surpassed low-middle and low SDI regions in ASPR burden with advancing age, maintaining the highest overall burden among all SDI groups. As age increased, ASPR in low-middle and low SDI regions fell below that of middle and high-middle SDI regions, though they remained elevated compared to high SDI regions. For women aged ≥ 40 years, high-middle and middle SDI regions exhibited higher infertility burdens than low and low-middle SDI regions, while high SDI regions maintained the lowest ASPR across all age categories (Figure 4).

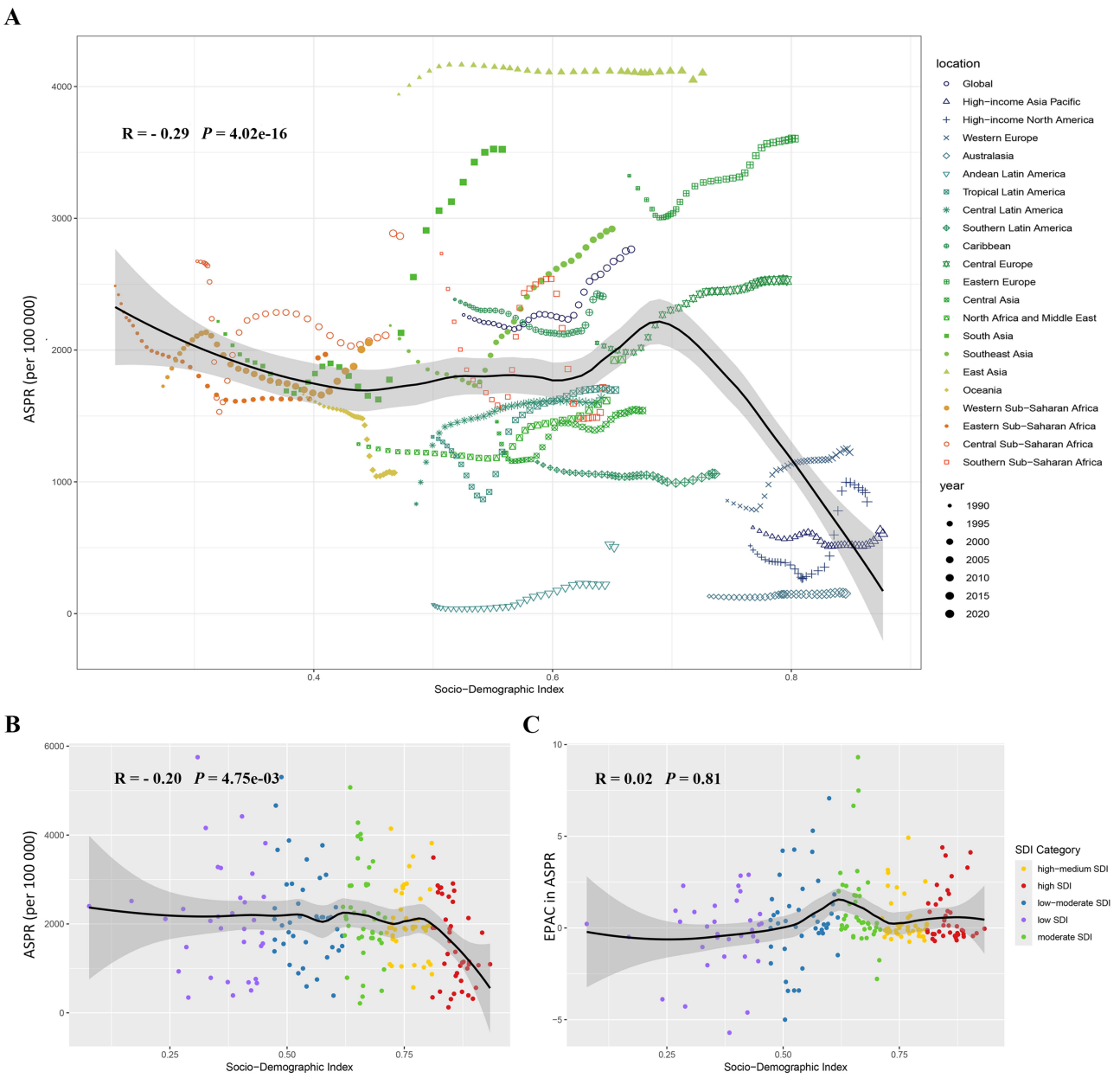

Figure 3 Impact of sociodemographic transition on the burden for ASPR of female infertility. (**A**) Association of SDI with ASPR of female infertility in global and 21 GBD regions and the same location markers represent changes in the same location from 1990–2021; (**B**) Association of SDI with ASPR of female infertility across 204 countries and territories in 2021; (**C**) Association of SDI with EAPC in ASPR of female infertility over three decades across 204 countries and territories.
Abbreviations: ASPR, age-standardised prevalence rate; EAPC, estimated annual percentage changes; SDI, Socio-demographic Index.

Temporal trends from 1990 to 2021, stratified by SDI level (Figure 5), revealed a significant increase in infertility ASPR in all SDI regions except the low SDI group ($P = 0.77$). High-middle SDI regions consistently bore the highest burden, while the high SDI group, despite having the lowest ASPR, experienced the steepest increase, with the AAPC of 1.41% (95% UI: 1.25–1.57, $P < 0.05$). In low and low-middle SDI regions, ASPR displayed a nonlinear trend, decreasing from 1990 to 2000, increasing slightly between 2000 and 2005, declining again until 2010, and rising significantly from 2010 onward. Similar inflection patterns were noted across all age groups between 20 and 44 years. Age-specific analyses indicated a decline in ASPR for the 15–19 age group across all SDI levels, with the steepest decline in low SDI regions (AAPC = −1.46). Conversely, the 20–24 age group exhibited increasing trends globally and within high, middle, and low-middle SDI regions. ASPR also rose in all SDI categories for the 25–29 and 30–34 age groups, with a similar pattern seen in the 35–39 group, except in low SDI regions. Among

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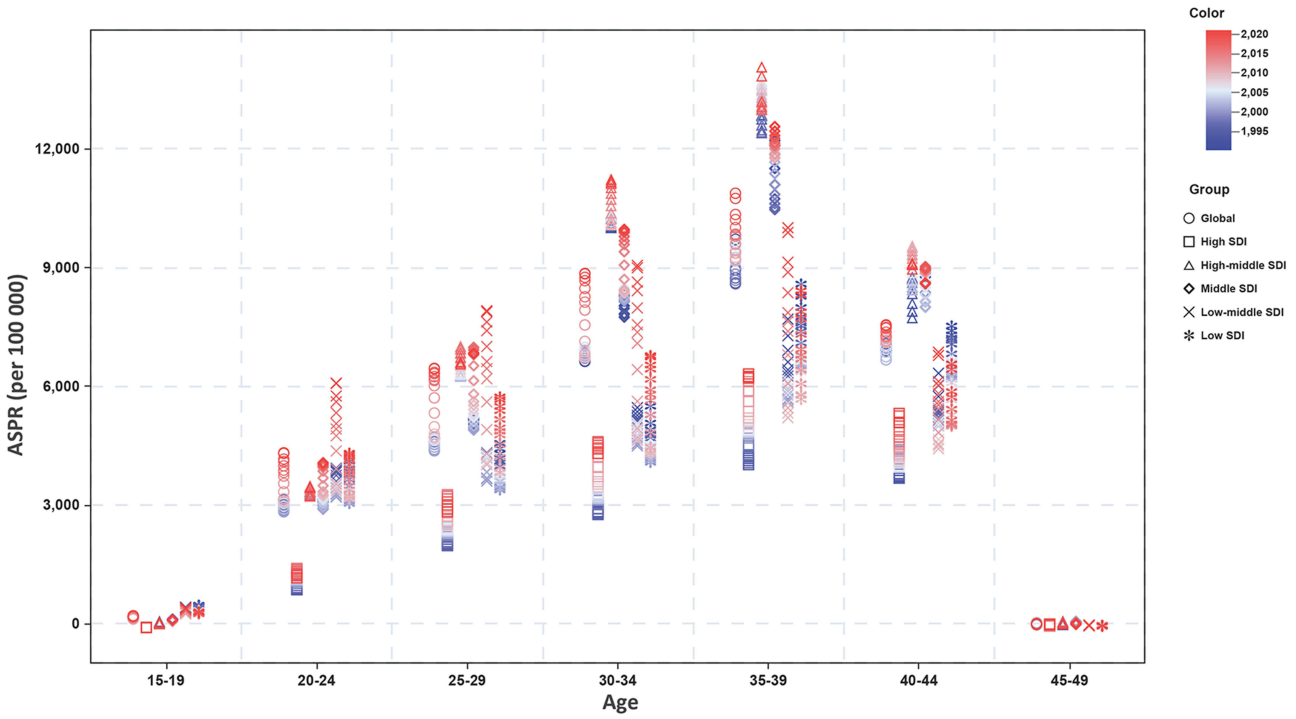

Figure 4 Age-specific ASPR of female infertility in global and all SDI regions from 1990–2021.
Abbreviations: ASPR, age-standardised prevalence rate; SDI, Socio-demographic Index.

women aged 40–44, ASPR trends increased globally and in high and high-middle SDI regions but declined in low SDI regions. For the 45–49 group, ASPR remained lowest across the board, with significant fluctuations and an overall decreasing trend, particularly in middle and low SDI regions.

Age-Period-Cohort Effects on the Prevalence Burden of Female Infertility

To further elucidate temporal dynamics in the prevalence of female infertility, we applied an Age-Period-Cohort analysis model (Figure 6). Globally, the burden of female infertility exhibited a statistically significant upward trend, as reflected by a net drift of 0.69 (95% CI: 0.44–0.93), indicating a consistent increase across time and age dimensions. Age effects demonstrated a clear nonlinear pattern: the prevalence of female infertility increased with age, peaking in the 35–39 age group, followed by a subsequent decline in older age cohorts. This trend was consistent across SDI regions, emphasizing the age-dependent nature of infertility risk. Period effects, using 2007 as the reference year, indicated an overall increasing trend in relative risk across global, high, high-middle, and middle SDI regions. Notably, high and high-middle SDI regions showed a brief decline in relative risk between 1992 and 1997, potentially reflecting improvements in reproductive health services during that period. In contrast, low-middle and low SDI regions initially demonstrated a declining trend in period effects prior to 2012, followed by a reversal with increasing prevalence, ultimately exceeding the reference period. Cohort effects, referenced to the 1975 birth cohort, revealed an initial increase in relative risk with more recent birth years, followed by a subsequent decline. Globally, the peak cohort effect occurred in individuals born around 2000. A similar peak was observed in middle and low-middle SDI regions, whereas high and high-middle SDI regions exhibited an earlier inflection point, with the highest relative risk observed among the 1990 birth cohort. In low SDI regions, cohort trends remained relatively stable across successive birth cohorts; however, a notable decline was observed in the 2005 birth cohort, which may partially reflect underestimation bias due to limited follow-up duration in the youngest age groups.

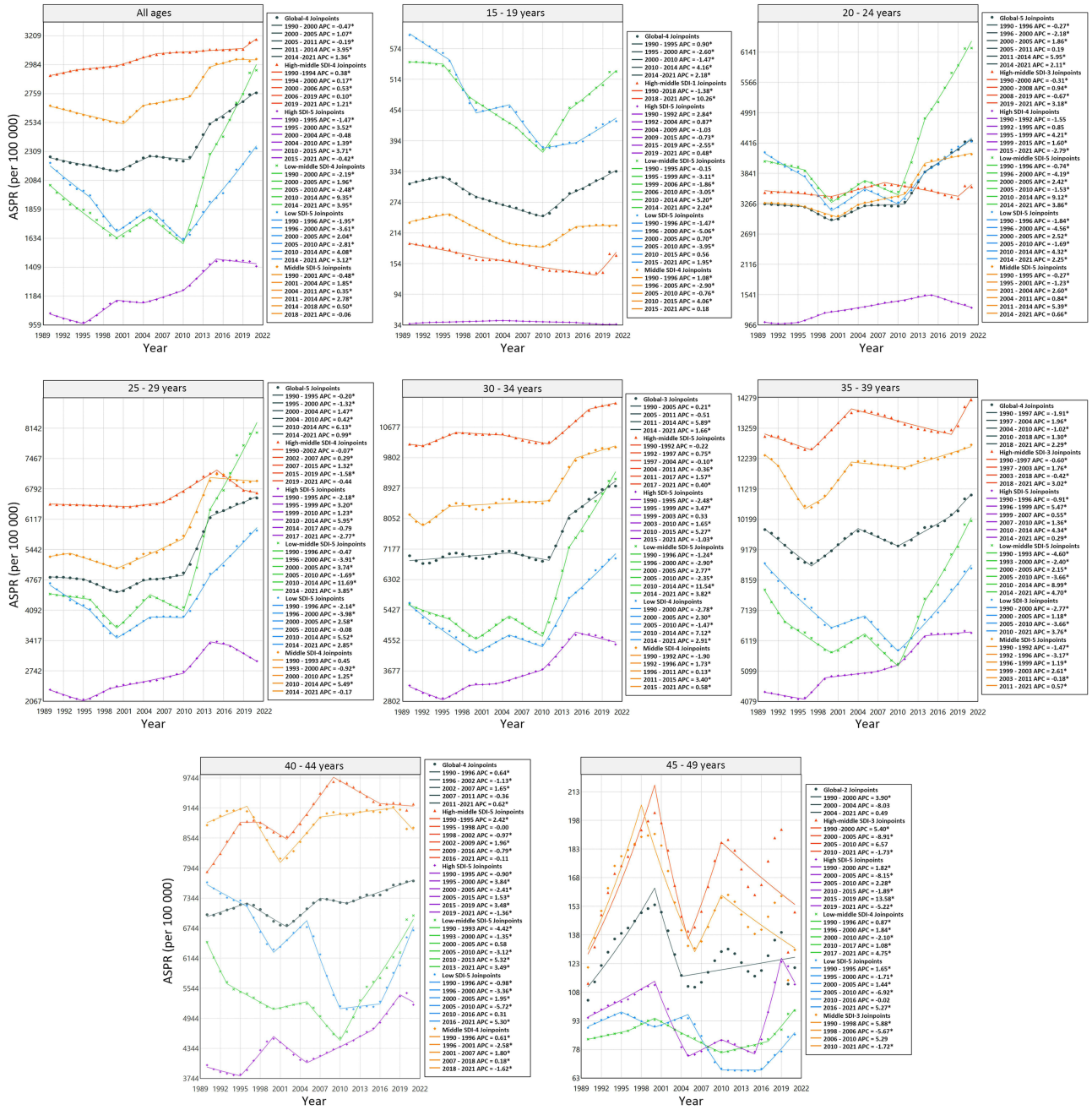

Figure 5 The ASPR trends of female infertility among global and different SDI regions from 1990 to 2021 in different age strata. * Indicates that the APC is significantly different from zero at the 0.05 alpha level.
Abbreviations: APC, the Annual Percent Change; ASPR, age-standardised prevalence rate; SDI, Socio-demographic Index.

Two-Sample MR Analysis of Modifiable Risk Factors and Blood Biomarkers Associated with Female Infertility

To investigate the potential causal relationships between modifiable risk factors, blood biomarkers, and female infertility, we conducted a two-sample MR analysis. All IVs selected for the exposures demonstrated sufficient strength, with F-statistics exceeding 10, indicating a low risk of weak instrument bias (Supplementary Tables S3 and S4). Sixteen modifiable risk factors were analyzed using multiple MR methods, including IVW, weighted median, weighted mode, and MR-Egger approaches. Horizontal pleiotropy and heterogeneity were assessed through the MR-Egger intercept test

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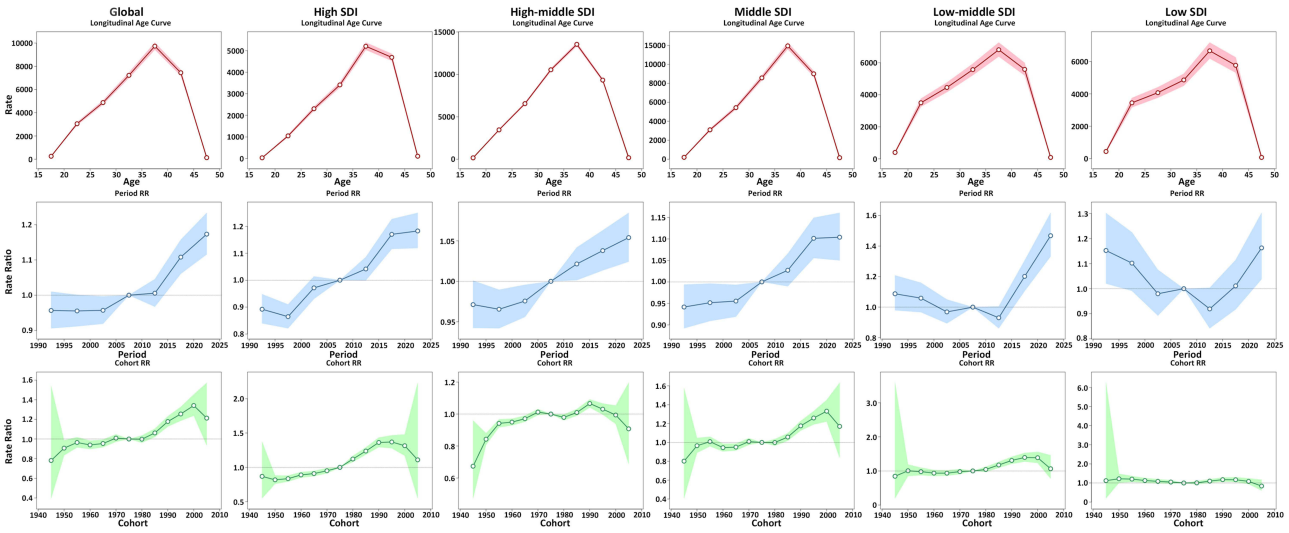

Figure 6 Age-period-cohort effect of burden for ASPR of female infertility. Red reflects the age factor, blue is the period factor, and green is the birth cohort factor.
Abbreviations: ASPR, age-standardised prevalence rate; SDI, Socio-demographic Index; RR, Rate Ratio.

and Cochran's Q statistic, respectively. The causal estimates and FDR-adjusted p-values are presented in Supplementary Table S5 and Figure 7.

At least two MR methods, including the IVW method, identified OHR, educational attainment, BMI-adjusted WHR, BFP, daytime napping, and neuroticism as significantly associated with female infertility. Specifically, poor overall health status was causally associated with an increased risk of female infertility (OR, 1.94; 95% CI, 1.49–2.52; P_{FDR} = 1.24×10^{-5}). Similarly, a higher WHR (OR, 1.12; 95% CI, 1.04–1.20; P_{FDR} = 3.26×10^{-3}) and increased neuroticism (OR, 1.10; 95% CI, 1.04–1.15; P_{FDR} = 1.25×10^{-3}) were associated with elevated infertility risk. In contrast, longer educational attainment (OR, 0.95; 95% CI, 0.93–0.97; P_{FDR} = 3.26×10^{-4}), greater body fat percentage (OR, 0.67; 95%

Exposure	Outcome	nSNP	OR (95%CI)	*P*-Value	FDR *P*-Value
Basic condition factor					
Overall health rating	**Female infertility**	105	1.94 (1.49 to 2.52)	**7.76e−07**	**1.24e-05**
Educational attainment (years of education)	**Female infertility**	207	0.95 (0.93 to 0.97)	**4.07e−05**	**3.26e-04**
Household income	Female infertility	35	1.16 (0.86 to 1.56)	0.32	0.43
Physical condition factor					
Body mass index	Female infertility	308	0.98 (0.90 to 1.06)	0.65	0.65
Waist Hip ratio adjusted for BMI	**Female infertility**	267	1.12 (1.04 to 1.20)	**1.63e-03**	**5.21e-03**
Body fat percentage	**Female infertility**	10	0.67 (0.52 to 0.85)	**1.03e-03**	**4.10e-03**
Lifestyle factor					
Smoking status	Female infertility	113	1.09 (0.82 to 1.44)	0.56	0.60
Alcoholic drinks per week	Female infertility	36	0.80 (0.57 to 1.11)	0.18	0.27
Coffee consumption	Female infertility	28	0.55 (0.35 to 0.84)	5.76e-03	0.02
Tea consumption	Female infertility	21	0.78 (0.46 to 1.32)	0.35	0.43
Sleep condition factor					
Nap during day	**Female infertility**	48	0.63 (0.45 to 0.89)	**8.49e-03**	**0.02**
Insomnia	Female infertility	28	0.70 (0.45 to 1.07)	0.10	0.21
Snoring	Female infertility	22	1.26 (0.67 to 2.39)	0.47	0.54
Major emotion factor					
Neuroticism	**Female infertility**	109	1.10 (1.04 to 1.15)	**2.35e-04**	**1.25e-03**
Depression	Female infertility	3	1.19 (0.94 to 1.51)	0.15	0.24
Anxiety	Female infertility	28	1.23 (0.94 to 1.61)	0.12	0.22

FDR *P*-Value < 0.05 was considered statistically significant

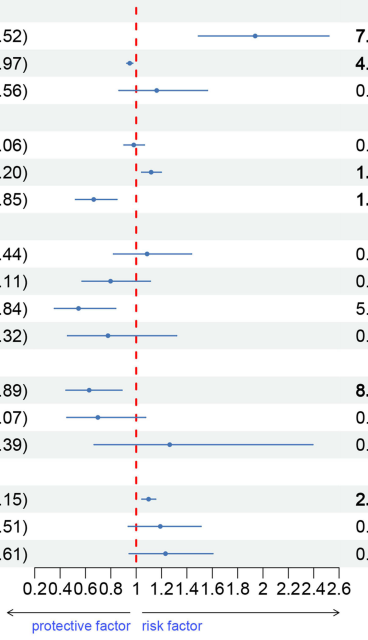

Figure 7 Forest plot showing the causal effects of modifiable lifestyle factors on female infertility. Statistically significant results are presented in bold typeface.
Abbreviations: SNP, single nucleotide polymorphisms; BMI, Body mass index; OR, Odds Ratio; CI, confidence intervals; FDR, false discovery rate.

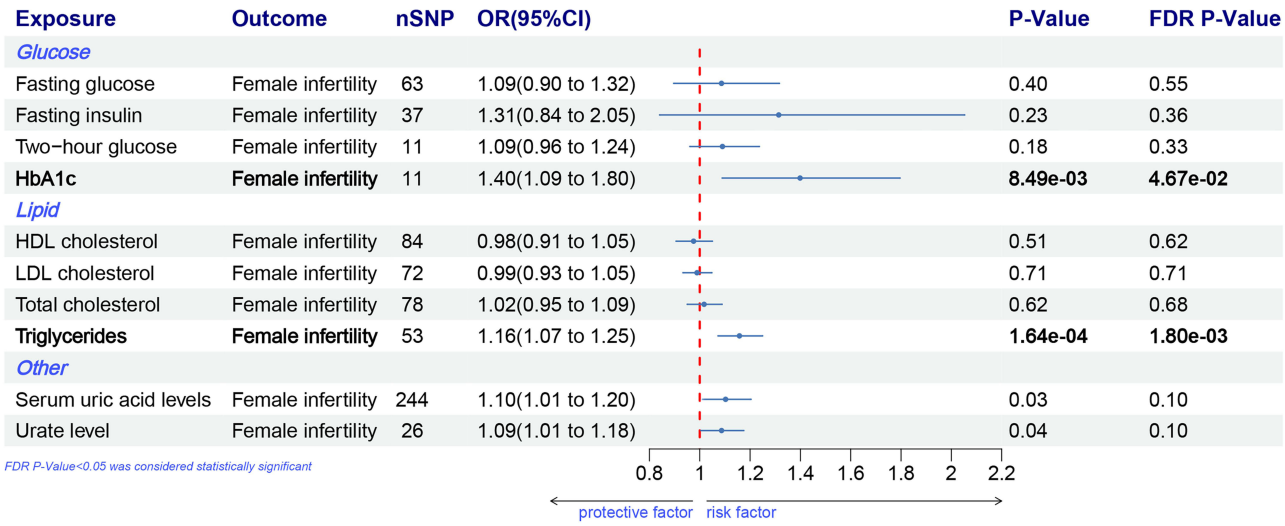

Figure 8 Forest plot showing the causal effects of blood biomarkers on female infertility. Statistically significant results are presented in bold typeface.
Abbreviations: SNP, single nucleotide polymorphisms; OR, Odds Ratio; CI, confidence intervals; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FDR, false discovery rate.

CI, 0.52–0.85; $P_{FDR} = 4.10\times10^{-3}$), and more frequent daytime napping (OR, 0.63; 95% CI, 0.45–0.89; $P_{FDR} = 1.94\times10^{-2}$) were associated with a reduced risk of infertility. No significant evidence of reverse causality was found for any of these six exposures (Supplementary Table S6).

Additionally, we evaluated the causal role of ten blood biomarkers in female infertility using two-sample MR analysis. Among these, two biomarkers, namely, HbA1c and TG, showed significant associations with infertility risk. Genetically predicted higher HbA1c levels were associated with increased risk (OR, 1.40; 95% CI, 1.09–1.80; $P_{FDR} = 4.67\times10^{-2}$), as were elevated TG levels (OR, 1.16; 95% CI, 1.07–1.25; $P_{FDR} = 1.80\times10^{-3}$). The MR-Egger intercept test indicated no evidence of directional pleiotropy, and Cochran's Q statistics showed minimal heterogeneity ($I^2 < 50\%$) (Supplementary Table S7 and Figure 8). Furthermore, leave-one-out sensitivity analyses confirmed the robustness of the IVW findings, with no single SNP disproportionately influencing the results (Supplementary Table S8). Reverse MR analyses revealed no evidence of bidirectional causality for both HbA1c and TG (Supplementary Table S9).

The Mediation Analysis of Blood Biomarkers Between Modifiable Risk Factors and Female Infertility

To explore the potential mediating role of blood biomarkers in the causal pathways linking modifiable risk factors to female infertility, we employed a two-step MR framework. Specifically, we investigated whether two blood biomarkers (HbA1c and TG) significantly associated with female infertility, could mediate the effects of six modifiable risk factors. Bidirectional two-sample MR was used to assess the associations between the risk factors and biomarkers. The IVW method was the primary analytical approach, and associations were deemed significant if the IVW *P*-value was < 0.05 and consistent across at least three additional MR methods. OHR (β = 0.12; 95% CI: 0.02–0.23; $P = 2.36\times10^{-2}$) and BMI-adjusted WHR (β = 0.046; 95% CI: 0.021–0.072; $P = 3.18\times10^{-4}$) were positively associated with HbA1c levels. Similarly, educational attainment (β = - 0.02; 95% CI: - 0.04 to - 0.01; $P = 8.69\times10^{-3}$) was inversely associated with TG levels, whereas BMI-adjusted WHR showed a strong positive association with TG (β = 0.34; 95% CI: 0.28–0.40; $P = 5.89\times10^{-32}$) (Figure S1 in Supplementary Material).

Assessment for horizontal pleiotropy using the MR-Egger intercept revealed no significant evidence of directional pleiotropy. However, Cochran's Q test indicated substantial heterogeneity in the association between BMI-adjusted WHR and TG ($I^2 = 82.35\%$). After applying MR-PRESSO to correct for potential outlier SNPs, the heterogeneity remained statistically significant (Q-test $P < 0.05$), yet all MR approaches, including the IVW random-effects model, MR-Egger, and Weighted Median, continued to show robust associations ($P < 0.05$). The final IVW estimate (β = 0.30; 95% CI:

0.27–0.33; $P_{adj} = 7.75\times10^{-76}$) and a reduced I^2 value of 37.5% further supported a stable causal effect (Supplementary Table S10). Leave-one-out analysis confirmed the robustness of these findings, and reverse causality was ruled out (Supplementary Tables S8 and S11).

Based on these results, we identified four potential mediation pathways: (1) OHR → HbA1c → Female infertility; (2) BMI-adjusted WHR → HbA1c → Female infertility; (3) BMI-adjusted WHR → TG → Female infertility; and (4) Educational attainment → TG → Female infertility. Two-step MR was subsequently used to quantify the mediated effect in each pathway. The proportion of the effect mediated by TG in the BMI-adjusted WHR-female infertility pathway was 39.22% ($P_{\text{mediator effect}} = 2.22\times10^{-4}$), while HbA1c mediated 13.93% of the same pathway ($P_{\text{mediator effect}} = 0.04$). TG also mediated 5.95% of the effect of educational attainment on female infertility ($P_{\text{mediator effect}} = 0.03$). In contrast, the mediation effect of HbA1c in the OHR-infertility pathway did not reach statistical significance, providing insufficient evidence to support this model (Supplementary Table S12 and Figure S2 in Supplementary Material).

Discussion

From a socioeconomic and regional perspective, while an overall negative correlation between SDI and ASPR was observed, notable heterogeneity exists across regions at different developmental stages. National-level analyses indicate that countries with the highest burden of female infertility are predominantly located in Asia and Africa, where sociocultural barriers, such as stigma associated with infertility, combined with economic limitations and inequitable healthcare distribution, significantly impede access to diagnosis and treatment.[18] Although assisted reproductive technologies are becoming more available in these regions, their high costs and limited accessibility remain major obstacles for many affected individuals.[19] Over the past three decades, the most substantial increases in infertility burden have been documented in low-middle and middle SDI regions. This trend may be attributable to delayed improvements in reproductive health infrastructure during economic transitions, as well as increasing environmental pollution.[20,21] Among environmental contributors, exposure to endocrine disruptors disrupts female reproductive health through estrogen signaling, oxidative stress, and immune regulation, increasing the risk of infertility.[22]

The age-specific burden of female infertility, measured by ASPR, exhibits significant variation across SDI levels. High SDI regions consistently report the lowest ASPR among women aged 15–39, likely due to greater access to reproductive healthcare, lower prevalence of untreated infections, and generally healthier lifestyle factors. However, these regions also exhibit the highest annual increase in ASPR, suggesting that economic development may paradoxically elevate infertility risks via mechanisms such as delayed childbearing, increased occupational stress, and greater exposure to endocrine-disrupting substances. In contrast, High-middle and Middle SDI regions bear the greatest infertility burden, which may reflect transitional dynamics wherein improving healthcare access coexists with the rising prevalence of risk factors, including environmental pollutants, urbanization-related stress, and evolving fertility behaviors (eg, postponement of marriage and childbirth). Low and Low-middle SDI regions demonstrate a declining ASPR trend among younger age groups, yet continue to exhibit the highest relative prevalence overall. Interestingly, among older age groups, the burden in these regions becomes comparatively lower than in higher SDI contexts, potentially reflecting earlier childbearing practices and shorter exposure windows to infertility-related risks. These findings emphasize the critical need for targeted reproductive health education, particularly in lower SDI settings, to promote fertility preservation and address preventable causes of infertility.

The global burden of female infertility is shaped by intricate interactions between biological aging, sociodemographic development, and generational exposure to risk factors. Due to social and occupational pressures, women are increasingly delaying childbearing until after the age of 30. However, as women age, their fertility declines slowly and steadily between the ages of 30 and 35. After the age of 35, fertility declines rapidly due to a decrease in ovarian reserve and oocyte quality.[23] Delayed childbearing and changes in modern lifestyles have affected women's physiological functions, increasing the risk of infertility.[7] The ASPR of female infertility exhibit a consistent pattern across all SDI regions, peaking in the 35–39 age group before declining in the later reproductive years. This uniform trend highlights the predominant influence of biological aging, particularly the decline in ovarian reserve and fertility potential, as a central determinant of infertility risk. Period effects analysis reveals a sustained upward trajectory in infertility prevalence, particularly in High, High-middle, and Middle SDI regions. This trend supports the hypothesis that modernization,

urbanization, and increasingly delayed childbearing contribute significantly to rising infertility burdens in these populations. In contrast, Low-middle and Low SDI regions initially demonstrated fluctuating or modestly declining prevalence trends, possibly reflecting improvements in sanitation, maternal health practices, and healthcare infrastructure. However, these gains were followed by a marked increase in prevalence after 2010, potentially driven by improved diagnostic capabilities, rising awareness, and the emergence of new risk factors such as environmental pollutants, nutritional deficiencies, and deteriorating maternal health conditions. Cohort effects further illuminate generational shifts in infertility risk profiles. With the exception of Low SDI regions, which display a steady upward trend across successive cohorts, the majority of regions exhibit increased infertility risk among more recent birth cohorts. This likely reflects cumulative exposure to modifiable lifestyle-related risk factors, including obesity, sedentary behavior, and poor dietary patterns. Notably, High and High-middle SDI regions show an earlier peak in infertility risk with the 1990 birth cohort, suggesting these populations may have been the earliest to encounter the reproductive consequences of lifestyle transitions and delayed parenthood. The relative cohort stability observed in Low SDI regions suggests that the infertility burden remains persistently high, driven less by modern demographic transitions and more by entrenched challenges such as untreated reproductive tract infections, malnutrition, and inadequate access to reproductive healthcare services.

To further investigate individual-level risk factors associated with female infertility, this study examined a range of modifiable exposures across five domains: baseline health status, physical condition, lifestyle behaviors, sleep patterns, and emotional well-being. The MR method indicated a positive association between poor self-rated health and infertility risk, suggesting that overall health status may play a critical role in reproductive outcomes. This aligns with findings from Abigail et al[24] who reported that infertility is associated with reduced perceived physical health in a cohort of 996 US women veterans. Similarly, Sheree et al[25] reported a higher frequency of poor physical health days among infertile women with chronic illness. MR analyses also provided evidence that higher educational attainment may confer a protective effect against female infertility. This finding is consistent with broader studies linking educational level with components of the SDI, although a definitive causal relationship remains unestablished. Notably, while infertility affects women across all education levels, those with higher education are more likely to seek medical care,[26,27] and demonstrate greater fertility awareness, as shown in a UK-based cross-sectional study.[28] Further mediation analysis identified TG levels as a partial mediator in the genetic pathway linking educational attainment to infertility risk. Women with higher education exhibited more favorable lipid profiles, characterized by lower total cholesterol, LDL-C, and TG, compared to their lower-educated counterparts, who showed elevated total cholesterol and HDL-C levels.[29] Elevated triglyceride levels have been strongly implicated in reproductive disorders such as polycystic ovary syndrome (PCOS)[30] and endometriosis.[31] Although TGs serve as an essential energy source for folliculogenesis and oocyte maturation, excessive TG concentrations can impair oocyte development.[30] Experimental studies on murine cumulus-oocyte complexes exposed to TG- and free fatty acid-rich follicular fluid revealed increased intracellular lipid accumulation, induction of endoplasmic reticulum stress markers, and impaired nuclear maturation.[32] Additionally, a randomized controlled trial by Pugh et al[33] found that women with dyslipidemia, characterized by high TG, total cholesterol, and LDL-C, and low HDL-C, experienced a 19–32% reduction in fecundability. These findings highlight the importance of addressing metabolic health, particularly lipid regulation, in infertility prevention and treatment strategies, especially among women with lower educational attainment who may be at greater risk due to both biological and healthcare access disparities.

Body fat percentage is a widely utilized metric for assessing obesity and overall adiposity, and its role in female reproductive health has been increasingly recognized. MR analyses from this study suggest that lower body fat percentage may be a risk factor for female infertility. Underweight women are susceptible to hypothalamic anovulation, resulting from chronic energy deficiency that disrupts the hypothalamic-pituitary-gonadal (HPG) axis. This energy deficit leads to reduced gonadotropin-releasing hormone (GnRH) pulsatility, impairing ovulation. Additionally, reduced adipose tissue limits estrogen production and can induce broader hormonal imbalances that compromise reproductive function.[34] Experimental studies support these observations. Alexander et al[35] demonstrated in a murine model that both nutritional deficiency and overnutrition adversely affect body fat composition, leading to impaired embryo quality and reduced developmental competence, thereby highlighting the critical role of optimal adiposity for fertility. WHR, a standard measure of abdominal obesity and an indirect marker of visceral fat, has also been strongly linked to female infertility.

A large cross-sectional study involving women aged 20–45 found that, after adjustment for key confounders, each 0.1-unit increase in WHR was associated with a 35% higher risk of infertility.[36] These findings are congruent with the present study's results. Although the precise biological mechanisms remain incompletely defined, visceral adiposity is believed to disrupt neuroendocrine signaling, negatively impacting ovarian steroidogenesis, ovulation rates, and endometrial receptivity.[37] Further mediation MR analyses from this study identified HbA1c and TG as significant mediators in the causal pathway between WHR and female infertility. A case-control study corroborated a positive association between WHR and HbA1c[38] and cross-sectional data showed that women with HbA1c $\geq$ 6.5% had significantly higher odds of infertility, even after controlling for age, BMI, and comorbidities.[39] The biological plausibility linking HbA1c levels to female infertility arises from the deleterious effects of chronic hyperglycemia on multiple physiological pathways. Severe hyperglycemia impairs luteinizing hormone/chorionic gonadotropin receptor (LHCGR)-mediated signaling, thereby disrupting key reproductive processes such as ovulation, oocyte maturation, luteinization, and preimplantation embryonic development.[40] Furthermore, persistent hyperglycemia induces oxidative stress and systemic inflammation, which collectively compromise ovarian function, diminish endometrial receptivity, and impair embryonic growth.[41] Moreover, a randomized controlled trial spanning seven European countries reported that WHR was associated with elevated postprandial triglycerides and remnant lipoprotein cholesterol following high-fat meals.[42] These metabolic disturbances, specifically impaired glucose regulation and dyslipidemia, may negatively influence oocyte quality, implantation, and early embryonic development. Taken together, these findings suggest that both insufficient and excessive adiposity, particularly central obesity, may impair female fertility via disruptions in glucose and lipid metabolism, neuroendocrine signaling, and ovarian function.

Sleep is a fundamental physiological process essential for maintaining metabolic, hormonal, and neuroendocrine homeostasis. Infertility may contribute to psychological distress and sleep disruption, while poor sleep may exacerbate hormonal dysregulation that impairs fertility.[43,44] In this study, MR analyses identified a causal association between daily napping and female infertility. Notably, a prospective cohort study reported that short naps had a modest beneficial effect, in contrast to habitual naps over one hour, which were associated with a 73.8% decline in oocyte maturation rates.[45] In addition to sleep-related behaviors, psychological and personality factors appear to play a significant role in female infertility risk. Our analyses revealed a positive association between neuroticism and infertility, consistent with a systematic review identifying neuroticism, harm avoidance, and psychoticism as potential psychological risk factors, while optimism was shown to have a protective effect.[46] Furthermore, linkage disequilibrium score regression demonstrated shared genetic architecture between female infertility and mental health traits such as depression, worry, and neuroticism, indicating a potential biological basis for the observed comorbidity.[47]

Limitations and Strengths

This study possesses several drawbacks that merit careful consideration. First, although the GBD database is continuously refined and expanded, comprehensive data acquisition from all countries and regions remains incomplete. Despite standardized international methodologies, variability in data quality persists due to differences in data collection practices, sources, coding systems, healthcare access, cultural norms, socioeconomic contexts, and definitions of reproductive age. These discrepancies may impact the accuracy and comparability of burden estimates across regions. Second, the GWAS data used to investigate spontaneous female infertility were derived exclusively from female participants; however, the associated SNPs were not gender-specific. This raises the possibility of undetected sex-based genetic biases. Moreover, the MR analyses were confined to European ancestry, limiting the applicability of results to other racial and ethnic groups. Future research should prioritize the inclusion of more diverse populations to enhance the external validity of genetic inferences related to infertility risk. Third, while MR is a powerful tool for causal inference, its reliance on summary-level data, as opposed to individual-level data, may introduce selection bias and limit the precision of effect estimates. Addressing these methodological constraints in future studies will be essential for improving the robustness and universality of conclusions in this domain.

Despite these limitations, the study provides compelling evidence that the ASPR of female infertility has increased globally over the past three decades, with significant heterogeneity across age groups, geographical regions, and SDI levels. Age-Period-Cohort modeling further highlights that these disparities may be attributed to age-related biological

fertility decline, temporal shifts in healthcare and societal structures, and generational changes in exposure to modifiable risk factors. Analysis of individual-level risk factors suggests that poor overall health, low body fat percentage, and elevated WHR are associated with increased infertility risk. In contrast, higher educational attainment and moderate daytime napping appear to confer protective effects. Additionally, elevated metabolic biomarkers, such as HbA1c and TG, were identified as independent risk factors and mediators in the causal pathway between WHR and infertility. Moreover, TG mediated the effect of educational attainment on female infertility. Targeted interventions focused on improving healthcare infrastructure, promoting reproductive health literacy, and addressing modifiable lifestyle and metabolic risk factors are critical to mitigating the global burden of female infertility.

Conclusions

The global burden of female infertility exhibited significant spatiotemporal variation, with notable differences across age groups, SDI levels, and geographic regions from 1990 to 2021. Age-Period-Cohort modeling indicates that changes in reproductive age patterns, environmental exposures, and cohort-specific risk profiles are major contributors to these disparities. In resource-limited settings, efforts should prioritize enhancing reproductive health education, especially among women with lower formal education levels. Health promotion strategies ought to incorporate lifestyle counseling targeting modifiable risk factors, including weight management, sleep hygiene, and metabolic health. For high-risk populations, such as those with abdominal obesity or metabolic syndrome, routine reproductive health screenings could be expanded to include metabolic biomarkers such as HbA1c and lipid profiles. Finally, integrating mental health support into fertility care is essential. A comprehensive, integrative approach that addresses metabolic, behavioral, and psychosocial risk factors may offer a more effective framework for reducing the global burden of female infertility.

Data Sharing Statement

The data used in this study were obtained from publicly accessible databases that are subject to established ethical approvals. All original studies contributing to these datasets received informed consent from participants and adhered to the ethical principles outlined in the Declaration of Helsinki. As this research exclusively utilized de-identified, aggregated data, additional institutional ethics approval was not required. The GBD 2021 data were obtained from the Institute for Health Metrics and Evaluation (IHME) and are available under standard terms of use at: https://ghdx.healthdata.org/gbd-2021. GWAS summary statistics for spontaneous female infertility were sourced from the FinnGen consortium and are publicly accessible at: https://www.finngen.fi. The GWAS summary statistics for modifiable risk factors and blood biomarkers analyzed in this study are detailed in the Supplementary Tables.

Ethics Approval

This research is based on a public database, so the Ethics Committee of Changde Hospital waived the requirement for approval.

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Disclosure

The authors report no conflicts of interest in this work.

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