

Global Burden of Polycystic Ovary Syndrome: A Systematic Analysis of Pre- and Post-Pandemic Trends from the 2021 Global Burden of Disease Study (1990–2021)

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Objective: The study systematically examines the long-term trends in the global burden of Polycystic ovary syndrome (PCOS) across 204 countries and territories, with a specific focus on comparing pre-pandemic (1990–2019) and post-pandemic (2019–2021) periods.

Methods: Using data from the Global Burden of Disease (GBD) 2021 for women aged 15–54, we estimated incidence, prevalence, and years lived with disability (YLDs). Age-standardized rates (ASIR, ASPR, ASYR) and estimated annual percentage change (EAPC) were calculated. Joinpoint, Age-Period-Cohort, and Bayesian models were used to analyze trends from 1990–2021 and project burden to 2050. Mendelian randomization (MR) assessed whether anxiety and guilt contribute to PCOS risk.

Results: All burden measures increased globally from 1990 to 2021. Post-2019, the rate of increase (EAPC) accelerated significantly compared to the pre-pandemic period. High-SDI regions showed the lowest pre-pandemic growth but the largest increases during the pandemic. Health inequalities modestly improved by 2021. Projections indicate continued growth, with ASIR, ASPR, and ASYR reaching 73.66, 2104.41, and 18.37 per 100,000 by 2050, respectively. MR supports anxiety and guilt as likely risk factors.

Conclusion: The post-pandemic rise in PCOS burden underscores systemic vulnerabilities in women's endocrine healthcare during health emergencies and signals a growing global health challenge.

Plain Language Summary:

What your research question was: The core objective of this study was to systematically assess the global disease burden, its distribution, and risk factors for Polycystic Ovary Syndrome (PCOS) from 1990 to 2021, particularly in the context of the COVID-19 pandemic.

What you found: The study found a significant and continuous increase in the global burden of PCOS, with an accelerated rise post-pandemic, notable geographic and age disparities in its distribution, and revealed for the first time through genetic methods that psychological factors like anxiety are causal risk factors for PCOS.

Why it is important: This research is critically important as it provides comprehensive epidemiological evidence for the global prevention and management of PCOS, highlights its escalating burden, and offers a crucial foundation for developing targeted public health interventions for high-risk regions and populations.

Keywords: polycystic ovary syndrome, COVID-19 pandemic, global burden of disease 2021, joinpoint regression model, Bayesian age-period-cohort model, two-sample mendelian randomization



Introduction

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder affecting 10% to 13% of women of reproductive age and represents one of the leading causes of female infertility. The infection has presented new challenges to women's health, particularly drawing attention to its effects on patients with PCOS.¹ PCOS patients often have obesity, insulin resistance, cardiometabolic disease, hyperandrogenism, and immune dysfunction.² These symptoms will increase the anxiety, worry, depression and other psychological problems of PCOS patients.³ These clinical characteristics overlap with the risk factors for severe COVID-19, making PCOS patients more vulnerable to severe COVID-19. COVID-19 not only increases the infection risk for PCOS patients but may also worsen their mental health issues and metabolic disorders.⁴ Depression and anxiety are associated with an increased risk of infertility and endometriosis. This suggests that psychological factors may disrupt endocrine function and contribute to the pathogenesis of these disorders. MR analysis identified evidence of a causal effect of polycystic ovary syndrome (PCOS) on the risk of anxiety.⁵ However, there's a lack of research on COVID-19's impact on the global burden of PCOS and psychological risk factors for PCOS. Thus, it's imperative to investigate the comprehensive effects of COVID-19 on PCOS patients' health, especially the changes in the global disease burden of PCOS.¹ However, despite growing recognition of PCOS as a significant health issue, there remains a critical research gap: no study has systematically compared the global burden of PCOS before and after the COVID-19 pandemic using the most recent GBD data. Furthermore, while psychological factors have been associated with PCOS, their causal role as risk factors has not been firmly established.

The Global Burden of Disease (GBD) 2021 study serves as a critical tool for assessing the health impacts of diseases, injuries, and risk factors at global and regional levels, providing data-driven support for public health policies and disease prevention and control strategies.⁶ Within the GBD 2021, PCOS is included in the assessment of various gynecological disorders and endocrine diseases. Therefore, this study aimed to: (1) compare global PCOS burden before (1990–2019) and after (2019–2021) the pandemic; (2) assess geographic and socioeconomic disparities; (3) project trends to 2050; and (4) examine causal relationships between psychological factors (anxiety and guilt) and PCOS risk using Mendelian randomization. Of note, GBD 2021 data only covers the early pandemic phase (2019–2021), as COVID-19 was declared ongoing until May 2023. Future studies with updated data are needed to capture the full impact. This study systematically analyzes the global health burden across 204 countries and territories from 1990 to 2021, evaluating changes in the disease burden of PCOS in the context of the COVID-19 pandemic, including metrics such as incidence, prevalence, and years lived with disability (YLDs), and to investigate the potential causal relationships between guilt, anxiety, and PCOS risk. These data not only reflect the epidemiological trends of PCOS in different countries and regions but also reveal the potential impact of the pandemic on its global burden. By comparing pre- and post-pandemic changes in the disease burden of PCOS, this research explores the influence of COVID-19 on the disorder. Such insights can enhance the understanding of PCOS and provide a scientific basis for global public health decision-making, facilitating the development of more effective interventions to mitigate its worldwide burden.

Materials and Methods

Data Source and Collection

The data on polycystic ovary syndrome (PCOS) were sourced from the Global Burden of Disease (GBD) 2021 study, which has obtained ethical approval from the University of Washington Institutional Review Board (IRB) and relevant ethics committees in participating countries. All data in GBD 2021 was open-source and publicly accessible. The datasets utilized in this study were derived from publicly available databases, and no additional ethical approval was required as the analysis exclusively employed aggregated, anonymized secondary data. According to Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (China, February 18, 2023), this research is exempt from institutional review board approval.

Within the GBD 2021 framework, PCOS cases were identified using ICD-10 code E28.2 (Polycystic ovarian syndrome) and ICD-9 code 256.4 (Polycystic ovaries). The GBD study utilizes a standardized case definition based on the Rotterdam criteria, incorporating data from systematic reviews, hospital records, claims data, and published studies. Detailed information on the GBD case definitions and modeling approaches is available in the GBD 2021 publications.^{7,8}

For the purpose of this analysis, we defined the pre-pandemic period as 1990–2019 and the pandemic/post-pandemic period as 2019–2021. The year 2019 was included in the pre-pandemic period as it represents the last full year before the global COVID-19 outbreak. This definition allows direct comparison of the immediate impact of the COVID-19 pandemic on PCOS burden.

Basic Indicators

This study selected incidence, prevalence, and Years Lived with Disability (YLDs) as comprehensive indicators to assess the disease burden of PCOS. To account for confounding effects arising from variations in age structures across populations, age-standardized rates (ASIR for incidence, ASMR for mortality, and ASYR for YLDs) based on the GBD world standard population were applied, thereby aligning the age distributions of study populations with the standardized reference population. The GBD methodology utilized the Bayesian meta-regression DisMod-MR 2.1 model for disease burden estimation, with 95% uncertainty intervals (UI) calculated to quantify measurement precision.

Trend Indicators

To analyze the temporal trends in the disease burden of PCOS from 1990 to 2021, the EAPC was employed to assess trends in ASIR, ASPR, and ASYR. The EAPC model was constructed through a linear regression model: $\ln(y) = \alpha + \beta x + \sigma$, where y represents ASIR, ASPR, or ASYR, α denoted the intercept, β indicates the slope coefficient, x corresponded to calendar year, and σ represented a normally distributed error term. The formula was: $EAPC = (e^{\beta} - 1) \times 100\%$.

Socio-Demographic Index

The Socio-demographic Index (SDI) was a composite metric that integrates indicators such as educational attainment, per capita income, and fertility rates to evaluate a society's overall socioeconomic development. The SDI ranges from 0 to 1, with higher values reflecting advanced socioeconomic status. Countries and regions were categorized into five quintiles based on SDI values: low (0–0.2), low-middle (0.2–0.4), middle (0.4–0.6), high-middle (0.6–0.8), and high (0.8–1.0).

Joinpoint Regression Model

To evaluate localized trends in the burden of PCOS, Joinpoint regression analysis was employed.⁹ This method identified inflection points (joinpoints) that partition the overall temporal trend into distinct sub-segments, allowing for the assessment of annual percentage change (APC) and its 95% confidence interval (CI) within each segment to quantify the magnitude of epidemiological shifts.¹⁰ Additionally, the average annual percentage change (AAPC) over specified time intervals was calculated by weighting the regression coefficients of each sub-segment by their interval span widths.

Health Inequality Analysis

To quantify transnational inequalities in the burden of PCOS, two distinct absolute and relative inequality metrics were applied: the Slope Index of Inequality (SII) and the Concentration Index (CI).¹¹ The SII represents the absolute difference in predicted burden values between the most advantaged and most disadvantaged populations across a socioeconomic or other ordered hierarchical dimension. The CI, a relative measure of inequality, captures the degree to which the burden is concentrated among disadvantaged or advantaged subgroups by evaluating health gradients across ordered population strata. A larger absolute value of the SII indicates a more pronounced absolute disparity in burden between the most advantaged and most disadvantaged groups; likewise, a CI value farther from zero (where a positive value signifies concentration among advantaged groups, and a negative value signifies concentration among disadvantaged groups) indicates a greater degree of relative inequality.

APC Model and BAPC Model

The APC model was utilized to evaluate the independent effects of age, period, and birth cohort factors in analyzing the spatiotemporal dynamics of PCOS disease burden. Using the Bayesian Age-Period-Cohort (BAPC) model to project future trends in ASIR, ASMR, and ASYR of PCOS up to 2050, with the calculation of their 95% confidence intervals (95% CI).

Human Development Index (HDI)

The HDI, developed by the United Nations Development Programme (UNDP), was a composite metric calculated from three core dimensions: the health dimension, measured by life expectancy at birth (LE) as a proxy for population health; the education dimension, assessed by the mean years of schooling (MYS) among those aged 25 years and older; and the standard of living dimension, quantified by the log-transformed gross national income (GNI) per capita adjusted for purchasing power parity (PPP) and expressed in constant 2017 international dollars (accounting for diminishing returns to income). These dimension indices were aggregated via geometric mean to produce a standardized, internationally comparable indicator of average achievement in key aspects of human development.

Mendelian Randomization (MR) Instrumental Variable Selection

To establish causal relationships, genetic instruments for the exposures were identified from the relevant Genome-Wide Association Study (GWAS) datasets using the `extract_instruments` function within the `TwoSampleMR` R package (Table S1).¹² Single nucleotide polymorphisms (SNPs) demonstrating genome-wide significant association ($p < 5 \times 10^{-8}$) with each exposure were selected as instrumental variables (IVs). To mitigate potential bias arising from linkage disequilibrium (LD), independent SNPs were retained by applying clumping criteria of $r^2 < 0.001$ within a 10,000 kb window. This stringent p-value threshold minimizes false positive instrument selection. Instrument strength and potential weak instrument bias were evaluated using the F-statistic. The F-statistic for each SNP was calculated as: $F = R^2 \times (N - 2) / (1 - R^2)$, where R^2 represent the proportion of variance in the exposure explained by the SNP, calculated as: $R^2 = 2 \times EAF \times (1 - EAF) \times \beta^2$

Here, EAF denotes the effect allele frequency, β was the estimated effect size of the SNP on the exposure, and N was the GWAS sample size. F-statistics exceeding 10 indicated robust instruments with minimal weak instrument bias (Table S2), consistent with established thresholds.

Exposure Factor Selection

MR analysis was subsequently performed via the `mr` function incorporating five methods: MR-Egger, weighted median, inverse variance weighted (IVW), simple mode, and weighted mode. Each exposure was analyzed separately. Based on IVW results, exposures with $p < 0.05$ were identified as candidate factors with potential causal relationships (Table S3) for downstream analyses.

Sensitivity and Steiger Directionality Analyses

Given that this MR analysis utilized SNP-exposure and SNP-outcome associations derived from potentially distinct populations and sequencing platforms, heterogeneity between samples could influence results. To address this, heterogeneity analysis was conducted using the `mr_heterogeneity` function (`TwoSampleMR`). Three validation methods were employed to assess result robustness: heterogeneity testing, horizontal pleiotropy evaluation, and leave-one-out sensitivity analysis. To verify that forward MR results were not confounded by reverse causation, Steiger filtering analysis was performed using the `directionality_test` function (`TwoSampleMR`). This MR Steiger directionality test examined reverse causality; a non-significant reverse analysis ($p > 0.05$) indicated reliable forward MR results.

Statistical Analysis

To evaluate the age-standardized rate (ASR) of PCOS, the ASR per 100,000 population was calculated using the following formula: $ASR = \frac{\sum_{i=1}^A \alpha_i w_i}{\sum_{i=1}^A w_i} \times 100,000$ Where α_i : age-specific rate for the i th age group; w_i : number of people in the standard population corresponding to the i th age group; A: number of age groups.

Results

Global Trends of PCOS

From 1990 to 2021, the global incidence cases, prevalence cases, YLDs cases, ASIR, ASPR, and ASYR of PCOS, along with their corresponding EAPC, showed a consistent upward trend. Pre-COVID-19 period, the incident cases rose from 1,476,225 (95% UI: 1,057,983–2,045,276) in 1990 to 2,211,741 (95% UI: 1,611,137–3,039,104) in 2019, representing an increase of 49.82%. The ASIR increased from 49.45 (95% UI: 35.57–68.45) per 100,000 population in 1990 to 62.01 (95% UI: 45.02–85.47) in 2019, with an EAPC of 0.78 (95% UI: 0.71–0.86). Post-COVID-19 period: By 2021, the incidence cases further increased to 2,301,505 (95% UI: 1,655,989–3,167,177), reflecting a 4.05% rise compared to 2019. The ASIR reached 63.26 (95% UI: 45.41–87.28), with an accelerated EAPC of 1.00 (95% UI: 0.90–1.10) ([Table S4](#)).

Similarly, the prevalent cases in 1990, 2019, and 2021 were 36,651,157 (95% UI: 26,227,943–50,603,929), 67,259,509 (95% UI: 48,442,515–92,225,415), and 69,473,252 (95% UI: 49,531,420–95,724,479), respectively, indicating an 83.51% increase from 1990 to 2019 and a 3.29% rise from 2019 to 2021. YLDs cases increased from 323,798 (95% UI: 144,342–675,926) in 1990 to 589,267 (95% UI: 264,085–1,226,850) in 2019 and further to 607,756 (95% UI: 272,745–1,268,607) in 2021, corresponding to an 81.98% growth in 1990–2019 and a 3.13% increase in 2019–2021. The ASPR exhibited an EAPC of 0.79 (95% UI: 0.71–0.87) during 1990–2019, which rose to 1.00 (95% UI: 0.90–1.10) in 2019–2021. The ASYR showed an EAPC of 0.77 (95% UI: 0.70–0.85) pre-pandemic, increasing to 0.96 (95% UI: 0.86–1.05) post-pandemic ([Tables S5](#) and [S6](#)). Following the COVID-19 pandemic, the ASIR, ASPR, and ASYR of PCOS increased globally, with higher EAPC values compared to the pre-pandemic period.

Global Disease Burden of PCOS Stratified by SDI and GBD Regions

Among the five SDI regions, both Middle SDI and High SDI regions exhibited higher incidence, prevalence, and YLDs of PCOS. The age-standardized indicators for 1990, 2019, and 2021 exhibited a consistent upward trend with increasing SDI levels, reaching their highest values in High SDI regions. For instance, in 2021, the High SDI regions demonstrated a PCOS ASIR of 144.89 per 100,000 (95%UI: 107.28, 196.81), an ASPR of 3554.29 per 100,000 (95%UI: 2624.21, 4816.07), and an ASYR of 31.37 per 100,000 (95%UI: 14.37, 64.00) ([Figure 1A–C](#)).

From 1990 to 2019, the EAPC for ASIR, ASPR, and ASYR showed an initial rise followed by a decline with increasing SDI, peaking in the Middle SDI region. The peak EAPC values were 1.58 (95%UI: 1.42–1.74), 1.74 (95% UI: 1.57–1.91), and 1.74 (95% UI: 1.57–1.91) for ASIR, ASPR, and ASYR, respectively. In contrast, the High SDI region recorded the lowest values: 0.35 (95% UI: 0.32–0.39), 0.33 (95% UI: 0.30–0.36), and 0.32 (95% UI: 0.29–0.35) for ASIR, ASPR, and ASYR, respectively ([Figure S1A](#)). During 2019–2021, the EAPCs for ASIR, ASPR, and ASYR remained stable in low SDI, low-middle SDI, middle SDI, and high-middle SDI regions but increased sharply in the high SDI region to 4.06 (95% UI: 3.66–4.47), 3.64 (95% UI: 3.28–4.01), and 3.60 (95% UI: 3.24–3.96), respectively ([Figure S1B](#) and [Tables S4–S6](#)).

Geographically, among the 21 regions analyzed, High-income Asia Pacific had the highest ASIR, ASPR, and ASYR values ([Figure 1](#)). Before the COVID-19 pandemic (1990–2019), High-income North America demonstrated the lowest EAPCs for ASIR, ASPR, and ASYR at 0.12 (95% UI: 0.11–0.13), 0.12 (95% UI: 0.11–0.13), and 0.10 (95% UI: 0.09–0.11), respectively. However, during the post-pandemic period (2019–2021), High-income North America exhibited the highest EAPC increases, reaching 10.19 (95% UI: 9.17–11.21), 10.04 (95% UI: 9.04–11.04), and 9.86 (95% UI: 8.87–10.84) for ASIR, ASPR, and ASYR, respectively ([Figure S1](#)). The COVID-19 pandemic has significantly exacerbated the disease burden of PCOS in High-income North America.

Country Burden of PCOS

The ASIR, ASPR, and ASYR for Italy and Japan were consistently highest in 2019 and 2021. For example, Italy reported ASIR values of 325.72 (95% UI: 230.49, 458.63) in 2019 and 326.17 (95% UI: 227.33, 458.58) in 2021, ASPR values of 8089.13 (95% UI: 5763.03, 11,252.64) in 2019 and 8113.15 (95% UI: 5757.73, 11,265.84) in 2021, and ASYR values of 71.56 (95% UI: 32.42, 150.77) in 2019 and 71.69 (95% UI: 32.15, 152.77) in 2021. In contrast, Albania and Bosnia and Herzegovina exhibited lower age-standardized metrics. For instance, Bosnia and Herzegovina recorded ASIR values of

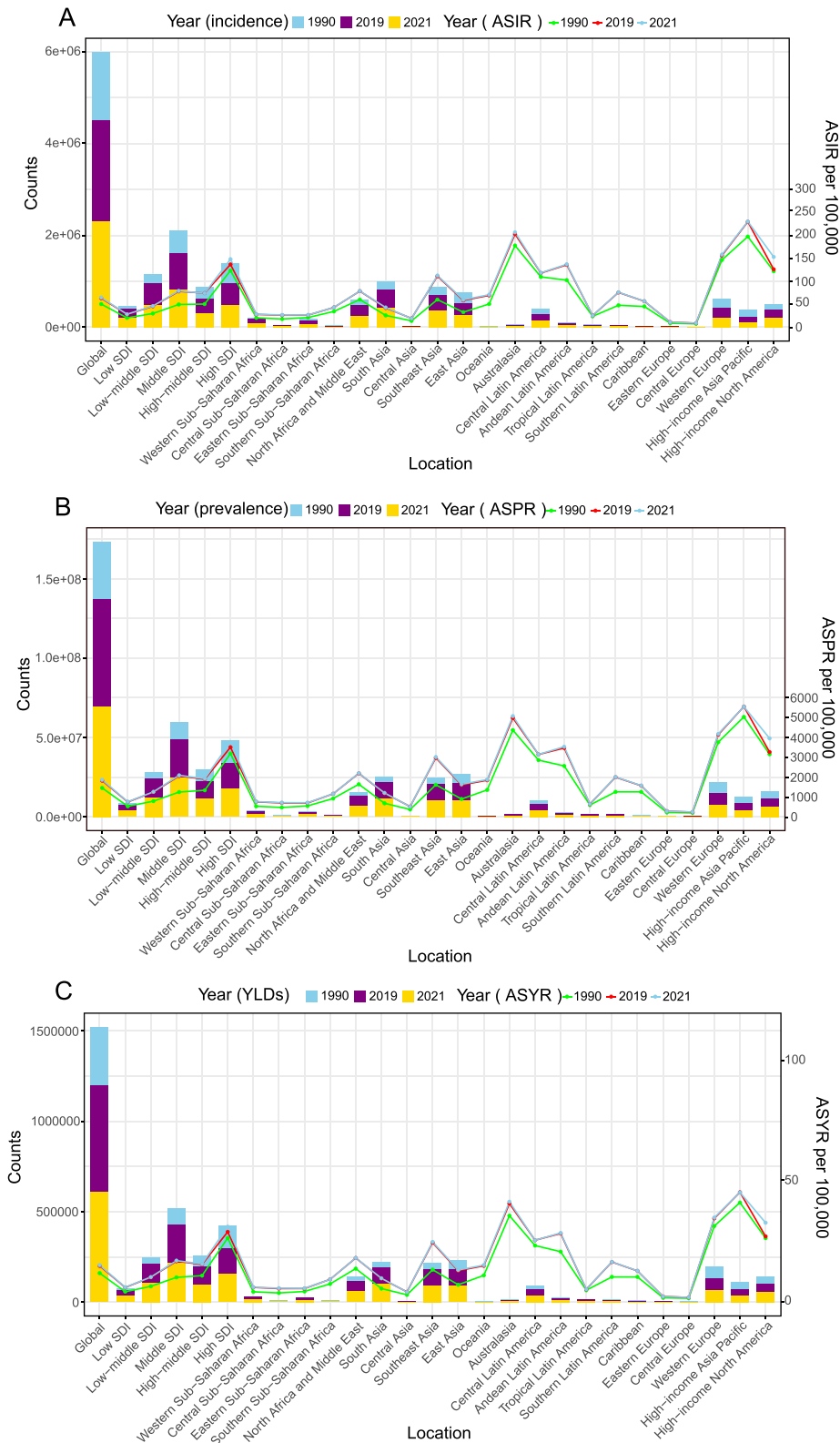


Figure 1 Global and regional burden of Polycystic Ovary Syndrome (PCOS) in the context of the COVID-19 pandemic, 1990–2021. **(A)** Incidence counts and Age-Standardized Incidence Rate (ASIR), **(B)** Prevalence counts and Age-Standardized Prevalence Rate (ASPR), **(C)** Years Lived with Disability (YLDs) counts and Age-Standardized YLDs Rate (ASYR).

7.57 (95% UI: 4.99, 11.09) in 2019 and 7.58 (95% UI: 5.07, 11.17) in 2021, while Albania reported ASIR values of 7.68 (95% UI: 5.19, 11.20) in 2019 and 7.70 (95% UI: 5.23, 11.28) in 2021 (Figure 2A–F).

Joinpoint Regression Model

The joinpoint regression analysis results provided further insights into the specific trends in the global burden of PCOS from 1990 to 2021. During this period, multiple indicators of PCOS-related disease burden exhibited a linear upward trend (Figure 3A–F). The slowest growth rates were observed between 2006 and 2009, with the following APCs: incidence cases (APC = 0.26), prevalence cases (APC = 1.56), YLDs (APC = 1.53), ASIR (APC = 0.51), ASPR (APC = 0.26), and ASYR (APC = 0.24). In contrast, the period from 2015 to 2019 witnessed a more rapid increase in disease burden across all indicators. However, the growth rate subsequently slowed from 2019 to 2021. For instance, the APC for incidence cases declined from 2.03 to 1.56 during this period (Table S7).

Age Groups Burden of PCOS

Between 1990 and 2021, the global incident cases of PCOS were predominantly concentrated in the 15–19 year age group (Figure 4A and B). Both the prevalent cases and YLDs associated with PCOS peaked in the 15–49 year age group, with disease burden declining notably after 50 years of age (Figure 4C and E). Across all age groups, the Middle SDI region exhibited the highest disease burden, followed by the high SDI region. From 1990 to 2019, the middle SDI region experienced a rapidly increasing proportion of disease burden with advancing age. In Low SDI regions, the burden share demonstrated a moderate decline among individuals aged 40–54 years, whereas High SDI regions showed a gradual increase in this age stratum. Between 2019 and 2021, the burden distribution across SDI regions became more balanced, with no marked predominance observed in any specific stratum (Figure 4).

Health Inequality Analysis of PCOS

Globally, the disease burden of PCOS demonstrated a positive correlation with socioeconomic development levels across all measured indicators in 1990, 2019, and 2021. The SII for incidence rate was 41.766, 23.922, and 23.553 in respective years, showing progressive improvement in health inequality by 2021 (Figure 5A and C). The CI for incidence rate remained stable at 0.990 across the three years (Figure 5B and D). For prevalence rate, the SII values were 1500.88, 1616.245, and 1570.521 (Figure 5E and G), while the CI remained unchanged at 0.990 (Figure 5F and H). For YLDs rate, the SII values were 13.466, 14.504, and 14.048 (Figure 5I and K), and the CI also remained stable at 0.990 (Figure 5J and L). Notably, the CI for all PCOS burden metrics remained statistically stable throughout the study period. Health inequality patterns revealed temporal variations: prevalence rate and YLDs rate demonstrated exacerbated inequality in 2019 with subsequent alleviation in 2021, whereas incidence rate inequality showed consistent improvement (Figure 5).

APC Model

The APC model was employed to analyze the independent effects of age, period, and birth cohort on PCOS (Figure S2). Age effect analysis revealed a persistent downward trend in global PCOS incident rate with increasing age. A gradual decline was observed in the 15–44 year age group, followed by a sharp reduction after age 44–54 years. Conversely, global PCOS prevalent rate and YLDs rate demonstrated an upward trend in the 15–29 year and 34–44 year age groups, a modest decline in the 30–34 year cohort, and a rapid decrease in the 44–54 year age group. Period effect analysis indicated that all PCOS-related disease burden metrics exhibited a non-linear temporal pattern from 1990 to 2021, characterized by an initial decline, subsequent increase, and final reduction. Cohort effect analysis identified the 2005–2009 birth cohort as bearing the highest disease burden. Females born during this period showed significantly elevated burden metrics compared to other birth cohorts.

Association Between PCOS and HDI Levels

A positive association ($p < 0.05$) was demonstrated between disease burden for PCOS, specifically ASIR, ASPR, and ASYR, and the HDI, LE, and MYS. Specifically, ASIR, ASPR, and ASYR for PCOS exhibited increasing trends with

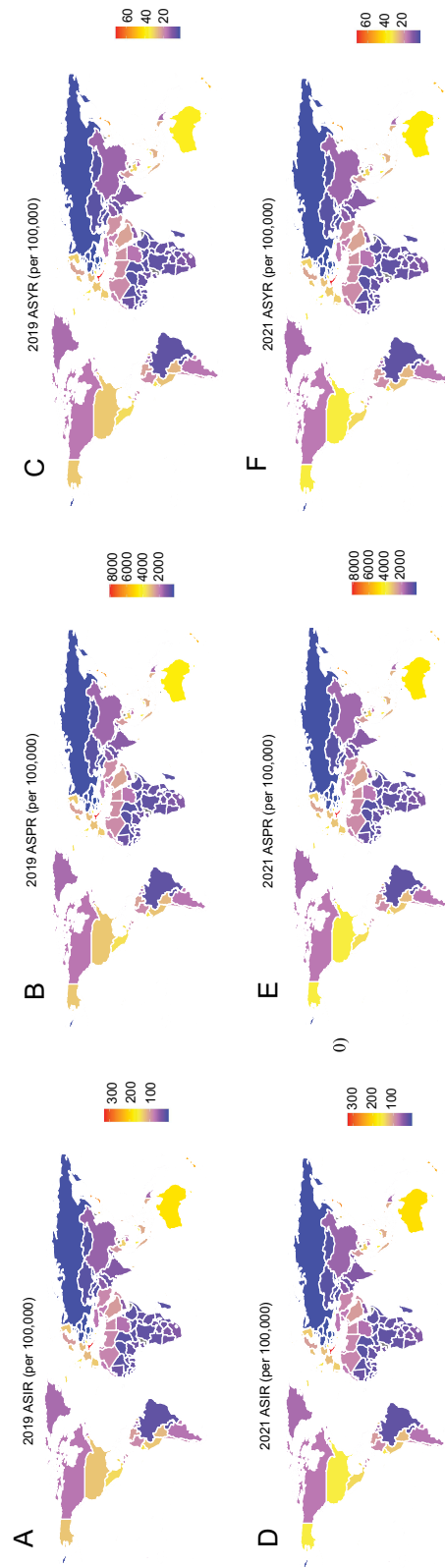


Figure 2 Global burden of PCOS by country in 2019 and 2021 (A) ASIR in 2019, (B) ASPR in 2019, (C) ASYR in 2019, (D) ASIR in 2021, (E) ASPR in 2021, (F) ASYR in 2021.

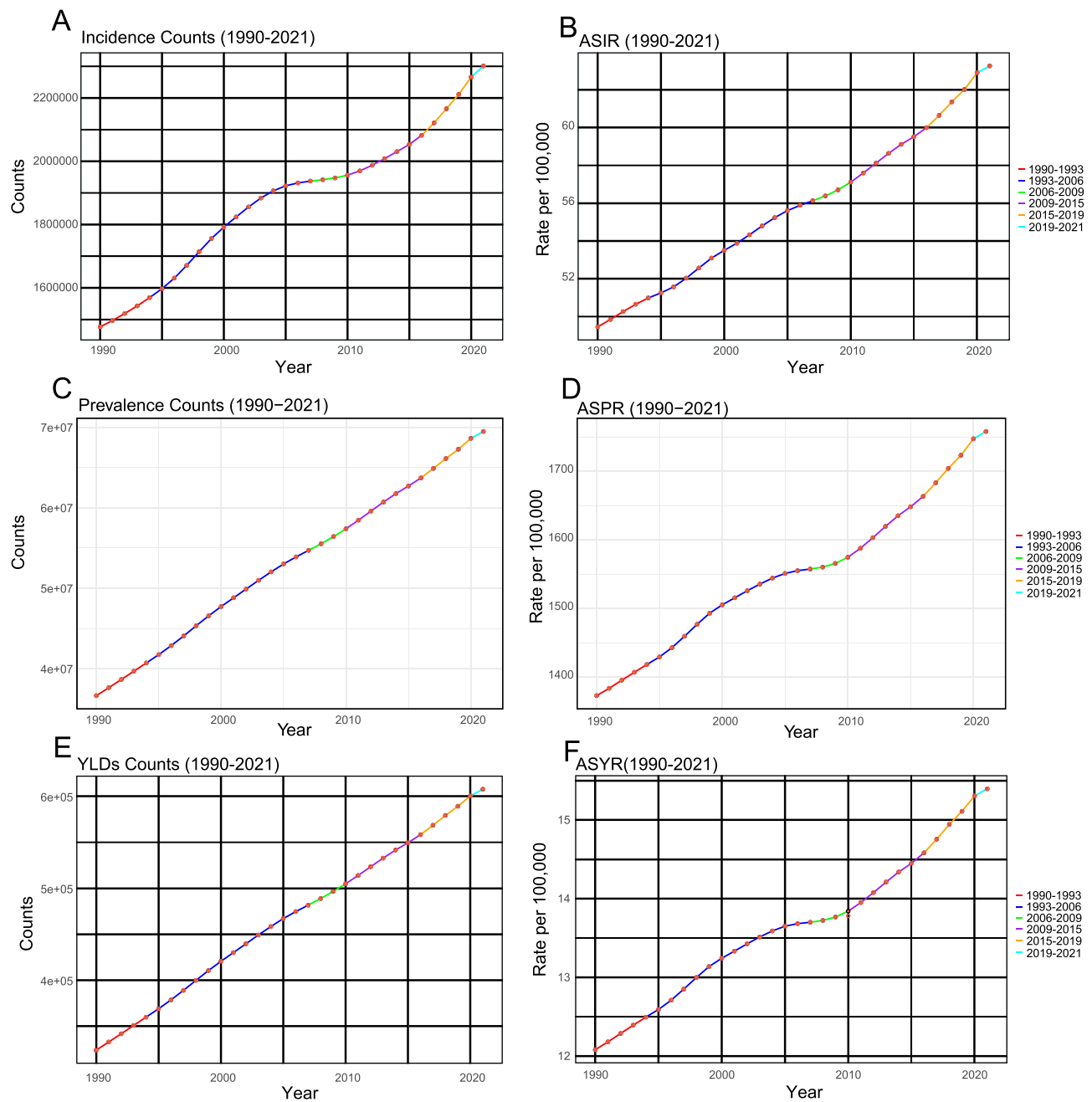


Figure 3 Joinpoint regression analysis of the disease burden of PCOS, 1990–2021 (A) Incidence counts, (B) ASIR, (C) Prevalence counts, (D) ASPR, (E) YLDs counts, (F) ASYR.

rising levels of HDI, LE, and MYS. In contrast, the relationship between GNIPC and PCOS burden indicators displayed a non-linear pattern, characterized by an inverted U-shaped curve; ASIR, ASPR, and ASYR initially increased but subsequently decreased as GNIPC rose (Figure 6A–C).

Future Projections of PCOS

The BAPC model was applied to forecast future trends in the global burden of PCOS. Projections indicate that ASIR, ASPR, and ASYR will continue to rise persistently. By 2050, these metrics are estimated to reach 73.66 (95% UI: 50.71–96.62), 2104.41 (95% UI: 1969.82–2239.01), and 18.37 (95% UI: 17.19–19.56) per 100,000 population, respectively (Figure S3A–C).

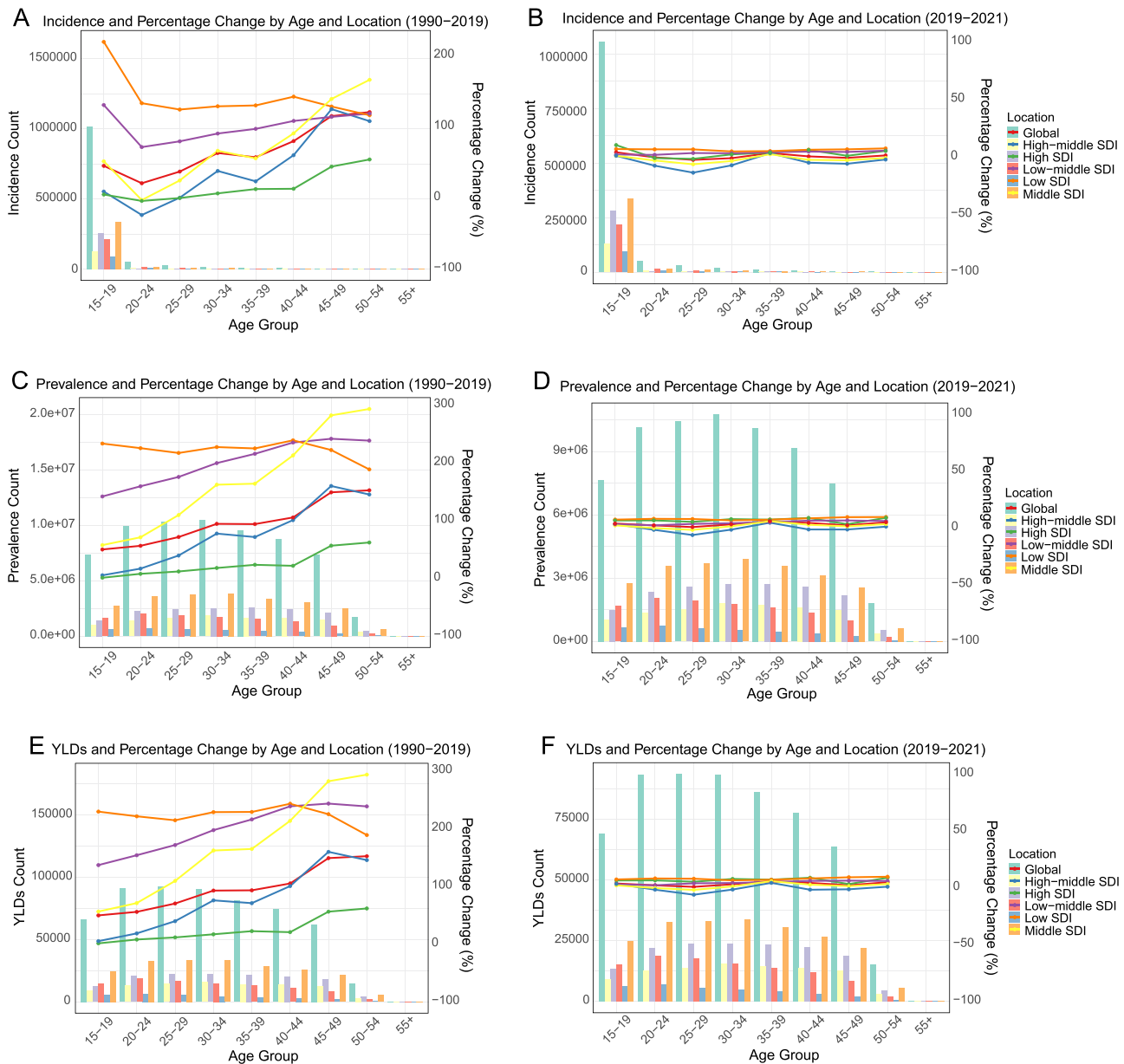


Figure 4 Global burden of disease for PCOS across SDI and age groups (A) 1990–2019 Incidence and percentage change, (B) 2019–2021 Incidence and percentage change, (C) 1990–2019 Prevalence and percentage change, (D) 2019–2021 Prevalence and percentage change, (E) 1990–2019 YLDs and percentage change, (F) 2019–2021 YLDs and percentage change.

Establishing Psychological States as Risk Factors for PCOS

This study employed MR to investigate the causal relationships between worry or anxiety, feelings of guilt, and PCOS. Initial observational analysis suggested positive associations between these exposures and PCOS. The IVW method further indicated that both exposures are likely risk factors for PCOS. The symmetry of the funnel plot, sensitivity analyses (revealing no significant heterogeneity or horizontal pleiotropy), and leave-one-out analysis all supported the robustness of the findings (Figure S4, S5 and Tables S8–S10).

Discussion

PCOS represents a significant contributor to global female health challenges.¹³ This study investigated the global disease burden of PCOS across 204 countries and territories from 1990 to 2021, with particular attention to the COVID-19 pandemic context. Analysis revealed a consistent upward trajectory in PCOS-related incidence cases, prevalence cases,

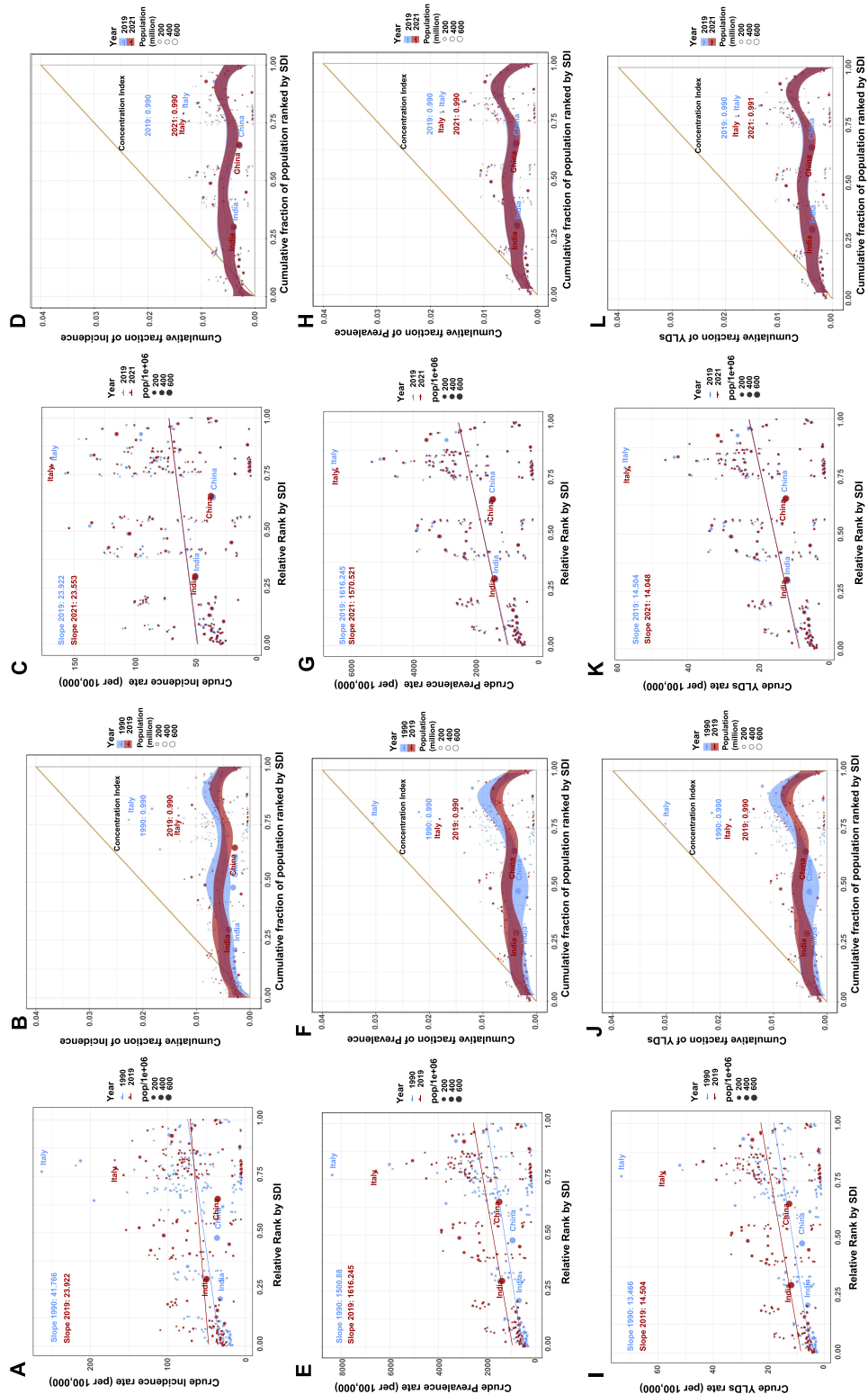


Figure 5 Health inequality regression curves and concentration curves assessing socioeconomic-related disparities in the disease burden of PCOS for the years 1990, 2019, and 2021 (A–D) Incidence rate, (E–H) Prevalence rate, (I–L) YLDs rate.

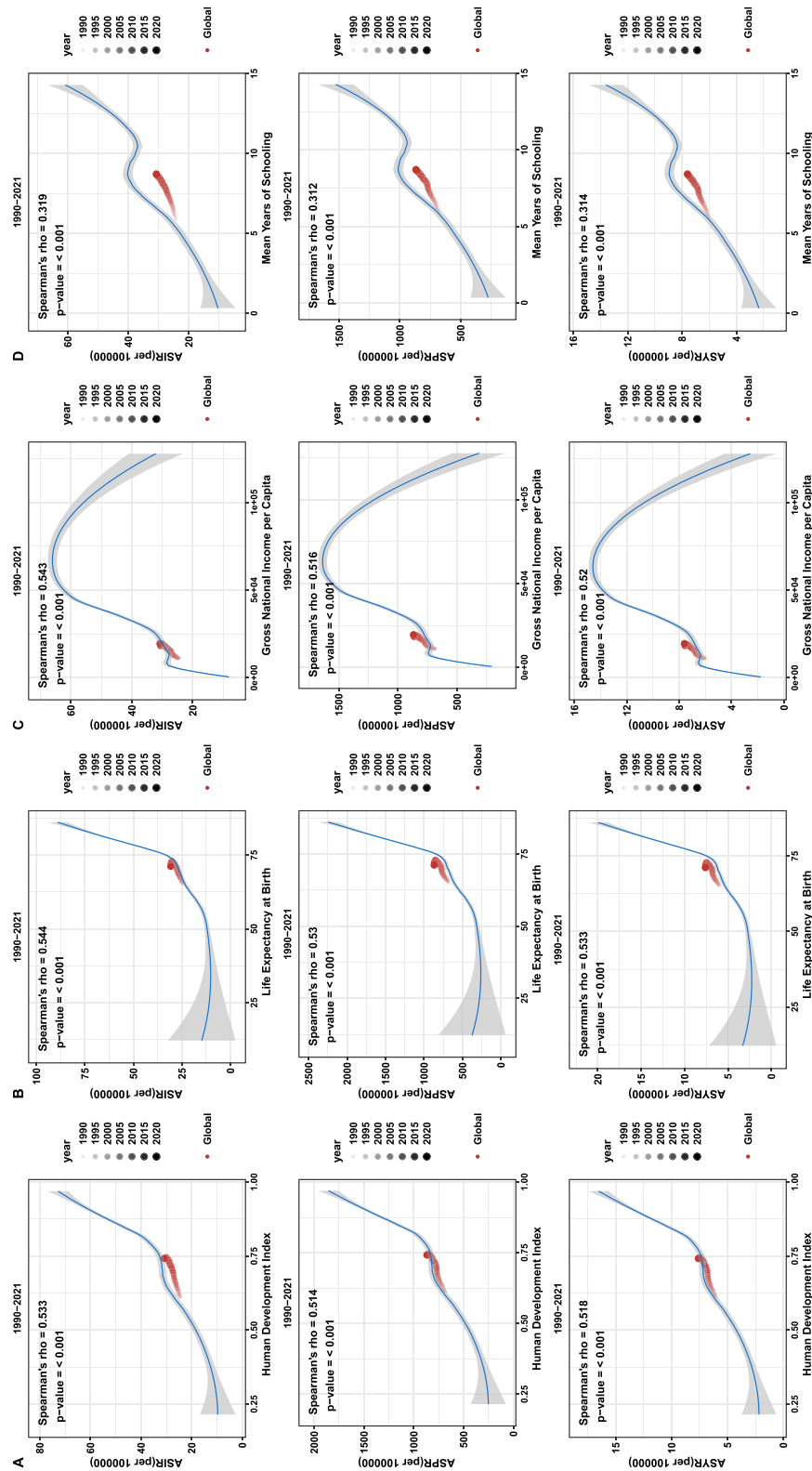


Figure 6 Correlation of PCOS-related ASIR, ASFR, and ASYR with HDI components. **(A)** Correlation by HDI. **(B)** Correlation by LE. **(C)** Correlation by GNI per capita. **(D)** Correlation by MYS.

YLDs, and their corresponding age-standardized metrics throughout this period. Comparative assessment of pre-pandemic and pandemic disease burden demonstrated elevated EAPC values for ASIR, ASPR, and ASYR during the pandemic phase, indicating COVID-19-associated exacerbation of PCOS burden. Pandemic-related stressors including psychological distress from health anxieties, social isolation, and financial pressures may precipitate endocrine dysregulation.¹⁴ A two-sample bidirectional MR analysis revealed several causal findings. First, neuroticism exerted a causal effect on the risk of several female reproductive diseases. Second, depression and anxiety significantly increased the risk of infertility and endometriosis. Conversely, polycystic ovary syndrome (PCOS) was causally linked to an increased risk of anxiety traits.⁴ Our MR analysis identified a significant causal effect of worry/anxiety symptoms and guilt on the risk of PCOS. Concurrently, COVID-19 infection potentially impacts endocrine and immune systems through direct pathophysiological mechanisms. For PCOS patients with pre-existing endocrine dysfunction and metabolic abnormalities, these dual pathways may synergistically disrupt physiological homeostasis.¹⁵ Such interactions could exacerbate PCOS symptomatology, increase complication risks, and ultimately amplify disease burden.¹⁶ This bidirectional relationship between pandemic conditions and PCOS pathophysiology warrants particular attention in contemporary women's health management strategies.

Globally, the SII for PCOS in 1990, 2019, and 2021 exhibited a positive correlation with the SDI, with health inequality showing improvement in 2021.¹⁷ Before the pandemic, the Middle SDI region displayed the most pronounced EAPC trends, likely due to its transitional economic and social development phase, characterized by high population mobility and rapid lifestyle shifts, which may have contributed to increased PCOS risk factors.¹⁸ Compared to other SDI regions, High SDI regions consistently exhibited higher age-standardized PCOS metrics both before and after the pandemic. This phenomenon stems from the interplay of demographic structure, healthcare system characteristics, and pandemic-related disruptions. An aging population and pre-existing chronic disease burdens were underlying factors, while the pandemic-induced strain on medical resources indirectly exacerbated adverse health outcomes.¹⁹

The global incidence of PCOS predominantly clusters in females aged 15–19 years, a critical developmental period marked by rapid physiological changes.²⁰ During adolescence, ovarian maturation and significant hormonal fluctuations create a susceptible window for endocrine disruption, thereby elevating PCOS risk.²¹ Both prevalence and YLDs peak among women aged 15–49 years the core reproductive age group before declining after age 50. As a chronic endocrine disorder, PCOS imposes its greatest burden during reproductive years, a life stage when women simultaneously navigate complex social roles and pressures, including occupational demands and family responsibilities.²² These epidemiological patterns underscore the necessity for targeted interventions.²³ Enhanced health education and monitoring for adolescent females could improve PCOS awareness and prevention.²⁴ Regionally tailored strategies should guide healthcare resource allocation across SDI tiers to optimize diagnostic and therapeutic approaches.^{25,26}

This study has several strengths. It used the most recent GBD 2021 database and multiple advanced methods (Joinpoint regression, APC/BAPC models, inequality indices, and Mendelian randomization) to provide a comprehensive analysis of global PCOS burden. Notably, it is the first to compare pre- and post-pandemic PCOS burden and to establish causal relationships between psychological factors (anxiety and guilt) and PCOS using MR analysis. However, limitations include potential estimation uncertainty from GBD modeling, data only covering the early pandemic phase (2019–2021) rather than its full duration, cross-country variations in diagnostic criteria, and the lack of PCOS phenotype data for subtype analyses. Future GBD updates will help address these limitations.

Conclusions

This study demonstrates a significant and accelerating global burden of PCOS, particularly in the post-pandemic period. The findings reveal substantial geographic and socioeconomic disparities, with high SDI regions experiencing the most pronounced increases during the pandemic. Projections to 2050 indicate a continued rise across all burden metrics. The MR analysis establishes anxiety and guilt as causal risk factors for PCOS, highlighting the need for integrated mental health support in PCOS management. These findings underscore the importance of targeted public health interventions for high-risk populations, particularly adolescents and women in high SDI regions, and call for strengthened women's endocrine healthcare preparedness for future health emergencies.

Abbreviations

APC, Age-Period-Cohort (model); APC, Annual Percentage Change (in Joinpoint regression); AAPC, Average Annual Percentage Change; ASIR, Age-Standardized Incidence Rate; ASPR, Age-Standardized Prevalence Rate; ASYR, Age-Standardized Years lived with Disability Rate; ASMR, Age-Standardized Mortality Rate; ASR, Age-Standardized Rate; BAPC, Bayesian Age-Period-Cohort (model); CI, Concentration Index (health inequality metric); COVID-19, Coronavirus Disease 2019; DALYs, Disability-Adjusted Life Years; EAPC, Estimated Annual Percentage Change; EAF, Effect Allele Frequency; GBD, Global Burden of Disease; GWAS, Genome-Wide Association Study; IV, Instrumental Variable; IVW, Inverse Variance Weighted (MR method); LD, Linkage Disequilibrium; MR, Mendelian Randomization; PCOS, Polycystic Ovary Syndrome; SDI, Socio-demographic Index; SII, Slope Index of Inequality (health inequality metric); SNP, Single Nucleotide Polymorphism; UI, Uncertainty Interval; YLDs, Years Lived with Disability; HDI, Human Development Index; LE, Life Expectancy; MYS, Mean Years of Schooling; GNIPC, Gross National Income per capita.

Data Sharing Statement

The datasets generated and/or analysed during the GBD database (<https://www.healthdata.org>).

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; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

References

- Ilias I, Goulas S, Zabulienė L. Polycystic ovary syndrome: pathways and mechanisms for possible increased susceptibility to COVID-19. *World J Clin Cases*. 2021;9(12):2711–2720. doi:10.12998/wjcc.v9.i12.2711
- Kyrou I, Karteris E, Robbins T, Chatha K, Drenos F, Randeva HS. Polycystic ovary syndrome (PCOS) and COVID-19: an overlooked female patient population at potentially higher risk during the COVID-19 pandemic. *BMC Med*. 2020;18(1):220. doi:10.1186/s12916-020-01697-5
- Yin MXC, Leng LL, Liang Z, Chen XY, Chan CHY, Chan CLW. Objectification and ambiguity of body image in women with polycystic ovary syndrome: a mixed-method study. *J Affect Disord*. 2022;310:296–303. doi:10.1016/j.jad.2022.05.028
- Zhang S, Wu Y, Mprah R, Wang M. COVID-19 and persistent symptoms: implications for polycystic ovary syndrome and its management. *Front Endocrinol*. 2024;15:1434331. doi:10.3389/fendo.2024.1434331
- Kong X, Jin F, Tang G, Qin Y, Liu D, Sun J. Causality between neuroticism personality clusters and female reproductive diseases in European population: a two-sample bidirectional mendelian randomization study. *BMC Women's Health*. 2024;24(1):507. doi:10.1186/s12905-024-03347-x
- Wu Z, Xia F, Lin R. Global burden of cancer and associated risk factors in 204 countries and territories, 1980–2021: a systematic analysis for the GBD 2021. *J Hematol Oncol*. 2024;17(1):119. doi:10.1186/s13045-024-01640-8
- Xu R, Li X, Sang L, et al. Global burden and future trends of polycystic ovary syndrome: insights from the GBD 2021 study. *Int J Womens Health*. 2025;17:3707–3720. doi:10.2147/IJWH.S556627
- GBD 2021 Diseases and Injuries Collaborators. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the global burden of disease study 2021. *Lancet*. 2024;403(10440):2133–2161. doi:10.1016/S0140-6736(24)00757-8

9. Ilic I, MJWjog I. International patterns in incidence and mortality trends of pancreatic cancer in the last three decades: a joinpoint regression analysis. *World J Gastroenterol.* **2022**;28(32):4698. doi:10.3748/wjg.v28.i32.4698
10. Cabrera A, Rodriguez A, Romero-Sandoval N, Barba S, Cooper J. Trends in hospital admissions and mortality rates for asthma in Ecuador: a joinpoint regression analysis of data from 2000 to 2018. *BMJ Open Respir Res.* **2021**;8(1).
11. Xu H, Liang X, Li K, et al. Trend analysis and cross-national inequity analysis of immune-mediated inflammatory diseases in children and adolescents aged 10–24 from 1990 to 2021. *World Allergy Organ J.* **2025**;18(3):101033. doi:10.1016/j.waojou.2025.101033
12. Rasooly D, Peloso GMJCP. Two-sample multivariable Mendelian randomization analysis using R. *Curr Protoc.* **2021**;1(12):e335. doi:10.1002/cpz1.335
13. Joshi SR. Polycystic ovary syndrome and COVID-19: an emerging risk factor. *J Hum Reproduct Sci.* **2021**;14(2):211–212. doi:10.4103/jhrs.jhrs_79_21
14. Subramanian A, Anand A, Adderley NJ, et al. Increased COVID-19 infections in women with polycystic ovary syndrome: a population-based study. *Eur J Endocrinol.* **2021**;184(5):637–645. doi:10.1530/eje-20-1163
15. Dilbaz B. Are women with polycystic ovary syndrome more vulnerable to COVID-19 infection? *Turkish J Obstet Gynecol.* **2021**;18(3):221–223. doi:10.4274/tjod.galenos.2021.05014
16. Jerzak M, Szafarowska M. Preliminary results for personalized therapy in pregnant women with polycystic ovary syndrome during the COVID-19 pandemic. *Archivum immunologiae et therapiae experimentalis.* **2022**;70(1):13. doi:10.1007/s00005-022-00650-z
17. Si Y, Fei Y, Ma H, et al. The causal association between polycystic ovary syndrome and susceptibility and severity of COVID-19: a bidirectional mendelian randomization study using genetic data. *Front Endocrinol.* **2023**;14:1229900. doi:10.3389/fendo.2023.1229900
18. Atkinson L, Kite C, McGregor G, et al. Uncertainty, anxiety and isolation: experiencing the COVID-19 pandemic and lockdown as a woman with Polycystic Ovary Syndrome (PCOS). *J pers Med.* **2021**;11(10):952. doi:10.3390/jpm11100952
19. Rezaq S, Huffman AM, Basnet J, Yanes Cardozo LL, Romero DG. Cardiac and renal SARS-CoV-2 viral entry protein regulation by androgens and diet: implications for polycystic ovary syndrome and COVID-19. *Int J Mol Sci.* **2021**;22(18):9746. doi:10.3390/ijms22189746
20. Rothenberg SS, Beverley R, Barnard E, Baradaran-Shoraka M, Sanfilippo JS. Polycystic ovary syndrome in adolescents. *Best Pract Res Clin Obstet Gynaecol.* **2018**;48:103–114. doi:10.1016/j.bpobgyn.2017.08.008
21. DiVall S, Merjaneh L. Adolescent polycystic ovary syndrome: an update. *Pediatr Ann.* **2019**;48(8):e304–e10. doi:10.3928/19382359-20190729-01
22. Barthelmess EK, Naz RK. Polycystic ovary syndrome: current status and future perspective. *Front Biosci.* **2014**;6(1):104–119. doi:10.2741/e695
23. McGowan L, Quinlivan J. Polycystic ovary syndrome (PCOS): moving from characterization to interventions. *J Psychosom Obstet Gynaecol.* **2019**;40(4):249. doi:10.1080/0167482x.2019.1672337
24. Alesi S, Ee C, Moran LJ, Rao V, Mousa A. Nutritional supplements and complementary therapies in polycystic ovary syndrome. *Adv Nutr.* **2022**;13(4):1243–1266. doi:10.1093/advances/nmab141
25. Guan C, Zahid S, Minhas AS, et al. Polycystic ovary syndrome: a “risk-enhancing” factor for cardiovascular disease. *Fertil Steril.* **2022**;117(5):924–935. doi:10.1016/j.fertnstert.2022.03.009
26. Huddleston HG, Dokras A. Diagnosis and treatment of polycystic ovary syndrome. *JAMA.* **2022**;327(3):274–275. doi:10.1001/jama.2021.23769

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