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Global Trends and Burden of Non-Neoplastic Gynecologic Diseases Among Women of Childbearing Age, 1990–2021: a GBD 2021 Analysis

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Background: Non-neoplastic gynecological diseases substantially impact women of childbearing age (WCBA), contributing to global burden. Despite growing awareness, disparities in healthcare access remain widespread across regions and socioeconomic groups.

Materials and Methods: Utilizing data from the Global Burden of Disease Study 2021, the study assess the prevalence and disability-adjusted life years (DALYs) of 7 non-neoplastic gynecological diseases in WCBA across 231 countries and regions from 1990 to 2021. Age-standardised rates (ASRs) and estimated annual percentage changes (EAPCs) were used to assess temporal trends. Additionally, the socio-demographic index (SDI) was explored for its association with disease burden.

Results: From 1990 to 2021, global age-standardised prevalence and DALY rates of the non-neoplastic gynecological diseases remained relatively stable (EAPC: 0.00%, −0.20%). In contrast, the absolute number of prevalent cases increased markedly, largely reflecting population growth and changes in age structure. Female infertility and polycystic ovary syndrome (PCOS) demonstrated increasing trends in both prevalence (EAPC: 0.69%, 0.74%) and DALYs (EAPC: 0.71%, 0.72%). In 2021, premenstrual syndrome (PMS) showed the highest prevalence (889.97 per 100,000) and DALY rate (74.27 per 100,000). North Africa and Middle East showed the highest ASR of prevalence (ASPR, 70,265.65) and DALYs (ASDR, 1,812.41) globally. Age-specific analyses indicated that prevalence and DALYs peaked among women aged 35–44 years. In addition, higher SDI correlated with lower ASPR and ASDR in overall non-neoplastic gynecological diseases, while PCOS exhibited upward trends.

Conclusion: The global burden of non-neoplastic gynecological diseases among WCBA remains substantial, with marked heterogeneity across regions and conditions. These findings underscore the importance of strengthened disease surveillance, improved and equitable access to reproductive health services, and greater integration of mental health support in women's health strategies.

Keywords: non-neoplastic gynecological diseases, global burden of disease study, prevalence, disability-adjusted life years, women of childbearing age

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Introduction

Women's reproductive health disorders, particularly the escalating global burden of infertility, have emerged as a critical public health priority in contemporary biomedical research.[1] According to the World Health Organization's (WHO) 2023 Global Fertility Report, about 17.5% of the global population of reproductive age will experience infertility during their lifetime. This prevalence shows little regional variation, emphasizing infertility as a significant global health challenge.[2] While assisted reproductive technology has achieved substantial clinical advancement and widespread adoption in contemporary medical practice,[3] prohibitive costs persist as a major impediment to accessibility across low- and middle-income countries.[4] Compounding this challenge, persistent racial and ethnic disparities in female reproductive health outcomes underscore the imperative for developing tailored therapeutic protocols.[5] These findings collectively emphasize the critical need for implementing comprehensive public health strategies focused on primary prevention initiatives.

Non-neoplastic gynecological diseases refer to diseases involving the female reproductive system and related tissues, including inflammation, tumors, endocrine disorders, structural abnormalities and other types. Existing research evidence indicates that certain non-neoplastic gynecological diseases can cause hormonal imbalances and excessive inflammation, leading to disruptions in the immune-endocrine crosstalk, severely affecting women's reproductive health.[6] In fact, non-neoplastic gynecological diseases have persistently constituted the predominance: global burden of non-communicable diseases among women of childbearing age (WCBA).[7,8] Within the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD), these conditions are systematically categorized under female reproductive system pathologies, encompassing seven principal disease entities: polycystic ovary syndrome (PCOS), female infertility, uterine fibroids, endometriosis, genital prolapse, premenstrual syndrome (PMS), and other non-neoplastic gynecological diseases. Within the standardized framework of the GBD, these conditions can be evaluated using consistent definitions and metrics, enabling direct comparison of their relative burden. Specifically, endometriosis is prevalent, affecting 5–10% of WCBA globally.[9] Uterine fibroids is also among the most common tumors in WCBA, with an estimated lifetime prevalence ranging from 40% to 89%.[10] PCOS impacts 8–13% of WCBA and is a major contributor to infertility.[11] Female infertility, a global health issue often overlooked, affects an estimated 48 million couples and 186 million individuals worldwide.[12] Approximately 5–8% of WCBA experience moderate to severe PMS globally.[13] Moreover, PMS shares a lifetime comorbidity of 30% to 70% with other mood disorders, highlighting a substantial overlap.[14] Genital prolapse, though often presenting subtle symptoms, is highly prevalent and can significantly impact patients' quality of life as they age.

Although the burden of these diseases is substantial, funding for women's health issues remains inadequate. According to data from the National Institutes of Health (NIH) in 2022, the expected funding for endometriosis is only $2 per patient per year.[15] Moreover, non-neoplastic gynecological diseases are almost absent from the open-access reference databases that advanced biological and molecular data sciences rely on, such as ENCODE, the NIH Roadmap Epigenomics, Genotype-Tissue Expression Project, and TissueNexus, which hinders new discoveries.[16] The significant disease burden and insufficient attention highlight the pressing need for a comprehensive study on common non-neoplastic gynecological diseases. Such research can help understand global burden trends, identify diseases requiring immediate attention, and facilitate the adoption of best practices from successfully controlled conditions worldwide, ultimately promoting reproductive health in women of reproductive age and improving the current state of infertility. Within the framework provided by the GBD, pronounced disparities in access to reproductive health care across regions can be systematically examined. Accordingly, the sociodemographic index (SDI) was selected as a key analytical variable, as it captures composite differences in income, educational attainment, and fertility patterns—factors closely linked to health system capacity, disease detection, and management of gynecological conditions.[17] As WCBA play a vital role in reproductive health and family planning, studying non-neoplastic gynecological diseases in this group helps identify trends in prevalence and disability-adjusted life years (DALYs). A three-decade spatiotemporal analysis of disease burden among WCBA was conducted to identify high-risk clusters and inform targeted public health strategies for infertility prevention. Using the most recent GBD 2021 data, this study provides a comprehensive and updated assessment of the burden of major non-neoplastic gynecological diseases among WCBA, extending previous GBD-based analyses. By jointly examining age-specific patterns, long-term temporal trends, and SDI-stratified disparities across

multiple conditions, this analysis offers a more integrated perspective on reproductive health challenges relevant to infertility prevention.

Materials and Methods

Study Population and Data Collection

This investigation was rigorously conducted in compliance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines,[18] employing methodological standards established by the Institute for Health Metrics and Evaluation (IHME) through its GBD initiative. As the coordinating entity, IHME's GBD framework delivers a harmonized comparative paradigm for quantifying epidemiological burdens through standardised disability weights and comorbidity-adjusted prevalence metrics, enabling systematic evaluation of disease/injury profiles and modifiable risk factor impacts across heterogeneous populations, geospatial contexts, and temporal dimensions. The GBD 2021 involved over 12,000 researchers from more than 160 countries and territories. All disease terms within the GBD 2021 initiative adheres to the International Classification of Diseases (ICD) codes (https://ghdx.healthdata.org/record/ihme-data/gbd-2021-cause-icd-code-mappings).

Detailed methodology for non-neoplastic gynecological diseases is described in the GBD 2021 methods appendices (https://www.healthdata.org/gbd/methods-appendices-2021/gynaecological-diseases). Based on this standardized framework, age-stratified epidemiological indicators for non-neoplastic gynecological diseases among WCBA were derived from the GBD 2021 Results Tool (https://ghdx.healthdata.org/gbd-2021/sources). The ICD codes mapping non-neoplastic gynecological diseases were systematically archived in the supplementary appendix. As chronic conditions with long preclinical courses that do not directly cause death, non-neoplastic gynecological diseases lack incidence and mortality estimates in GBD 2021.

The SDI,[19] a composite development metric operationalized within the GBD analytical paradigm, quantifies population-level progress through three demographically sensitive proxies: age-standardised total fertility rate < 25 years, age-weighted educational attainment (mean schooling years ≥ 15 years), and lag-distributed income per capita. The SDI scale ranges from 0 (lowest development) to 1 (highest development). Following the GBD 2021 methodological protocol, we stratified 204 geopolitical entities into five development quintiles: Low SDI, Low-middle SDI, Middle SDI, High-middle SDI and High SDI.[17]

Statistical Analysis

This study implemented a stratified epidemiological analysis to evaluate the burden of non-neoplastic gynecological diseases among the WBCA. We compared the age-standardised prevalence rate (ASPR) and DALYs rate (ASDR) of non-neoplastic gynecological diseases across different age groups, regions, and countries based on the subsequent standard formula:[1,20]

$$ASR = \frac{\sum_{i=1}^{N} \alpha_i W_i}{\sum_{i=1}^{N} W_i} \tag{1}$$

In equation (1), N represented the upper age limit, α_i corresponded to age-specific rate, and W_i represented the population count for a particular age group. The 95% CIs were computed through the direct standardization methodology implemented in the "ageadjust.direct" function of the "epitools" epidemiological analysis package within R statistical environment.[21]

$$\ln(ASR) = \beta_0 + \beta_1 \cdot \mathrm{t} + \varepsilon \tag{2}$$

$$EAPC = 100 \times \left(e^{\beta_1} - 1\right) \tag{3}$$

To assess the overall trend in prevalence and DALYs over a given period, we computed the estimated annual percentage change (EAPC) of ASRs.[22] In formula,[2] t represented the calendar year in continuous scale, and β_1 was calculated from the natural logarithm of the ASRs. The EAPC values were derived through the computational transformation specified in

formula.[2] Subsequent scalar multiplication by 100 yields the final EAPC metric, as formally defined in formula.[3] The ASR trend was classified as increasing or decreasing when both the EAPC and its 95% CI were entirely above or below zero, respectively.[23]

To examine the association between the gynecological disease burden and SDI across 21 regions and 204 countries, we employed local regression smoothing (loess). Spearman correlation analysis was conducted to determine the *r* indices and p-values for the relationship between burden and SDI in 2021. Given the shifts in SDI distribution from 1990 to 2021, we further calculated the EAPC of SDI for 204 countries and assessed its correlation with ASR trends. A significance threshold of $P < 0.05$ was applied, and all statistical analyses and visualizations were conducted in R (version 4.2.2).

Results

Global and Regional Burden of Non-Neoplastic Gynecological Diseases

The Global Gynecological Epidemiology Indicators for 2021 show a high burden of disease, with total prevalence estimated at 121.15 million worldwide. When standardized by age demographics, this equates to 61,819.79 per 100,000 people affected. The number of DALYs associated with these diseases totaled 2.23 million globally, equating to an age-adjusted life year ratio of 1,130.76 per 100,000 inhabitants. A geospatial analysis of 21 global burden areas and 204 national entities determined that the North Africa and Middle East (70,265.65), Iran (Islamic Republic of) (71,340.68) had the highest ASPR (Table S1), and the highest ASDR were recorded in North Africa and Middle East (1,812.41) and Qatar (1,929.43), respectively (Table 1, Table S1, Figure 1A, B, Figure S1A and S2A–B).

During the three-decade observation period, the global ASPR showed no trend of decline, evidenced by an EAPC of 0.00 (95% CI: −0.02 to 0.02). Concurrently, the ASDR exhibited a statistically significant downward trajectory, registering an EAPC of −0.20 (95% CI: −0.24 to −0.15). At the national level, the most pronounced reductions in ASPRs were observed in Italy (EAPC = −0.29), China (−0.24) and Norway (−0.16) while the most increased ones were Taiwan (0.30), Philippines (0.28) and United States of America (0.23) (Table 1, Table S1, Figure 1C, Figure S1B and S2C). The ASDR displayed universal improvement across all regions, with the exception of Eastern Europe where a marginal elevation was recorded (EAPC = 0.02). At the national level, the most rapid increases in ASDRs were recorded in Taiwan (EAPC = 0.30) and Philippines (0.30) (Table 1, Table S1, Figure 1D, Figure S1B and S2D).

Regional Disparities in the Burden of Non-Neoplastic Gynecological Diseases

In 2021, the global prevalence estimates (case counts ×1,000,000) of accumulated cases among WCBA were documented as 6.58 for PCOS, 3.20 for genital prolapse, 11.01 for female infertility, 8.52 for uterine fibroids, 2.10 for endometriosis, 89.00 for PMS, and 40.07 for other types of non-neoplastic gynecological diseases. The ASPRs (per 100,000 population) for these conditions were 3,367.7, 1,061.4, 5,580.1, 4,270.4, 1,074.2, 45,552.4, and 20,211.5, respectively. What's more, the global DALYs (years ×1,000,000) for each of these conditions among WCBA, along with their corresponding ASDRs (per 100,000 population), were as follows: 0.6 (29.53), 0.1 (5.10), 0.6 (30.52), 0.1 (4.98), 1.9 (99.00), 7.4 (380.31), and 11.5 (581.33). Notably, the highest numbers of both prevalence and DALYs for these non-neoplastic gynecological diseases were observed in regions such as South Asia, East Asia, and North Africa and the Middle East (Tables S2–S8, Figure 2A and 2B, Figure S1A).

Excluding other non-neoplastic gynecological diseases, PMS accounted for the highest global prevalence (55.46%) and DALYs (33.33%) among non-neoplastic gynecological conditions, followed by female infertility (6.86%), uterine fibroids (5.31%), PCOS (4.10%), genital prolapse (2.00%), and endometriosis (1.31%) in prevalence, and endometriosis (8.70%), female infertility (2.70%), PCOS (2.58%), genital prolapse (0.45%), and uterine fibroids (0.44%) in DALYs (Figure 2C and D). In 2021, the highest ASRs (per 100,000 population) were observed as follows: PCOS in High-income Asia Pacific (prevalence: 10,126.7; DALYs: 88.2), genital prolapse in Tropical Latin America (3,540.8; 11.3), female infertility in East Asia (8,286.6; 43.5), uterine fibroids in Eastern Europe (ASPR: 10,084.0), endometriosis in Oceania (1,910.2; 175.9), PMS in South Asia (50,323.4; 417.47), and other non-neoplastic gynecological diseases in North Africa and the Middle East (47,402.5; 1,279.0). Notably, although uterine fibroids exhibited the highest prevalence rate in

Table 1 Prevalence and DALYs of Non-Neoplastic Gynecological Diseases in 1990 and 2021, and Their Estimated Annual Percentage Changes from 1990 to 2021

Characteristics	Prevalence					DALYs				
	Number of cases,1990 (×100,000)	Age-standardised rate per 100,000 population, 1990	Number of cases to 2021 (×100,000)	Age-standardised rate per 100,000 population,2021	Estimated annual percentage change,1990–2021	Number of cases,1990 (×100,000)	Age-standardised rate per 100,000 population, 1990	Number of cases,2021 (×100,000)	Age-standardised rate per 100,000 population,2021	Estimated annual percentage change,1990-2021
Global	797.2 (706.6, 884.7)	61,157.43 (61,153.14, 61,161.73)	1,211.5 (1,085.0, 1,336.6)	61,819.79 (61,816.31, 61,823.28)	0 (−0.02 to 0.02)	15.0 (10.5, 21.1)	1175.72 (1175.12, 1176.32)	22.3 (15.6, 31.2)	1,130.76 (1,130.29, 1,131.23)	−0.2 (−0.24 to −0.15)
Cause										
Polycystic ovarian syndrome	34.8 (24.9, 47.9)	2,632.04 (2,631.16, 2,632.93)	65.8 (46.7, 90.6)	3367.68 (3366.87,3368.5)	0.74 (0.70 to 0.77)	0.3 (0.1, 0.6)	23.19 (23.11, 23.27)	0.6 (0.3, 1.2)	29.53 (29.45, 29.6)	0.72 (0.68 to 0.75)
Genital prolapse	23 (17.6, 29.1)	2,032.91 (2,032.07, 2,033.75)	32.0 (24.4, 40.6)	1601.37 (1600.82,1601.93)	−0.96 (−1.04 to −0.88)	0.1 (0.0, 0.2)	6.48 (6.43, 6.53)	0.1 (0.0, 0.2)	5.10 (5.07, 5.13)	−0.96 (−1.03 to −0.88)
Female infertility	59.7 (32.6,104.6)	4,578.45 (4,577.28, 4,579.62)	110.1 (58.6, 195.0)	5580.11 (5579.07,5581.16)	0.69 (0.53 to 0.86)	0.3 (0.1, 0.8)	24.87 (24.79, 24.96)	0.6 (0.2, 1.5)	30.52 (30.44, 30.59)	0.71 (0.54 to 0.88)
Uterine fibroids	48.1 (35.3, 64.7)	4,059.38 (4,058.22, 4,060.53)	85.2 (62.3, 113.5)	4270.38 (4269.47,4271.29)	0.15 (0.12 to 0.18)	0.1 (0.0, 0.1)	5.02 (4.97, 5.06)	0.1 (0.1, 0.1)	4.98 (4.95, 5.01)	0.03 (−0.01 to 0.07)
Endometriosis	19.1 (13.0, 26.7)	1,460.48 (1,459.82, 1,461.14)	21.0 (14.6, 29.1)	1074.21 (1073.75,1074.67)	−1.02 (−1.07 to −0.97)	1.8 (1.0, 2.8)	134.42 (134.22, 134.62)	1.9 (1.1, 3.0)	99.00 (98.86, 99.14)	−1.01 (−1.06 to −0.96)
Premenstrual syndrome	593.8 (479.5, 710.6)	45,003.04 (44,999.38, 45,006.7)	890.0 (712.0, 1069.1)	45,552.41 (45,549.41,45,555.4)	0.01 (−0.01 to 0.03)	5.0 (3.0, 7.6)	375.91 (375.58, 376.25)	7.4 (4.5, 11.3)	380.31 (380.03, 380.58)	0.01 (−0.01 to 0.03)
Other non-neoplastic gynecological diseases	258.7 (208.8, 314.4)	20,839.49 (20,836.93, 20,842.06)	400.7 (326.8, 482.7)	20,211.52 (20,209.54, 20,213.5)	−0.21 (−0.27 to −0.15)	7.5 (4.9, 10.8)	605.83 (605.39, 606.27)	11.5 (7.5, 16.6)	581.33 (581.00, 581.67)	−0.25 (−0.32 to −0.19)
Location name										
High SDI	136 (121.4, 150.4)	59,174.49 (59,164.52, 59,184.47)	150.7 (135.4, 166.3)	60,212.58 (60,202.81,60,222.35)	0.03 (0 to 0.07)	2.6 (1.9, 3.7)	1,132.25 (1,130.88, 1,133.62)	2.8 (1.9, 3.9)	1,089.70 (1,088.40, 1,091.00)	−0.18 (−0.25 to −0.12)
High-middle SDI	170.4 (151.5, 189.2)	61,975.48 (61,966.1, 61,984.85)	192.0 (172.0, 212.6)	60,715.22 (60,706.4,60,724.04)	−0.14 (−0.17 to −0.11)	3.2 (2.2, 4.5)	1,183.7 (1,182.39, 1,185)	3.6 (2.4, 5.0)	1,085.77 (1,084.62, 1,086.93)	−0.42 (−0.49 to −0.34)
Middle SDI	260.9 (228.5, 291.3)	60,555.05 (60,547.52, 60,562.58)	385 (343.0, 425.8)	61,410.01 (61,403.85,61,416.17)	0 (−0.03 to 0.03)	4.6 (3.2, 6.5)	1,115.4 (1,114.36, 1,116.44)	6.7 (4.7, 9.5)	1,054.03 (1053.23, 1,054.83)	−0.28 (−0.34 to −0.22)
Low-middle SDI	164.1 (146.0, 180.7)	62,922.61 (62,912.77, 62,932.46)	319.3 (286.1, 351.6)	63,916.07 (63,909.04,63,923.11)	0.04 (0.02 to 0.05)	3.1 (2.2, 4.3)	1,214.75 (1,213.36, 1,216.13)	5.8 (4.0, 8.1)	1,168.16 (1,167.20, 1,169.11)	−0.15 (−0.17 to −0.13)
Low SDI	65.2 (58.6, 71.8)	62,263.17 (62,247.59, 62,278.75)	163.6 (146.3, 180.4)	63,092.59 (63,082.67,63,102.51)	0.04 (0.03 to 0.06)	1.4 (1.0, 2.0)	1,437.95 (1,435.53, 1,440.36)	3.5 (2.4, 4.8)	1,401.48 (1,399.98, 1,402.99)	−0.09 (−0.1 to −0.08)

(*Continued*)

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Table 1 (Continued).

Characteristics	Prevalence					DALYs				
Andean Latin America	5.7 (5.1, 6.3)	63,224.63 (63,171.37, 63,277.93)	11.3 (10.2, 12.4)	64,522.97 (64,485.26,64,560.69)	0.06 (0.06 to 0.07)	0.1 (0.1, 0.2)	1,313.74 (1,305.96, 1,321.55)	0.2 (0.2, 0.3)	1,273.78 (1,268.49, 1,279.08)	−0.1 (−0.1 to −0.09)
Australasia	3.3 (2.9, 3.6)	60,451.1 (60,385.44, 60,516.81)	4.4 (3.9, 4.9)	59,556.02 (59,499.69,59,612.4)	−0.05 (−0.05 to −0.04)	0.1 (0.0, 0.1)	1,177.67 (1,168.56, 1,186.83)	0.1 (0.1, 0.1)	1,136.09 (1,128.43, 1,143.79)	−0.1 (−0.12 to −0.08)
Caribbean	5.4 (4.8, 6.1)	60,553.56 (60,501.89, 60,605.25)	7.3 (6.5, 8.1)	60,763.62 (60,719.62,60,807.64)	0.01 (0 to 0.01)	0.1 (0.1, 0.1)	1,098.45 (1,091.41, 1,105.53)	0.1 (0.1, 0.2)	1,065.76 (1,059.95, 1,071.59)	−0.09 (−0.1 to −0.08)
Central Asia	9.6 (8.4, 10.8)	59,784.38 (59,745.07, 59,823.71)	14.8 (13.1, 16.5)	60,054.01 (60,023.25,60,084.78)	0.01 (0 to 0.02)	0.2 (0.1, 0.2)	1.069.95 (1.064.66, 1,075.26)	0.3 (0.2, 0.4)	1,048.9 (1,044.88,1,052.94)	−0.02 (−0.04 to −0.01)
Central Europe	17.8 (15.5, 20.1)	57,392.45 (57,365.7, 57,419.21)	15.2 (13.3, 17.1)	57,033.99 (57,004.27,57,063.73)	−0.02 (−0.05 to 0)	0.3 (0.2, 0.4)	830.06 (826.85, 833.27)	0.2 (0.1, 0.3)	785.84 (782.40, 789.31)	−0.16 (−0.21 to −0.1)
Central Latin America	24.4 (21.4, 27.2)	61,011.7 (60,986.69, 61,036.71)	42.2 (37.5, 46.7)	61,695.75 (61,677.13,61,714.38)	0.03 (0.02 to 0.04)	0.4 (0.3, 0.6)	1,059.01 (1,055.67, 1,062.37)	0.7 (0.5, 0.9)	959.66 (957.34, 961.99)	−0.2 (−0.28 to −0.12)
Central Sub-Saharan Africa	7.2 (6.4, 7.9)	62,793.11 (62,745.55, 62,840.7)	19.6 (17.5, 21.6)	63,778.66 (63,749.66,63,807.67)	0.04 (0.01 to 0.06)	0.2 (0.1, 0.2)	1,639.00 (1,631.16, 1,646.88)	0.5 (0.3, 0.7)	1,597.35 (1,592.66, 1,602.04)	−0.08 (−0.09 to −0.07)
East Asia	189.2 (165.1, 213.5)	58,250.2 (58,241.74, 58,258.67)	192.7 (169.0, 217.2)	56,503.45 (56,495.19,56,511.72)	−0.23 (−0.29 to −0.16)	3.4 (2.4, 4.8)	1,085.29 (1,084.12, 1,086.47)	3.2 (2.2, 4.6)	909.34 (908.31, 910.37)	−0.83 (−0.98 to −0.69)
Eastern Europe	38.2 (34.7, 41.7)	67,790.39 (67,768.71, 67,812.08)	34.5 (31.8, 37.3)	67,868.66 (67,844.92,67,892.4)	−0.01 (−0.02 to 0)	0.7 (0.5, 1)	1,273.51 (1,270.56, 1,276.46)	0.7 (0.5, 0.9)	1,264.65 (1,261.52, 1,267.79)	0.02 (0.01 to 0.04)
Eastern Sub-Saharan Africa	24.6 (22.0, 27.3)	61,777.94 (61,752.4, 61,803.5)	63.3 (56.4, 70.3)	62,883.27 (62,867.26,62,899.28)	0.06 (0.05 to 0.07)	0.6 (0.4, 0.8)	1,525.39 (1,521.26, 1,529.52)	1.4 (1.0, 1.9)	1,476.33 (1,473.82, 1,478.85)	−0.08 (−0.09 to −0.08)
High-income Asia Pacific	26 (22.9, 29.2)	56,551.31 (56,529.51, 56,573.12)	21.7 (19.0, 24.4)	55,730.02 (55,705.66,55,754.39)	−0.11 (−0.19 to −0.04)	0.4 (0.3, 0.6)	886.07 (883.34, 888.80)	0.3 (0.2, 0.5)	811.81 (808.90, 814.74)	−0.42 (−0.54 to −0.29)
High-income North America	39.8 (34.9, 44.8)	52,555.54 (52,539.11, 52,571.98)	48.1 (42.4, 53.8)	56,275.03 (56,259.05,56,291.01)	0.2 (0.13 to 0.28)	0.7 (0.5, 1.0)	878.78 (876.68, 880.89)	0.7 (0.5, 1.0)	803.66 (801.76, 805.56)	−0.41 (−0.53 to −0.29)
North Africa and Middle East	50.5 (45.4, 55.5)	69,863.35 (69,843.51, 69,883.19)	112.5 (103.2, 121.9)	70,265.65 (70,252.64,70,278.65)	0 (−0.01 to 0.01)	1.3 (0.9, 1.8)	1,859.12 (1,855.83, 1,862.42)	2.9 (2.0, 4.1)	1812.41 (1810.32,1814.49)	−0.09 (−0.1 to −0.09)
Oceania	0.8 (0.7, 0.9)	53,883.52 (53,762.23, 54,005.04)	1.8 (1.6, 2.1)	54,046.04 (53,967.71,54,124.46)	0.01 (0 to 0.02)	0.0 (0.0, 0.0)	1,041.02 (1,023.99, 1,058.30)	0.0 (0.0, 0.0)	1010.38 (999.64,1021.23)	−0.09 (−0.1 to −0.08)
South Asia	158.1 (141.1, 173.6)	64,300.59 (64,290.38, 64,310.79)	321.5 (287.2, 353.5)	65,536.3 (65,529.11,65,543.48)	0.06 (0.04 to 0.08)	2.7 (1.9, 3.9)	1,146.37 (1,144.99, 1,147.75)	5.2 (3.6, 7.4)	1,074.44 (1,073.52, 1,075.36)	−0.24 (−0.27 to −0.21)
Southeast Asia	67.2 (57.9, 76.0)	57,429.21 (57,415.12, 57,443.3)	107.4 (93.6, 120.5)	58,258.11 (58,247.08,58,269.14)	0.04 (0.04 to 0.05)	1 (0.7, 1.5)	892.1 (890.33, 893.88)	1.6 (1.1, 2.3)	854.30 (852.96, 855.63)	−0.15 (−0.17 to −0.13)
Southern Latin America	7.3 (6.5, 8.1)	59,662.54 (59,619.18, 59,705.92)	10.5 (9.4, 11.7)	59,494.97 (59,458.95,59,531)	−0.02 (−0.03 to −0.02)	0.1 (0.1, 0.2)	1,140.32 (1,134.3, 1,146.36)	0.2 (0.1, 0.3)	1,122.45 (1,117.54, 1,127.37)	−0.06 (−0.08 to −0.04)

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Southern Sub-Saharan Africa	8.2 (7.4, 9.0)	65,883.2 (65,836.63, 65,929.81)	14.2 (12.9, 15.5)	65,488.88 (65,454.65,65,523.12)	−0.01 (−0.02 to 0.01)	0.2 (0.1, 0.3)	1,586.97 (1,579.56, 1,594.40)	0.3 (0.2, 0.5)	1,528.03 (1,522.79, 1,533.28)	−0.1 (−0.12 to −0.08)
Tropical Latin America	23.7 (20.8, 26.4)	60,672.1 (60,647.26, 60,696.95)	36.9 (32.6, 41.2)	59,788.91 (59,769.52,59,808.31)	−0.09 (−0.11 to −0.08)	0.4 (0.3, 0.5)	1,018.73 (1,015.49, 1,021.98)	0.6 (0.4, 0.8)	944.98 (942.56, 947.41)	−0.47 (−0.55 to −0.38)
Western Europe	65.8 (60.2, 71.2)	68,039.65 (68,023.18, 68,056.13)	63.6 (58.3, 69.0)	66,384.49 (66,367.87,66,401.11)	−0.08 (−0.09 to −0.08)	1.5 (1.1, 2.2)	1,576.27 (1,573.78, 1,578.77)	1.4 (1.0, 2.0)	1,473.73 (1,471.29, 1,476.18)	−0.22 (−0.24 to −0.21)
Western Sub-Saharan Africa	24.3 (21.7, 27.1)	61,035.23 (61,009.88, 61,060.59)	68.1 (60.6, 75.7)	61,250.6 (61,235.59,61,265.6)	0 (−0.02 to 0.02)	0.6 (0.4, 0.8)	1,581.61 (1,577.43, 1,585.8)	1.6 (1.1, 2.3)	1,551.4 (1,548.96, 1,553.85)	−0.06 (−0.07 to −0.06)

Abbreviation: DALYs, disability-adjusted life-years.

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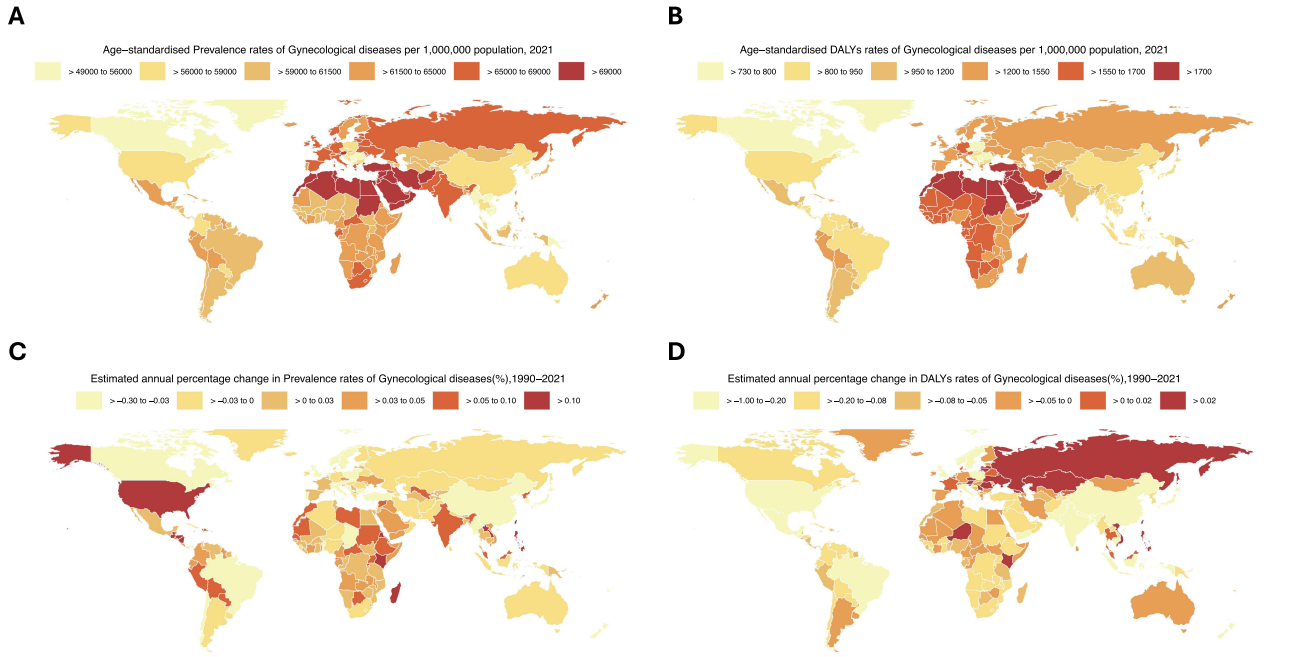

Figure 1 National age-standardised prevalence and DALY rates in 2021, and their estimated annual percentage changes from 1990 to 2021 for non-neoplastic gynecological diseases among women of childbearing age. (**A** and **B**) show the age-standardised rates of prevalence and DALYs, respectively. (**C** and **D**) illustrate the estimated annual percentage changes for age-standardised prevalence rates and DALY rates. Non-neoplastic gynecological diseases included polycystic ovary syndrome (PCOS), genital prolapse, female infertility, uterine fibroids, endometriosis, premenstrual syndrome (PMS), and other non-neoplastic gynecological diseases.
Abbreviation: DALY, disability-adjusted life years.

Eastern Europe, its highest DALY rate was recorded in Southern Sub-Saharan Africa (14.8). (Tables S2–S8 and Figure S1A).

The three-decade (1990–2021) analysis revealed divergent trajectories in age-standardised global disease burdens: PCOS (EAPC = 0.74), female infertility (0.69), and uterine fibroids (0.15) exhibited sustained upward prevalence trends, contrasting sharply with the marked decline genital prolapse (−0.96), endometriosis (−1.02), and other non-neoplastic gynecological diseases (−0.21). The EAPC for PMS (0.01) showed no significant change. On the other hand, the global ASDRs exhibited divergent trends among gynecological conditions, with PCOS (0.72) and female infertility (0.71) showing significant increases, whereas genital prolapse (−0.96), endometriosis (−1.01) and other non-neoplastic gynecological disorders (−0.25) demonstrated marked declines. Across the 21 regions, increases in the ASPRs were observed in 19 regions for PCOS, 4 for genital prolapse, 12 for female infertility, 14 for uterine fibroids, 1 for endometriosis, 12 for PMS, and 1 for other non-neoplastic gynecological diseases. Notably, the largest increases were recorded in Southeast Asia (2.30) for PCOS, Eastern Europe (0.68) for genital prolapse, Andean Latin America (8.19) for female infertility, Tropical Latin America (1.20) for uterine fibroids, Eastern Europe (0.33) for endometriosis, High-income North America (0.53) for PMS, and Eastern Sub-Saharan Africa (0.03) for other non-neoplastic gynecological diseases. Similarly, the ASDR rose in 19 regions for PCOS, 1 for genital prolapse, 12 for female infertility, 3 for uterine fibroids, 1 for endometriosis, 10 for PMS, and 4 for other non-neoplastic gynecological diseases. The most substantial DALY increases were found in Southeast Asia (2.26) for PCOS, Eastern Europe (0.67) for genital prolapse, Andean Latin America (8.08) for female infertility, East Asia (1.45) for uterine fibroids, Eastern Europe (0.33) for endometriosis, High-income North America (0.52) for PMS, and Western Sub-Saharan Africa (0.04) for other non-neoplastic gynecological diseases (Tables S2–S8 and Figure S1B).

At the national level, the highest ASPR and ASDR for PCOS, genital prolapse, female infertility, endometriosis, and PMS were observed in Italy, Paraguay, Djibouti, Niger, and Pakistan, respectively. For uterine fibroids and other non-neoplastic gynecological diseases, the peak prevalence rates were recorded in Latvia and Yemen, whereas Guyana and Qatar exhibited the highest DALY rates. Notably, the most pronounced annual percentage increases in both prevalence

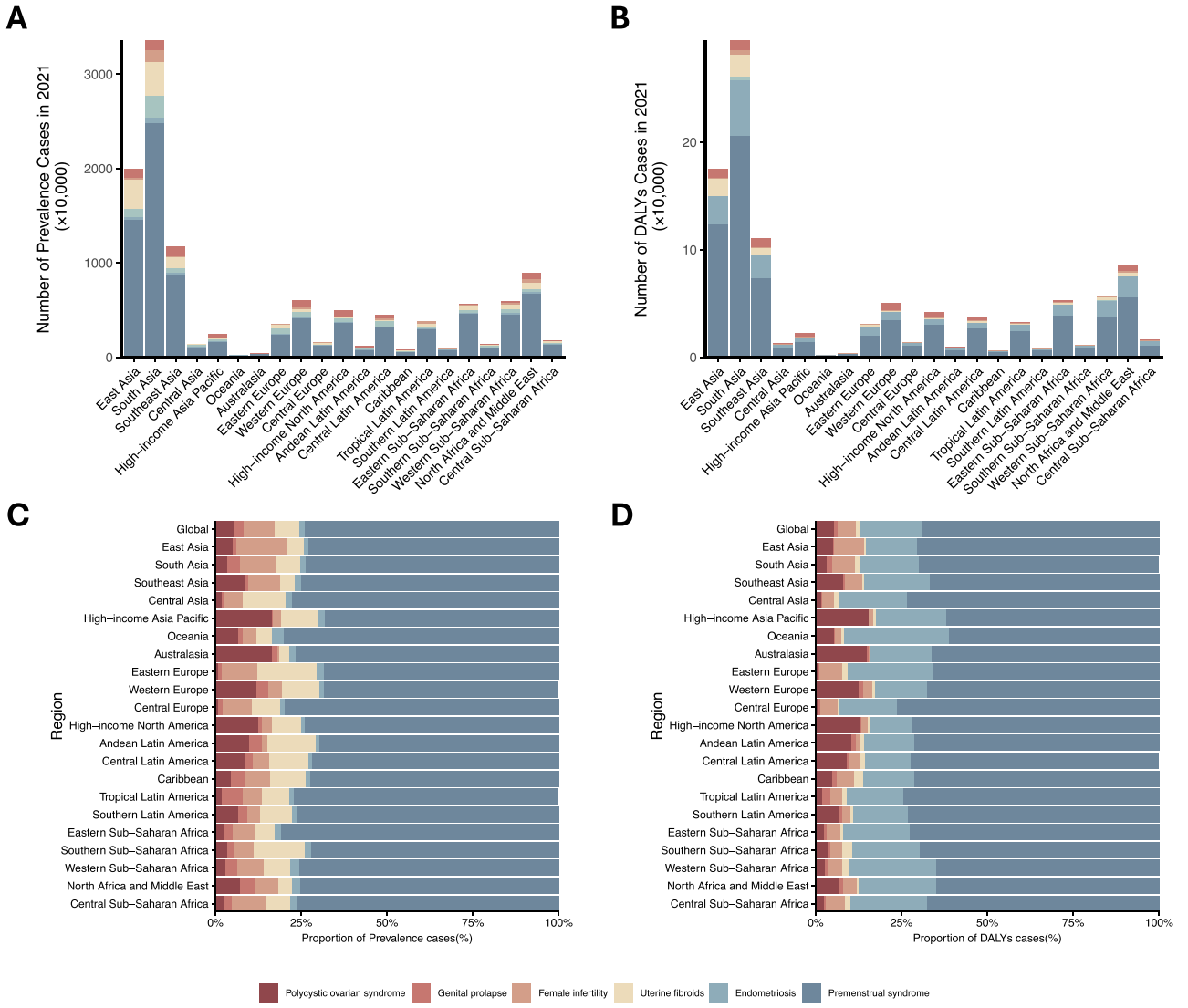

Figure 2 Numbers and proportions of prevalence cases and DALYs contributed by 21 GBD regions, for non-neoplastic gynecological diseases among women of childbearing age, in 2021. (**A**) shows the number of prevalence cases, and (**B**) displays the corresponding DALYs for each disease. (**C** and **D**) show the proportions of prevalence cases and DALYs accounted for by each disease. Non-neoplastic gynecological diseases included polycystic ovary syndrome (PCOS), genital prolapse, female infertility, uterine fibroids, endometriosis, premenstrual syndrome (PMS), and other non-neoplastic gynecological diseases.
Abbreviation: DALY, disability-adjusted life years.

and DALY rates were seen in Maldives for PCOS (EAPC = 3.39 for both), Ecuador for female infertility (9.31 and 9.13), Iceland for endometriosis (1.22 and 1.23), the United States for PMS (0.61 and 0.60), and Taiwan (Province of China) for other non-neoplastic gynecological diseases (1.20 and 0.60). Additionally, for genital prolapse and uterine fibroids, the fastest rises in prevalence occurred in the Russian Federation (0.88) and Brazil (1.22), while the most significant DALY increases were observed in Poland (0.86) and Cabo Verde (2.38), respectively (Tables S9–S15 and Figures S2–S8).

Age-Group Disparities in the Burden of Non-Neoplastic Gynecological Diseases

Our study reveals a consistent global age distribution pattern for both prevalence and DALY metrics of the seven specific and overall non-neoplastic gynecological diseases among WCBA. In 2021, the absolute numbers and rates for most conditions—including PMS, female infertility, uterine fibroids, PCOS, endometriosis, and other gynecological disorders—increased with age, peaking in the 35–44 age group before declining (Figure 3A and B). Moreover, PMS consistently exhibited the highest prevalence values and rates across all age groups. Other non-neoplastic gynecological diseases had

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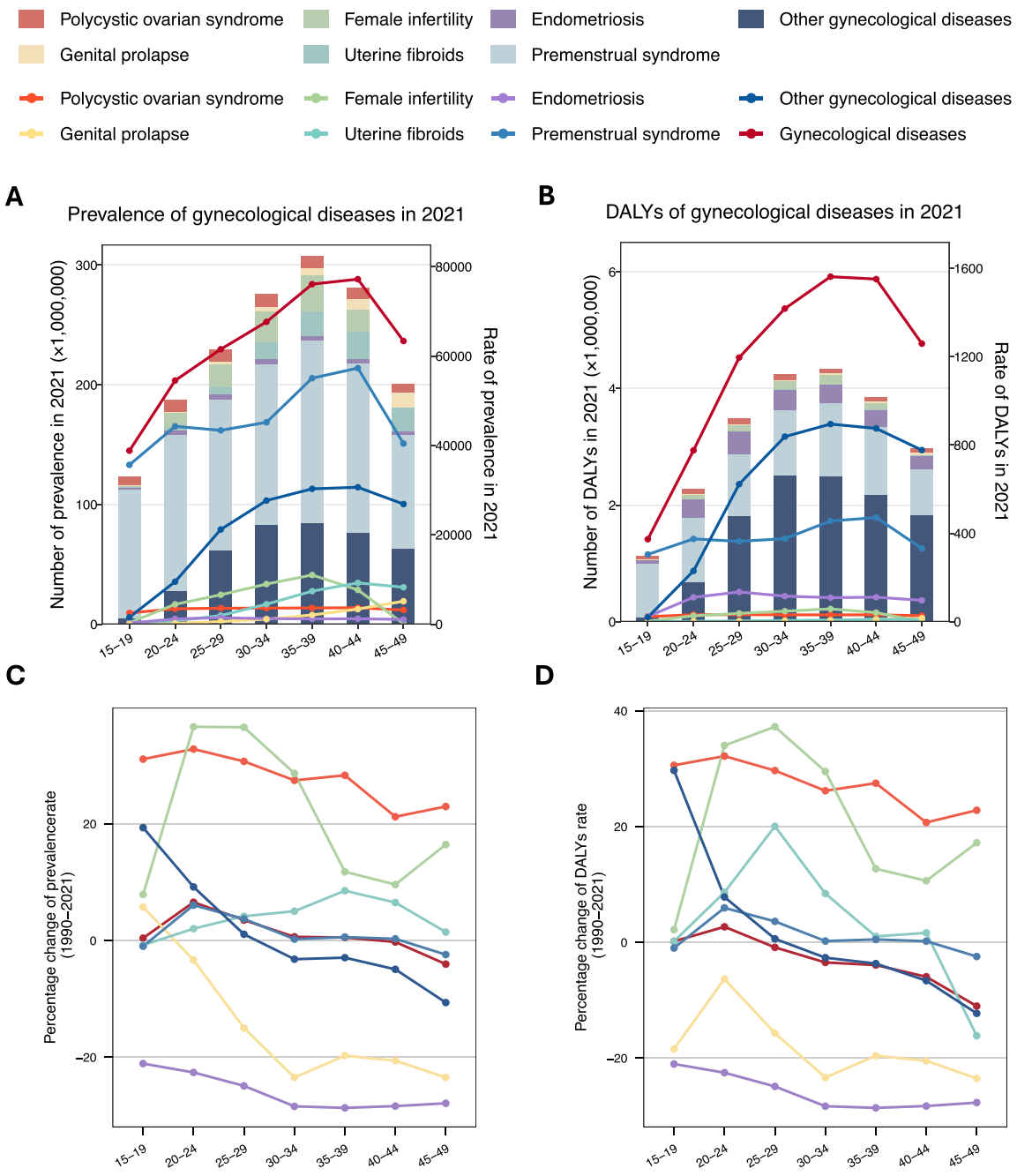

Figure 3 The cross-sectional (2021) and longitudinal trends (1990–2021) of prevalence and DALYs of non-neoplastic gynecological diseases among women of child-bearing age. (**A**) presents the numbers and rates of prevalence, and (**B**) shows the numbers and rates of DALY. (**C** and **D**) depict the percentage changes in prevalence rates and DALY rates over time. Non-neoplastic gynecological diseases included polycystic ovary syndrome (PCOS), genital prolapse, female infertility, uterine fibroids, endometriosis, premenstrual syndrome (PMS), and other non-neoplastic gynecological diseases.
Abbreviation: DALY, disability-adjusted life years.

the highest numbers and rates of DALYs in each age group except 15–19 and 20–24 years. Although the prevalence numbers and rates of endometriosis were low in each age group, the DALYs were high. Between 1990 and 2021, the burdens of PCOS, genital prolapse, uterine fibroids, endometriosis, PMS, other non-neoplastic gynecological diseases, and overall non-neoplastic gynecological diseases demonstrated a declining trend. In contrast, female infertility exhibited a fluctuating upward trend with increasing female age. Notably, the most pronounced rises in prevalence and DALY rates

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for overall non-neoplastic gynecological diseases, PCOS, and female infertility were concentrated in the 15–19 and 20–24 age groups (Figure 3C and D). These trends highlight a growing impact of these conditions on younger women.

The Association Between ASR, EAPC, and SDI

Our study indicated that from 1990 to 2021, an increase in SDI across 21 regions corresponded with a general decline in the overall ASPR of non-neoplastic gynecological diseases. Specifically, as SDI rose, the prevalence rates for genital prolapse, female infertility, endometriosis, and other gynecological conditions tended to decrease, whereas PCOS and uterine fibroids showed upward trajectories. PMS displayed a distinctive pattern by initially rising and then declining once SDI reached 0.7. A comparable trend was observed for the overall ASDR, which decreased with increasing SDI; this pattern held for genital prolapse, female infertility, uterine fibroids, endometriosis, and other non-neoplastic gynecological diseases, though PCOS exhibited an opposing trend. Notably, the DALY rate for PMS increased with SDI until about 0.7, then reversed (Figure 4).

In 2021, when examining 204 countries and territories, the overall ASPR of non-neoplastic gynecological diseases generally declined as SDI increased, only to rise again when SDI exceeded 0.7. Genital prolapse and other non-neoplastic gynecological diseases mirrored this pattern. A similar pattern was observed for genital prolapse and other non-neoplastic gynecological diseases. In contrast, female infertility and PMS initially increased with rising SDI but started to decline after SDI exceeded 0.7. PCOS and uterine fibroids exhibited a continuous upward trend with increasing SDI, whereas endometriosis showed a persistent decline. The overall ASDR mirrored the prevalence trend, with most conditions following the same pattern, except for uterine fibroids (Figure S9–S15).

Furthermore, between 1990 and 2021, countries and territories with middle SDI experienced the most rapid increases in the ASPR for overall non-neoplastic gynecological diseases, PCOS, uterine fibroids, and PMS, as well as significant rises in the DALY rates for PCOS and PMS. Conversely, regions with either low or high SDI saw more modest declines in the prevalence and DALY rates of genital prolapse and endometriosis (Figure S9–S15).

Discussion

This study comprehensively examines the prevalence and DALYs associated with non-neoplastic gynecological diseases among WCBA on a global scale from 1990 to 2021. The key observations are as follows: First, the overall global ASPR of non-neoplastic gynecological diseases remained relatively stable over the study period, while the ASDR experienced a significant decline. Secondly, PCOS, female infertility, uterine fibroids showed annual increases in ASPR, while PCOS, female infertility also increased in ASDR. Third, ASR for PMS, female infertility, uterine fibroids, PCOS, endometriosis, and other gynecological disorders increased with age and peaked in the 35–44 age group. Lastly, ASPRs of genital prolapse, female infertility, endometriosis, and other non-neoplastic gynecological diseases generally increased with higher SDI, while PMS showed an initial rise before declining at an SDI of approximately 0.7.

Consistent with our results showing increasing ASPRs and ASDRs for PCOS, female infertility, and uterine fibroids over the past three decades. Our findings are consistent with previous reports, especially the increased prevalence of PCOS, female infertility and uterine fibroids in the WCBA, emphasizing the concern for reproductive health issues in this population.[24–26] The widespread obesity epidemic appears to be a key contributor, as research has demonstrated that various phenotypes of adolescent obesity considerably raise the risk of developing PCOS.[27,28] Meanwhile, obesity is associated with ovulation dysfunction and female infertility.[29] Hyperandrogenism is a significant risk factor in female reproductive dysfunction. As a hallmark feature of PCOS, excessive androgen levels induce premature luteinization, impair dominant follicle selection, and ultimately disrupt ovulation.[30,31] In addition, elevated androgens can lead to infertility by up regulating the expression of androgen receptors and its co-regulatory proteins in the endometrium and disrupting the critical window period for embryo implantation.[32] Although lacking evidence for the association between androgens and uterine fibroids, estrogen and progesterone are considered protective factors of uterine fibroids.[33,34] Notably, epidemiological evidence of elevated androgen concentrations in perimenopausal women aligns with our findings,[35] further underscoring the broader implications of androgen excess in female reproductive disorders. Moreover, evidence suggests that improved lifestyle practices associated with rapid socioeconomic development can mitigate the prevalence of these disorders.[36] For instance, moderate aerobic exercise has been shown to temporarily

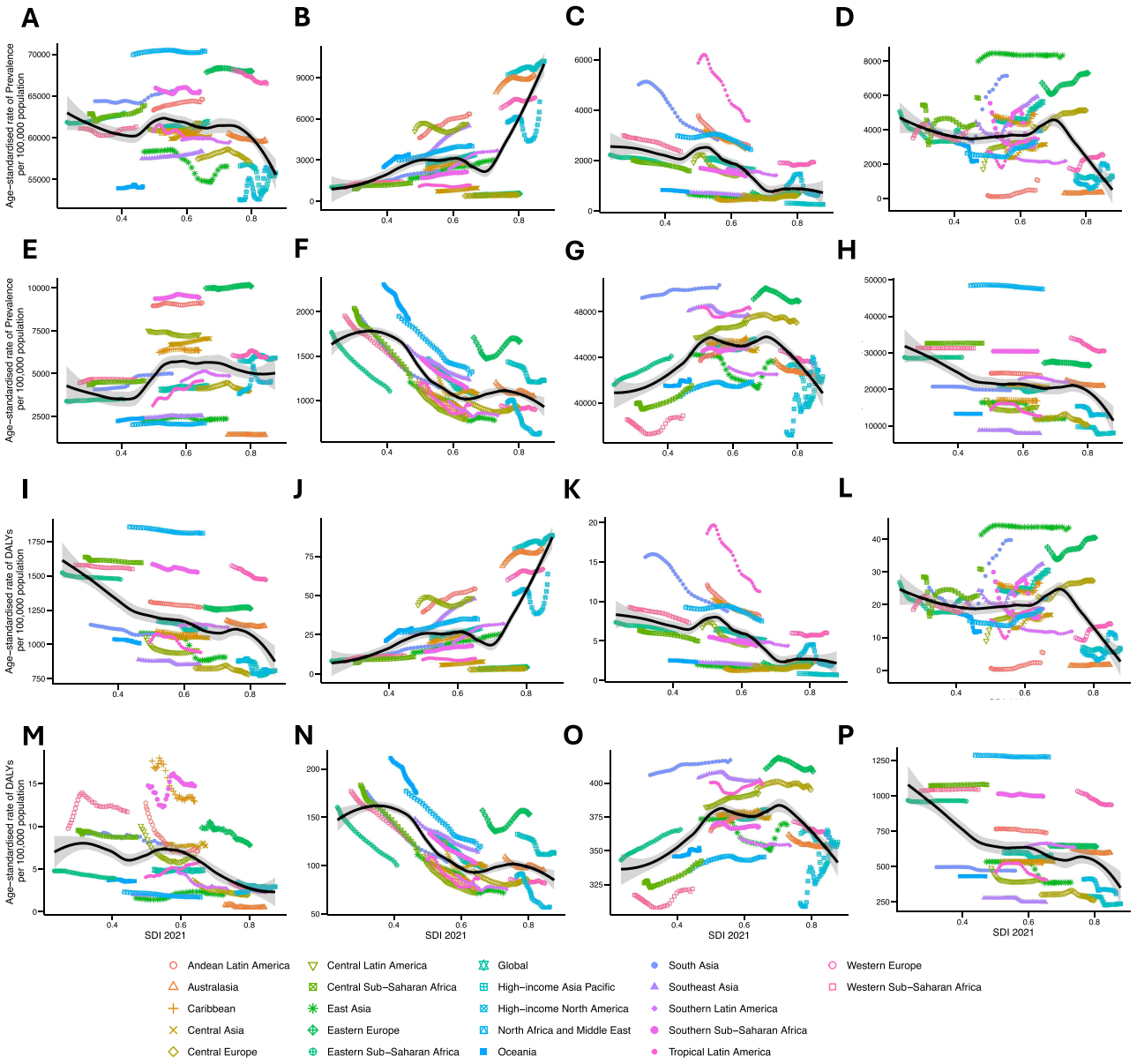

Figure 4 Age-standardised rates of prevalence and DALYs of each gynecological disease among women of childbearing age, globally and for 21 GBD regions, by SDI (2021), from 1990 to 2021. (**A**–**H**) show age-standardised prevalence rates for overall non-neoplastic gynecological diseases, polycystic ovary syndrome (PCOS), genital prolapse, female infertility, uterine fibroids, endometriosis, premenstrual syndrome (PMS), and other non-neoplastic gynecological diseases, while (**I**–**P**) present age-standardised DALY rates for these diseases. The solid line represents expected values based on SDI and disease rates, with the shaded area indicating the 95% confidence interval (CI). Points above the solid line indicate a higher-than-expected burden, while points below it suggests a lower-than-expected burden.
Abbreviations: DALY, disability-adjusted life years; GBD, Global Burden of Disease Study; SDI, socio-demographic index.

improve insulin sensitivity in PCOS, while more intense aerobic and resistance training further enhance both insulin sensitivity and androgen abnormalities.[37] Several epidemiological investigations have also established significant associations between these risk factors and the incidence of non-neoplastic gynecological diseases.[38–41] However, given the heterogeneity and limited statistical power of existing studies, further research is necessary for a better understanding of the contribution of modifiable risk factors to these diseases, which is a key step in formulating targeted early prevention strategies.[42]

In line with our findings that higher ASPRs of PCOS, female infertility, and uterine fibroids were observed in higher-SDI regions, which coincide with greater prevalence of Western dietary patterns and sedentary lifestyles reported in previous studies.[43] These factors have been associated with obesity and insulin resistance, which may partially

contextualize the regional differences observed.[44,45] Additionally, socioeconomic progress has enhanced diagnostic and treatment technologies, allowing for earlier detection and leading to higher reported incidence rates. In contrast, low-SDI regions may underestimate the prevalence due to limited healthcare resources and less advanced diagnostic technologies. For example, our study found that Eastern Europe exhibits the highest ASPR of uterine fibroids, while Brazil shows the most significant annual percentage increase in prevalence. Despite Brazil's substantial progress in enhancing disease diagnosis and reducing female mortality through rapid economic development and improvements in primary healthcare services,[46] income inequality and health disparities have resulted in lower levels of healthcare accessibility for women in rural areas.[47] Therefore, more resources should be allocated to the healthcare sector to expand primary healthcare coverage, reduce urban-rural disparities in medical services, and improve the technical expertise of healthcare professionals.

In addition, our results demonstrated a global decline in ASDRs for most non-neoplastic gynecological diseases from 1990 to 2021, with the notable exception of PCOS and female infertility. This declining trend aligns with the period during which global health initiatives promoting healthier lifestyles were widely implemented. These initiatives promote healthy lifestyle choices such as smoking and alcohol cessation, a balanced diet, and regular physical activity.[48] However, PCOS and female infertility have experienced stable increases in many regions compared to the other non-neoplastic gynecological diseases, indicating the need for more standardized clinical guidelines and policy adjustments to address this issue effectively. The WHO Global Strategy for Women's, Children's, and Adolescents' Health (2016–2030) has contributed to raising awareness of non-neoplastic gynecological diseases and encouraging early medical consultations among women. However, targeted strategies and measures are still lacking to address the increasing burden of PCOS and female infertility.[8] Currently, the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome provides recommendations for the prevention, diagnosis, and management of PCOS. However, this guideline may not be fully adaptable to all regions, highlighting the need for region-specific adaptations and policy implementations.[49] Existing research reported that the incidence of PCOS is the highest among adolescents aged 15 to 19, suggesting that this group is a key target for the early diagnosis and treatment of PCOS.[50] However, characteristics such as polycystic ovary morphology, irregular menstruation and acne may confuse PCOS with the normal characteristics of adolescent development.[51] Therefore, healthcare providers must actively carry out primary prevention and formulate accurate diagnostic criteria for differentiation. Meanwhile, the strong heritability of PCOS provides new opportunities for epigenetic diagnosis and offers clearer criteria for identifying PCOS.[52] Furthermore, therapies targeting specific methylation sites to restore aberrant gene expression may enhance the potential for secondary prevention of PCOS.[53] For female infertility, DALYs peak from 20 to 34 years old in WCBA, linked to fertility demands. By the end of the reproductive age, the relative burden of female infertility diminishes due to reduced fertility demands and a shift in health priorities. Although female infertility does not directly result in mortality, it significantly contributes to the burden of disease by impacting fertility, psychological well-being, and social standing.[54] It is estimated that 30–40% of women undergoing fertility treatments experience clinically significant levels of depression or anxiety.[55,56] Psychological interventions for women with infertility have been shown to significantly improve mental health, reduce fertility-related stress, and increase pregnancy rates.[57,58] Therefore, healthcare providers, particularly in low-SDI regions, should prioritize addressing the mental health needs of individuals with female infertility.

Interestingly, our study findings indicate that PMS has the highest ASPR, peaking in the 40–44 age group. This pattern may be related to hormonal fluctuations during the menopausal transition, as suggested by previous clinical and epidemiological studies.[59,60] The Seattle Midlife Women's Health Study (SMWHS) further highlights that perimenopausal women bear significant responsibilities and juggle multiple roles,[61] with 86% of women moderately or highly exposed to stressful life events. Therefore, hormone therapy instead of surgical operation can be regarded as a conservative treatment option during the perimenopausal to menopausal transition period.[62] Moreover, policymakers should pay attention to the mental health issues of perimenopausal women.

Global data from 1990 to 2021 indicate a sustained decline in the ASDRs for non-neoplastic gynecological diseases among WCBA, with endometriosis and genital prolapse demonstrating the most pronounced reductions. This trend is strongly associated with socioeconomic development, as evidenced by the negative correlation between the ASDRs and the SDI. The declining ASDRs for endometriosis and genital prolapse coincides with advances in diagnostic imaging,

laparoscopic techniques and surgical management reported in previous studies.[9,63–65] These developments may help contextualize the observed reductions in disease burden. However, the negative association between SDI and the ASDRs suggests that both endometriosis and genital prolapse still present room for improvement. Health organizations worldwide must enhance interventions in low- and middle-income regions by improving diagnostic capabilities, promoting regional economic development, and addressing income inequality to mitigate health disparities in these areas.

Limitations

The limitations of our study include several key aspects. First, the reliability of GBD data is affected by discrepancies in national surveillance systems. Notably, many low- and middle-income countries exhibit a high rate of missing primary data, which diminishes the overall quality and accessibility of the 2021 estimates for gynecological disease burden. Second, our analysis was confined to six common conditions—PCOS, genital prolapse, female infertility, uterine fibroids, endometriosis, and PMS—leaving the impact of emerging non-neoplastic gynecological diseases less well understood. Third, evolving diagnostic techniques over different time periods may have introduced biases in historical records, thereby undermining the temporal comparability of disease trends among WCBA. Consequently, caution is needed when interpreting these trends. Future research should aim to integrate more comprehensive data sources and standardize diagnostic criteria across regions and time periods to enhance the robustness and comparability of burden assessments.

Conclusion

Non-neoplastic gynecological diseases remain a major global public health challenge among WCBA. Between 1990 and 2021, while overall ASPRs remained relatively stable and ASDRs declined worldwide, the prevalence of PCOS, female infertility, and uterine fibroids increased markedly, with corresponding increases in DALYs for PCOS and female infertility. These contrasting patterns suggest that existing prevention and management efforts have been uneven across disease subtypes. Substantial variation was observed by age and socio-demographic development, with the burden peaking during mid-reproductive ages and remaining particularly high in low- and middle-income regions, where constrained healthcare capacity and delayed diagnosis continue to amplify disease impact. These findings highlight the importance of developing disease- and age-specific prevention strategies, improving early detection, and expanding access to reproductive healthcare. Greater emphasis on mental health support for women affected by infertility, together with efforts to reduce health system inequalities in resource-limited settings, will be essential to lessen the long-term global burden of non-neoplastic gynecological diseases.

Abbreviations

WCBA, women of childbearing age; GBD, Global Burden of Diseases, Injuries, and Risk Factors Study; PCOS, polycystic ovary syndrome; PMS, premenstrual syndrome; DALYs, disability-adjusted life years; ASR, age-standardised rate; EAPC, estimated annual percentage changes; SDI, socio-demographic index.

Data Sharing Statement

The data used in this study were obtained from the Global Burden of Disease (GBD) 2021 study and are publicly available through the Global Health Data Exchange (GHDx) at https://ghdx.healthdata.org/gbd-results-tool. As all analyses were conducted using publicly available, aggregated data, no additional individual-level data are available. Any questions regarding data access can be directed to the corresponding author.

Ethics Approval and Consent to Participate

The University of Washington's Institutional Review Board approved an informed consent exemption for the GBD 2021 study (study number 9060) (https://www.healthdata.org/research-analysis/gbd). As the data are fully de-identified, individual consent was not required. Ethics approval was not required for this study because it was based exclusively on publicly available, anonymized secondary data from the Global Burden of Disease (GBD) 2021 study. According to the Measures for the Ethical Review of Life Science and Medical Research Involving Human Subjects issued by the

National Health Commission of China (February 18, 2023), ethical review is exempt for research using legally obtained public data that does not involve identifiable personal information (Article 32, Items 1 and 2).

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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.

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