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# Global Burden of Inflammatory Bowel Disease Among Women of Reproductive Age From 1990 to 2021 and Future Projections to 2050: A Comprehensive Analysis Using Eight Machine Learning Algorithms

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**Background:** To comprehensively analyze the global burden of inflammatory bowel disease (IBD) among women of reproductive age from 1990 to 2021 and make future projections to 2050.

**Methods:** We utilized GBD2021 data to conduct a comprehensive analysis of IBD burden across five social-demographic index (SDI) regions, 21 GBD regions, and 204 countries. We assessed trends in IBD-related incidence, prevalence, mortality, and disability-adjusted life years (DALYs) and performed decomposition analysis to identify contributing factors. Additionally, we predicted the future trends of IBD burden from 2022 to 2050 using eight machine learning models.

**Results:** From 1990 to 2021, global IBD burden among women of reproductive age showed a slight upward trend in incidence, prevalence, DALYs, and mortality. Population growth was the primary contributor to these increases. Significant regional disparities were observed, with high SDI regions continuing to bear the heaviest burden. While mortality rates declined in high SDI regions due to improved healthcare, low- and lower-middle SDI regions experienced higher mortality due to limited resources and access to diagnostic and treatment options. Age-specific trends revealed a higher burden in older age groups (40–49), while younger women (20–24) in low SDI regions exhibited higher mortality and disability.

**Conclusion:** This study provides in-depth insights into the global burden of IBD among women of reproductive age, which can guide the formulation of targeted prevention and management strategies and rational resource allocation to address the challenges posed by IBD in the future.

**Keywords:** inflammatory bowel disease, women of reproductive age, global burden of disease, regional trend, machine learning

## Introduction

Inflammatory bowel disease (IBD) is a group of chronic inflammatory disorders of the gastrointestinal tract, primarily comprising ulcerative colitis (UC) and Crohn's disease (CD).[1] Typical clinical manifestations of IBD include diarrhea, abdominal pain, and rectal bleeding associated with UC, while Crohn's disease can affect the entire gastrointestinal tract, from the mouth to the anus. In contrast, ulcerative colitis primarily involves the colonic mucosa.[2] Despite the availability of therapeutic interventions that alleviate symptoms, IBD remains largely incurable, with a significant proportion of

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patients ultimately requiring surgical interventions. Moreover, these patients may experience a range of complications, including extra-intestinal manifestations, and disease-specific complications such as strictures, fistulas, and abscesses.[3]

Historically, IBD was regarded as a disease predominantly affecting Western countries, with fewer cases reported in developing regions, reflecting a significant geographical disparity.[4] However, recent decades have seen a rapid rise in the incidence of IBD in emerging industrialized nations. Data from 2019 reported 4.9 million IBD patients globally, with age-standardized prevalence rates rising in 147 countries or regions compared to 1990.[5] The high prevalence, low cure rates, and heterogeneous treatment responses impose a significant burden on healthcare systems worldwide.[6] According to the Lancet Gastroenterology & Hepatology Commission, direct medical costs for IBD patients in high-income countries range from $9000 to $12,000 per person annually as of 2021.[7] Therefore, understanding the evolving epidemiology of IBD is critical for developing effective prevention and treatment strategies, and for guiding public health policies and resource allocation to mitigate the disease burden.

Women's health during the reproductive years is of paramount importance due to its impact on fertility and overall well-being. This period, generally spanning from late adolescence to menopause (approximately ages 15–49), is a critical window for health interventions. Women with autoimmune diseases, such as IBD, are at increased risk for pregnancy-related complications, including potentially life-threatening conditions.[8] Previous studies have shown that IBD significantly increases the risk of gestational diabetes.[9] The complex interplay between pregnancy's physiological changes and IBD may influence placental development, gut microbiota composition, and treatment responses.[10] Therefore, assessing the burden of IBD in women of reproductive age is especially important. However, current research on the disease burden in this specific demographic remains sparse, and there is a lack of systematic analysis on a global scale.

This study aims to fill this gap by conducting a comprehensive analysis of the global burden of IBD among women of reproductive age from 1990 to 2021 using the most recent data from the Global Burden of Disease (GBD) 2021 database. Additionally, this study will employ several machine learning techniques, including random forests, support vector machines, and neural networks, to provide prospective projections of the IBD burden for the next 40 years (2022–2050). The results from this study are expected to offer valuable insights into future trends in IBD and provide evidence-based recommendations for targeted intervention strategies tailored to different regions and populations, ultimately contributing to the improvement of global women's health.

# Methods

## Data Sources and Study Design

This study utilized data from the Global Burden of Disease Study 2021 (GBD 2021) database (https://ghdx.healthdata.org/gbd-2021), which provides comprehensive estimates for 204 countries and territories, 371 diseases and injuries, and 88 risk factors. We extracted data on incidence, prevalence, disability-adjusted life years (DALYs), and mortality for inflammatory bowel disease (IBD) among women of reproductive age from 1990 to 2021. Both absolute numbers and rates per 100,000 population were obtained.[11–14]

## Disease Definition and Classification

According to the GBD 2021 classification system, IBD is categorized as a level 3 disease under digestive diseases, which falls under the level 1 category of non-communicable diseases. In the International Classification of Diseases (ICD)-10, IBD is primarily coded as K50 (Crohn's disease) and K51 (Ulcerative colitis). In ICD-11, the corresponding codes are DD70 (Crohn disease) and DD71 (Ulcerative colitis).[11,12]

## Estimated Annual Percentage Change (EAPC) Model

To quantify long-term trends in the age-standardized rates (ASRs) of IBD burden, we calculated the estimated annual percentage change (EAPC) using a log-linear regression model. The natural logarithm of ASR was regressed on calendar year: $\ln(ASR) = \alpha + \beta \times year + \varepsilon$, where $\varepsilon$ represents the error term. The EAPC was then calculated as $100 \times (e\beta - 1)$, with its 95% confidence interval derived from the standard error of $\beta$.

## Socio-Demographic Index

The socio-demographic index (SDI), developed by GBD researchers, is a composite measure of development status closely associated with health outcomes. It is calculated as the geometric mean of indices of total fertility rate under age 25, mean education for those aged 15 and older, and lag distributed income per capita. SDI values range from 0 (theoretical minimum level of development) to 1 (theoretical maximum level). We applied LOESS smoothing to visualize trends and conducted Spearman's rank correlation tests to quantify the relationship between SDI and IBD burden indicators.

## Decomposition Analysis

To elucidate the factors contributing to global differences in IBD burden, we employed decomposition analysis. This method allows for the disaggregation of overall health disparities into contributions from various factors, including population growth, population aging, and epidemiological changes. This method allows us to determine whether the increase (or decrease) in disease burden stems primarily from demographic changes or from shifts in actual disease risk. This is particularly important for providing a basis for targeted interventions, as it clarifies whether public health efforts should focus on modifying risk factors, addressing demographic transition, or need to address both.

## Ensemble of Eight Advanced Machine Learning Algorithms for Time Series Forecasting

We utilized two authoritative data sources: age-standardized rates from 1990 to 2021 from the Global Burden of Disease (GBD) database, and population data from 1990 to 2050.[15] To enhance model predictive capacity, we conducted extensive feature engineering. Time and population data were standardized to eliminate scale effects. We constructed lag features, including disease rates from the previous one and two years, to capture short-term trends. Additionally, we calculated 3-year moving averages to smooth short-term fluctuations and created interaction terms between population and year to explore their joint effects.

In our study, we employed an ensemble of eight advanced time series prediction methods and machine learning algorithms. The Prophet model was implemented with logistic growth and 15 changepoints, utilizing 10-fold cross-validation and dynamic smoothing constraints. For the ARIMA model, we used auto.arima for parameter selection, incorporating external regression variables and their quadratic terms. The TBATS model was simplified without Box-Cox transformation, employing damped trend methods and square root transformations. Our Elastic Net model balanced L1 and L2 regularization, capturing non-linear relationships through exponential decay and quadratic terms. The ETS model adopted an additive error, additive trend, no seasonality (AAN) approach with carefully tuned smoothing parameters. For the VAR model, we used a first-order lag structure, introducing interaction terms and quadratic components to handle non-linear relationships. The Holt-Winters model was modified with an additive seasonal component and damped forecasting to control long-term prediction uncertainty. Lastly, our improved Theta model incorporated a cyclical fluctuation component with controlled amplitude and growth rate limitations.

This study selects 8 algorithms to construct prediction models, and matches the characteristics of each algorithm in response to the short-term fluctuations, long-term trends, and population-year interaction effects of IBD burden among women of reproductive age, so as to avoid the limitations of a single algorithm. To rigorously evaluate these models, we implemented a 10-fold time series cross-validation strategy. Data from 1990–2010 served as our training set, 2011–2021 as the validation set, and 2022–2050 as the final prediction set. We employed a comprehensive set of six evaluation metrics to assess model performance from multiple perspectives. These metrics included Mean Squared Error (MSE), Mean Absolute Percentage Error (MAPE), Root Mean Square Error (RMSE), Symmetric Mean Absolute Percentage Error (SMAPE), Coefficient of Determination ($R^2$), and Mean Absolute Scaled Error (MASE). This multi-faceted evaluation approach allowed us to thoroughly assess each model's predictive performance, providing insights into both absolute and relative errors, explanatory power, and performance relative to simple prediction methods.

## Statistical Analysis

All data processing, statistical analyses, and visualizations were performed using R version 4.4.1. We calculated 95% uncertainty intervals (UIs) for all estimates using the 2.5th and 97.5th percentiles of 1000 draws from the posterior

distribution of each estimate. Differences were considered statistically significant if the 95% UIs did not overlap. The work has been reported in line with the strengthening the reporting of cohort, cross-sectional, and case–control studies in surgery (STROCSS) criteria.[16]

# Results

## Global Burden of Inflammatory Bowel Disease Among Women of Reproductive Age

Globally, the burden of IBD among women of reproductive age has remained relatively stable Specifically, incidence, prevalence, DALYs, and mortality have all shown slight increasing trends. In 1990, the global incidence was 60,926 cases (95% UI: 47,520–77,956), which increased to 98,975 cases (95% UI: 75,475–128,649) by 2021. The number of prevalent cases rose from 604,755 (95% UI: 494,158–744,022) to 866,997 (95% UI: 680,024–1,095,078). DALYs increased from 193,091 (95% UI: 142,652–251,820) to 281,580 (95% UI: 214,213–359,521), while the number of deaths grew from 1737 (95% UI: 1073–2342) to 2587 (95% UI: 1796–3330). The annual growth rates for these indicators were 0.62%, 0.43%, 0.46%, and 0.49%, respectively (Figures 1 and 2, Tables 1 and S1–3).

The ASIR of IBD among women of reproductive age globally has shown a slight increase, rising from 4.84 (95% UI: 3.77–6.19) in 1990 to 4.97 (95% UI: 3.79–6.46) in 2021, with an EAPC of 0.22 (95% CI: 0.10–0.34). However, other disease burden indicators, including ASPR, ASDR, and ASMR, demonstrated relatively small changes, despite an overall decreasing trend. Specifically, the ASPR decreased from 49.45 (95% UI: 40.42–60.81) to 43.17 (95% UI: 33.85–54.55), with an EAPC of −0.35 (95% CI: −0.51 to −0.19); the ASDR decreased from 15.46 (95% UI: 11.47–20.12) to 14.16 (95% UI: 10.76–18.08), with an EAPC of −0.28 (95% CI: −0.35 to −0.21); and the ASMR decreased from 0.14 (95% UI: 0.09–0.19) to 0.13 (95% UI: 0.09–0.17), with an EAPC of −0.32 (95% CI: −0.38 to −0.26). These changes indicate a gradual reduction in the global burden of IBD, although the overall magnitude of the change remains modest (Figures 1 and 2, Tables 1 and S1–3).

## Disparities in Inflammatory Bowel Disease Burden Among Reproductive-Age Women Across Sociodemographic Index Regions

Analysis of the burden of IBD among women of reproductive age across the five SDI regions reveals that, in 2021, the High SDI region had the highest burden of IBD. This is reflected in the highest number for incidence, prevalence, and DALYs, which were 38,912 cases (95% UI: 30,094–49,251), 389,202 individuals (95% UI: 308,921–487,792), and 75,867 (95% UI: 54,154–102,734), respectively. Additionally, the ASIR, ASPR, and ASDR were also significantly higher in this region, at 14.93 (95% UI: 11.52–18.97), 142.76 (95% UI: 113.14–179.36), and 27.94 (95% UI: 19.97–37.87), respectively. Although the overall burden in this region has increased less over the past 32 years compared to other regions, the current high burden warrants ongoing attention (Figures 1 and 2, Tables 1 and S1–3).

In contrast, the Low SDI and Low-Middle SDI regions show higher mortality rates from IBD, with death tolls of 740 (95% UI: 396–1049) and 786 (95% UI: 499–1137), respectively, significantly higher than in other regions. The ASMR for these regions was also notably higher, at 0.29 (95% UI: 0.16–0.42) and 0.16 (95% UI: 0.10–0.23), respectively. Over the past 32 years, the Low SDI region has experienced the highest growth rates in incidence, prevalence, DALYs, and mortality, and is the only region where ASIR, ASPR, ASDR, and ASMR all show an increasing trend. This indicates a growing burden of IBD in this region that requires urgent attention. Additionally, while the ASDR and ASMR in the Middle SDI region have shown a decreasing trend, the increases in ASIR and ASPR have been the most pronounced, suggesting that IBD burden continues to rise in this region and further interventions are necessary (Figures 1 and 2, Tables 1 and S1–3).

## Global Disparities in Inflammatory Bowel Disease Among Reproductive-Age Women

In terms of geographic region, among the 21 regions, South Asia had the highest burden of IBD in terms of incidence, prevalence, DALYs, and mortality, with values of 29,476 cases (95% UI: 22,217–39,080), 214,335 individuals (95% UI: 164,319–278,693), 67,327 (95% UI: 47,120–96,585), and 544 (95% UI: 322–957), respectively. In contrast, Oceania had the lowest burden, with incidence, prevalence, DALYs, and mortality figures of 30 cases (95% UI: 22–41), 223 individuals (95%

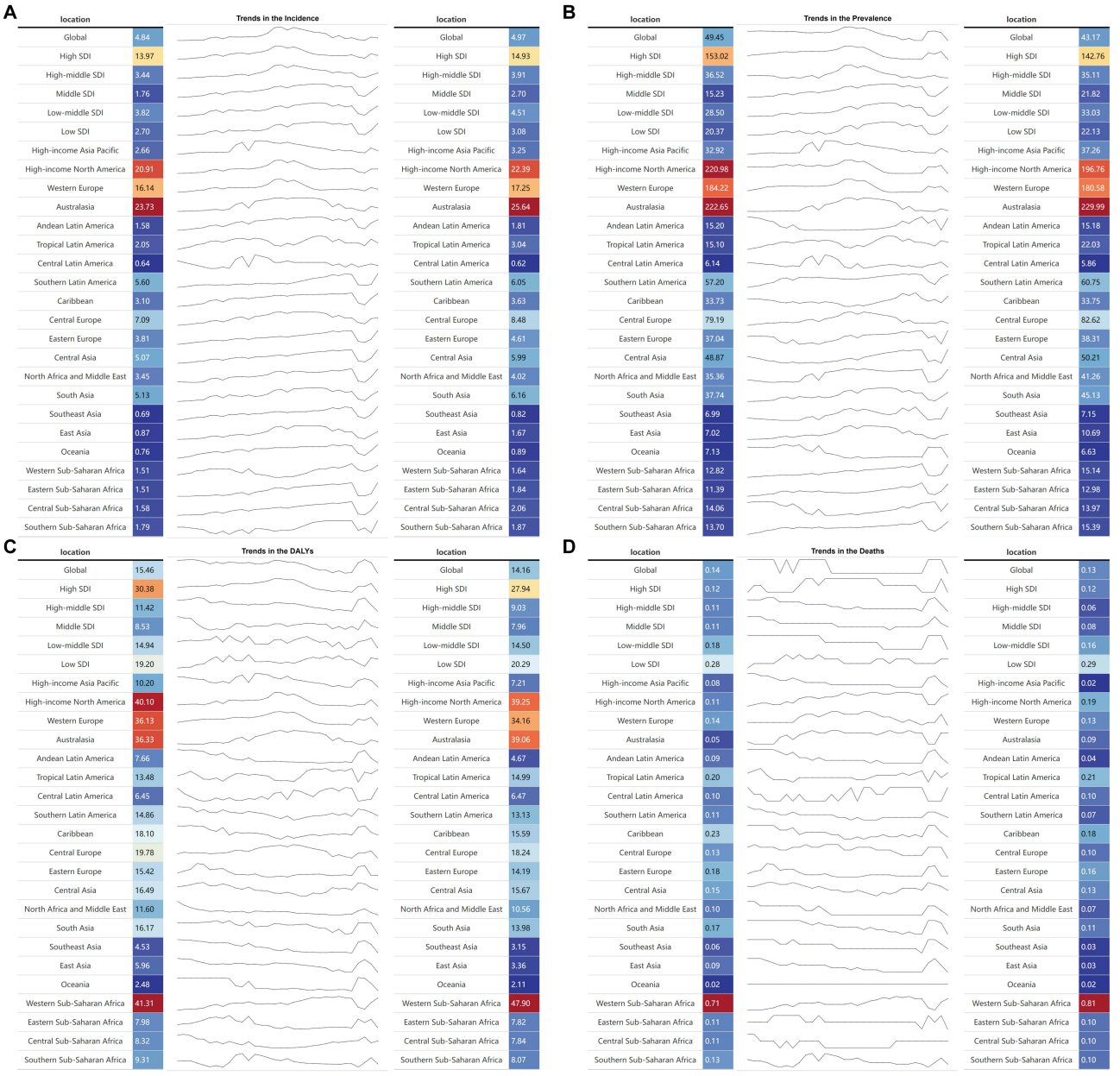


**Figure 1** Trends in Age-Standardized Rates of Inflammatory Bowel Disease Among Women of Reproductive Age, 1990–2021. (**A**) Global, SDI-specific, and regional trends in age-standardized incidence rates. (**B**) Global, SDI-specific, and regional trends in age-standardized prevalence rates. (**C**) Global, SDI-specific, and regional trends in age-standardized DALY rates. (**D**) Global, SDI-specific, and regional trends in age-standardized mortality rates.

UI: 158–310), 69 (95% UI: 42–105), and 1 (95% UI: 0–1), respectively (Tables 1 and S1–3). After age-standardization, Australasia, Western Europe, and High-income North America exhibited higher disease burdens in terms of ASIR and ASPR. Conversely, Western Sub-Saharan Africa displayed higher ASDR and ASMR. Furthermore, Central Latin America had the lowest ASIR and ASPR, while Oceania had the lowest ASDR and ASMR (Figure 1, Tables 1 and S1–3).

Analysis over the past 32 years indicates that incidence has increased in all regions. Central Sub-Saharan Africa exhibited the greatest increase in incidence, with a rise of 2.46%. Western Sub-Saharan Africa saw the largest increases in prevalence, DALYs, and mortality, with growth rates of 2.32%, 2.33%, and 2.30%, respectively. Central Europe was the only region where prevalence declined, with a decrease of −0.02%. High-income Asia Pacific had the largest declines in DALYs and mortality, with reductions of −0.33% and −0.74%, respectively (Figure 2, Tables 1 and S1–3). East Asia experienced the highest increase in both ASIR and ASPR, with EAPC values of 3.09 (95% CI: 2.45–3.74) and 2.46 (95% CI: 1.71–3.22), respectively. Central

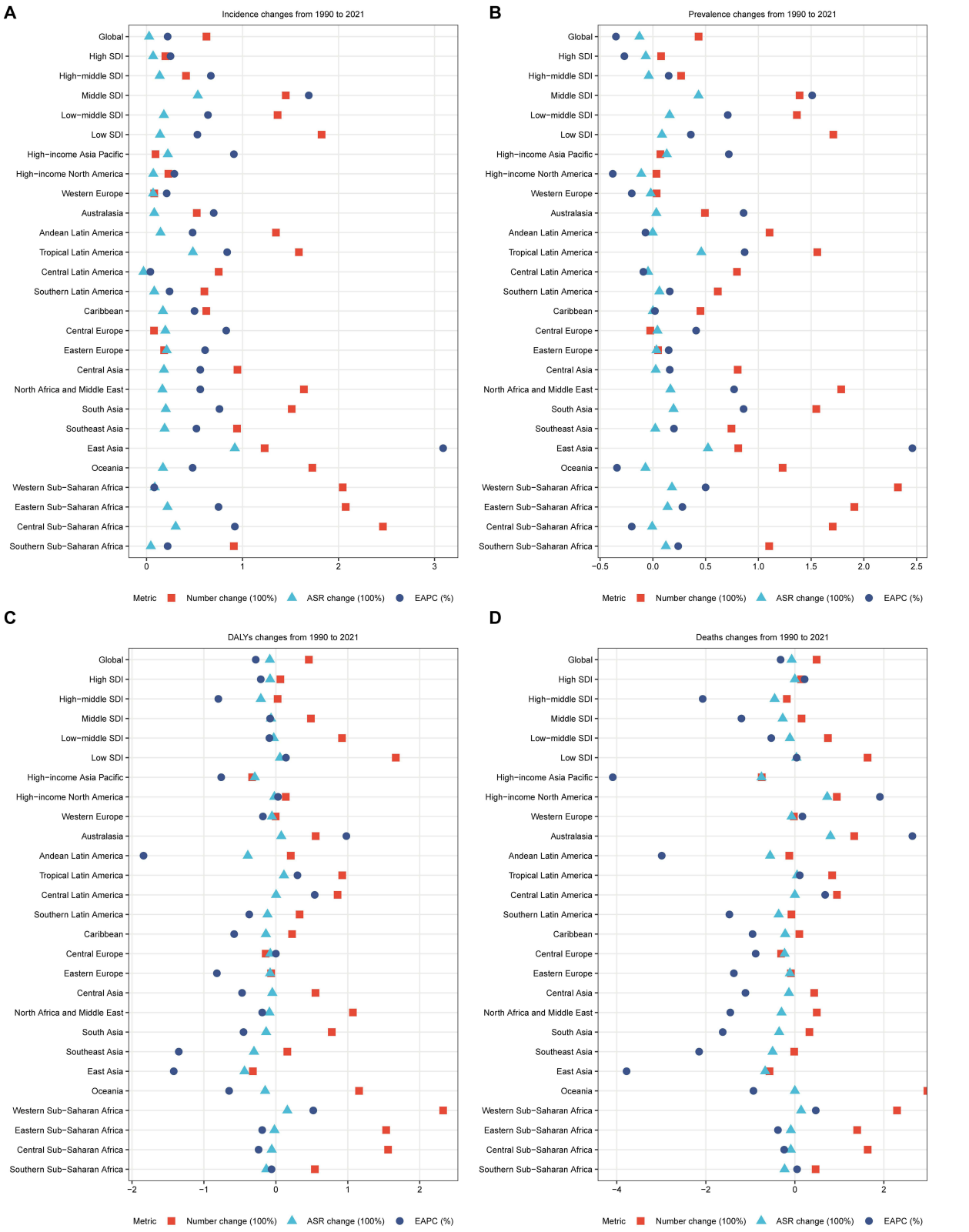


**Figure 2** Percentage Changes and EAPC in Inflammatory Bowel Disease Burden Among Women of Reproductive Age, 1990–2021. (**A**) Global, SDI-specific, and regional changes in incidence numbers, rates, and EAPC. (**B**) Global, SDI-specific, and regional changes in prevalence numbers, rates, and EAPC. (**C**) Global, SDI-specific, and regional changes in DALY numbers, rates, and EAPC. (**D**) Global, SDI-specific, and regional changes in death numbers, rates, and EAPC.

**Table 1** Global Incidence of Inflammatory Bowel Disease Among Women of Reproductive Age in 1990 and 2021, with Trends From 1990 to 2021

| Location | Incidence Cases | | | Incidence Rates | | | |
|---|---|---|---|---|---|---|---|
| | 1990_Numbers (95% UI) | 2021_Numbers (95% UI) | Percentage Change in Case (100%) | 1990_per100000 (95% UI) | 2021_per100000 (95% UI) | Percentage Change in ASRs (100%) | EAPC (95% CI) |
| Global | 60926 (47,520, 77,956) | 98,975 (75,475, 128,649) | 0.62 | 4.84 (3.77,6.19) | 4.97 (3.79,6.46) | 0.03 | 0.22(0.1 to 0.34) |
| Low SDI | 2625 (1962, 3502) | 7412 (5558, 9880) | 1.82 | 2.7 (2.02,3.6) | 3.08 (2.32,4.1) | 0.14 | 0.53(0.46 to 0.59) |
| Low-middle SDI | 9269 (6981, 12,275) | 21,925 (16,444, 29,158) | 1.37 | 3.82 (2.89,5.06) | 4.51 (3.38,5.99) | 0.18 | 0.64(0.54 to 0.73) |
| Middle SDI | 7158 (5329, 9515) | 17,540 (13,150, 23,285) | 1.45 | 1.76 (1.32,2.34) | 2.7 (2.02,3.58) | 0.53 | 1.69(1.48 to 1.9) |
| High-middle SDI | 9288 (7166, 12,002) | 13,109 (9910, 17,260) | 0.41 | 3.44 (2.66,4.44) | 3.91 (2.96,5.16) | 0.14 | 0.67(0.44 to 0.9) |
| High SDI | 32524 (25,938, 40,475) | 38,912 (30,094, 49,251) | 0.20 | 13.97 (11.15,17.38) | 14.93 (11.52,18.97) | 0.07 | 0.25(0.08 to 0.42) |
| High-income Asia Pacific | 1232 (947, 1612) | 1347 (1015, 1782) | 0.09 | 2.66 (2.04,3.48) | 3.25 (2.44,4.3) | 0.22 | 0.91(0.26 to 1.57) |
| High-income North America | 16181 (12,865, 20,234) | 19,865 (15,496, 24,997) | 0.23 | 20.91 (16.64,26.13) | 22.39 (17.43,28.25) | 0.07 | 0.29(0.13 to 0.44) |
| Western Europe | 15691 (12,640, 19,344) | 16,952 (12,964, 21,735) | 0.08 | 16.14 (13.01,19.89) | 17.25 (13.16,22.2) | 0.07 | 0.21(−0.01 to 0.43) |
| Australasia | 1297 (981, 1729) | 1976 (1512, 2604) | 0.52 | 23.73 (17.97,31.63) | 25.64 (19.59,33.85) | 0.08 | 0.7(0.38 to 1.03) |
| Andean Latin America | 135 (98, 183) | 317 (231, 427) | 1.35 | 1.58 (1.15,2.14) | 1.81 (1.32,2.44) | 0.15 | 0.48(0.4 to 0.56) |
| Tropical Latin America | 758 (565, 1012) | 1961 (1455, 2642) | 1.59 | 2.05 (1.53,2.73) | 3.04 (2.26,4.1) | 0.48 | 0.84(0.27 to 1.42) |
| Central Latin America | 242 (176, 332) | 424 (303, 581) | 0.75 | 0.64 (0.47,0.88) | 0.62 (0.44,0.84) | −0.03 | 0.04(−0.09 to 0.18) |
| Southern Latin America | 680 (497, 924) | 1090 (803, 1492) | 0.60 | 5.6 (4.09,7.6) | 6.05 (4.46,8.27) | 0.08 | 0.24(0.2 to 0.28) |
| Caribbean | 273 (203, 366) | 443 (331, 590) | 0.62 | 3.1 (2.3,4.16) | 3.63 (2.72,4.84) | 0.17 | 0.5(0.44 to 0.55) |
| Central Europe | 2230 (1738, 2865) | 2404 (1837, 3110) | 0.08 | 7.09 (5.53,9.11) | 8.48 (6.46,11) | 0.20 | 0.83(0.6 to 1.06) |
| Eastern Europe | 2186 (1635, 2902) | 2587 (1931, 3460) | 0.18 | 3.81 (2.85,5.05) | 4.61 (3.44,6.17) | 0.21 | 0.61(0.58 to 0.63) |
| Central Asia | 774 (581, 1019) | 1507 (1137, 1996) | 0.95 | 5.07 (3.82,6.66) | 5.99 (4.52,7.92) | 0.18 | 0.56(0.54 to 0.57) |
| North Africa and Middle East | 2452 (1859, 3231) | 6471 (4816, 8709) | 1.64 | 3.45 (2.61,4.54) | 4.02 (3,5.41) | 0.17 | 0.56(0.51 to 0.6) |
| South Asia | 11732 (8809, 15,599) | 29,476 (22,217, 39,080) | 1.51 | 5.13 (3.86,6.81) | 6.16 (4.64,8.16) | 0.20 | 0.76(0.62 to 0.89) |
| Southeast Asia | 789 (579, 1067) | 1533 (1131, 2061) | 0.94 | 0.69 (0.51,0.94) | 0.82 (0.61,1.11) | 0.19 | 0.52(0.49 to 0.55) |

(*Continued*)

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**Table 1** (Continued).

| Location | Incidence Cases | | | Incidence Rates | | | |
|---|---|---|---|---|---|---|---|
| | 1990_Numbers (95% UI) | 2021_Numbers (95% UI) | Percentage Change in Case (100%) | 1990_per100000 (95% UI) | 2021_per100000 (95% UI) | Percentage Change in ASRs (100%) | EAPC (95% CI) |
| East Asia | 2748 (2022, 3707) | 6130 (4588, 8151) | 1.23 | 0.87 (0.64,1.17) | 1.67 (1.25,2.23) | 0.92 | 3.09(2.45 to 3.74) |
| Oceania | 11 (8, 15) | 30 (22, 41) | 1.73 | 0.76 (0.56,1.05) | 0.89 (0.65,1.23) | 0.17 | 0.48(0.44 to 0.52) |
| Western Sub-Saharan Africa | 568 (425, 755) | 1729 (1298, 2286) | 2.04 | 1.51 (1.13,1.99) | 1.64 (1.23,2.16) | 0.09 | 0.08(−0.02 to 0.18) |
| Eastern Sub-Saharan Africa | 563 (420, 748) | 1731 (1302, 2300) | 2.07 | 1.51 (1.13,2) | 1.84 (1.39,2.44) | 0.22 | 0.75(0.7 to 0.81) |
| Central Sub-Saharan Africa | 173 (128, 232) | 599 (449, 805) | 2.46 | 1.58 (1.17,2.11) | 2.06 (1.55,2.76) | 0.30 | 0.92(0.89 to 0.94) |
| Southern Sub-Saharan Africa | 210 (157, 280) | 401 (302, 531) | 0.91 | 1.79 (1.34,2.37) | 1.87 (1.4,2.46) | 0.04 | 0.22(0.13 to 0.3) |


https://doi.org/10.2147/IJWH.S551115

Latin America was the only region showing a decrease in ASIR, although the change was not statistically significant. The largest reductions in ASPR, ASDR, and ASMR were observed in High-income North America, Andean Latin America, and High-income Asia Pacific, with EAPC values of −0.38 (95% CI: −0.61 to −0.15), −1.84 (95% CI: −2.09 to −1.59), and −4.09 (95% CI: −4.38 to −3.79), respectively (Figure 2, Tables 1 and S1–3).

## Country-Level Variations in the Burden of Inflammatory Bowel Disease Among Reproductive-Age Women

At the national level, India demonstrated the highest burden of IBD among women of reproductive age, with the largest figures for incidence, prevalence, DALYs, and mortality, reaching 22,541 (95% UI: 16,944–29,878), 164,271 (95% UI: 125,897–213,523), 48,131 (95% UI: 33,204–70,387), and 357 (95% UI: 195–681), respectively. The United States also exhibited a substantial disease burden, ranking just below India in these metrics. Additionally, China and Germany ranked third in incidence and prevalence, respectively. In terms of DALYs and mortality, Nigeria showed significant burdens, underscoring its public health challenges (Tables S4–7). Over the past 32 years, Georgia experienced the most pronounced reductions in incidence and prevalence, with decreases of 34.25% and 32.65%, respectively. Latvia showed the largest decline in DALYs, at 68.42%. Mortality reductions were notable in Estonia, Latvia, Lithuania, Republic of Moldova, Slovenia, and Finland, where deaths from IBD decreased by 100%. Among countries with increasing disease burdens, Qatar and the United Arab Emirates exhibited the largest rises in incidence, prevalence, and DALYs. Mortality saw the most significant increases in Zimbabwe, Gambia, Sierra Leone, and Benin, with all experiencing a 300% rise (Figure 3 and Tables S4–7).

In 2021, Mexico recorded the lowest ASIR and ASPR. The Northern Mariana Islands reported the lowest ASDR, while three countries—Sri Lanka, Singapore, and the Northern Mariana Islands—reported an ASMR of zero. Conversely, Canada had the highest ASIR and ASPR, at 37.31 (95% UI: 28.72–48.35) and 404.64 (95% UI: 304.16–560.89), respectively. Guinea-Bissau, Mali, and Gambia were the top three countries for ASDR and ASMR (Figure 3 and Table S4–7). From 1990 to 2021, 18 countries experienced reductions in ASIR, with the largest decrease observed in Finland (EAPC: −1.69, 95% UI: −2.14 to −1.23). The largest declines in ASPR were seen in Italy and Canada, with EAPCs of −1.13 (95% UI: −1.41 to −0.85) and −1.26 (95% UI: −1.73 to −0.79), respectively. In contrast, Libya and China showed the largest increases in both ASIR and ASPR. Taiwan (Province of China) experienced the greatest decline in ASDR, while Sri Lanka and Singapore achieved a 100% reduction in ASMR. The most significant increases in ASMR and ASDR were recorded in Mauritius (Figure 3 and Table S4–7).

## Age-Specific Patterns in the Global Burden of Inflammatory Bowel Disease Among Reproductive-Age Women

In this analysis, reproductive-age women (15–49 years) were divided into seven age groups to explore the disease burden at different ages. Overall, the risk of developing IBD, as well as the associated disability and mortality risk, increases with age. In terms of absolute numbers, the highest incidence, DALYs, and mortality were observed in the 40–44 age group, while the highest prevalence occurred in the 45–49 age group. From 1990 to 2021, the incidence and prevalence of IBD increased slightly across all age groups, with the rate of increase higher among older age groups. The 45–49 age group showed the largest increases in incidence (1.19%) and prevalence (0.85%). DALYs and mortality increased most in the 45–49 and 40–44 age groups, while a decreasing trend was observed in the 15–19 age group (Figures 4 and 5, Tables 2 and S8–10).

In 2021, the highest ASIR and ASPR were seen in the 45–49 age group, while the highest ASDR and ASMR occurred in the 40–44 age group. The 15–19 age group exhibited the lowest disease burden overall. Compared to 1990, there was no significant change in the ASIR, with a rate change close to zero. A slight upward trend was observed in women aged 35 and older. The ASPR showed a declining trend across all age groups, with the most significant decrease observed in the 30–34 age group (EAPC: −0.48, 95% CI: −0.69 to −0.28). The 15–19 age group showed minimal and non-significant changes. The ASDR exhibited an increasing trend in the 20–24 age group (EAPC: 0.49, 95% CI: 0.41 to 0.58), while other age groups saw a decrease. The largest decrease in ASDR was in the 15–19 age group (EAPC: −0.8, 95% CI: −0.94 to −0.65). The ASMR

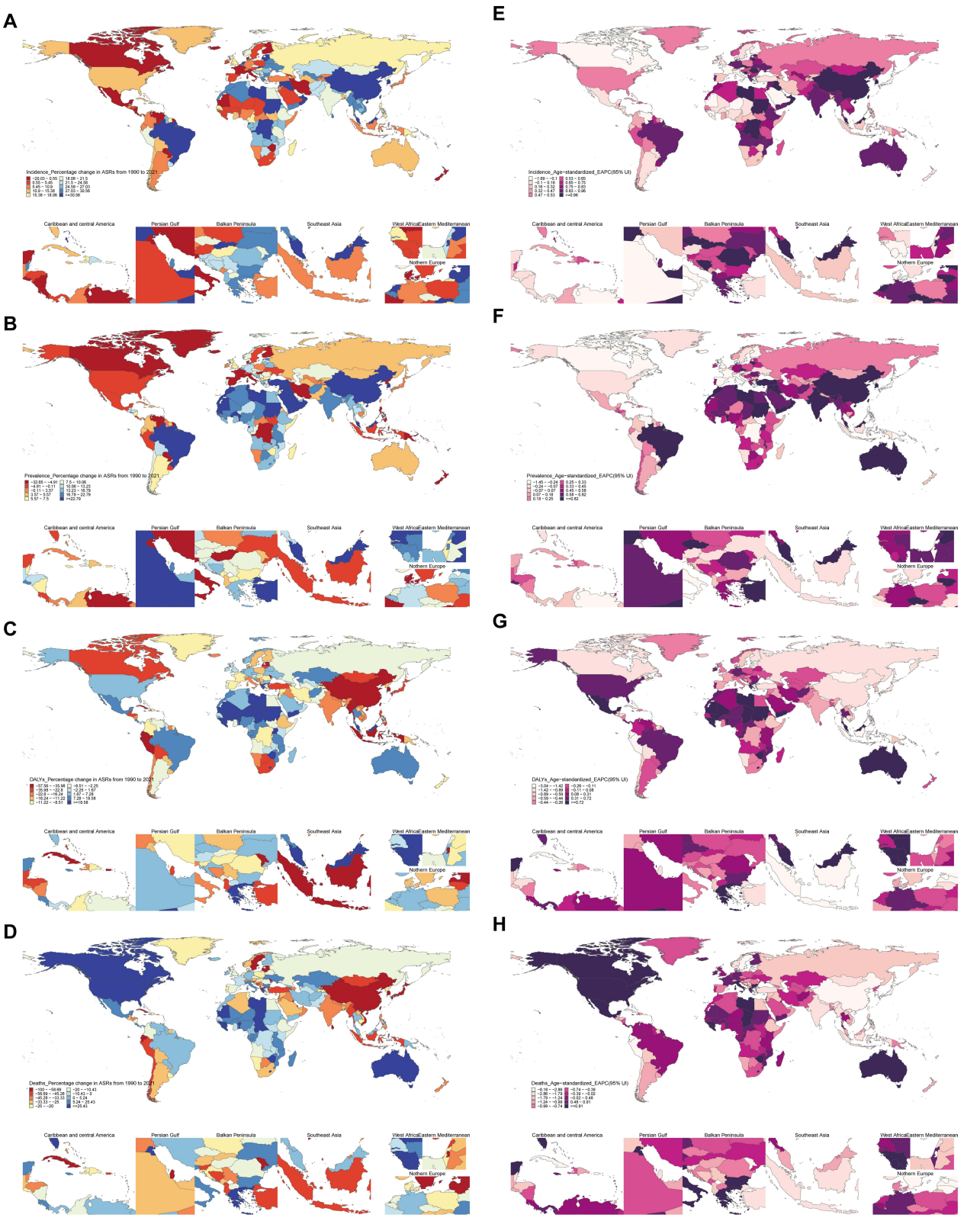


**Figure 3** National-Level ASRs change and EAPC in Inflammatory Bowel Disease Burden Among Women of Reproductive Age, 1990–2021. (**A**) Age-standardized incidence rates change across 204 countries and territories. (**B**) Age-standardized prevalence rates change across 204 countries and territories. (**C**) Age-standardized DALY rates change across 204 countries and territories. (**D**) Age-standardized mortality rates change across 204 countries and territories. (**E**) EAPC in age-standardized incidence rates across 204 countries and territories. (**F**) EAPC in age-standardized prevalence rates across 204 countries and territories. (**G**) EAPC in age-standardized DALY rates across 204 countries and territories. (**H**) EAPC in age-standardized mortality rates across 204 countries and territories.

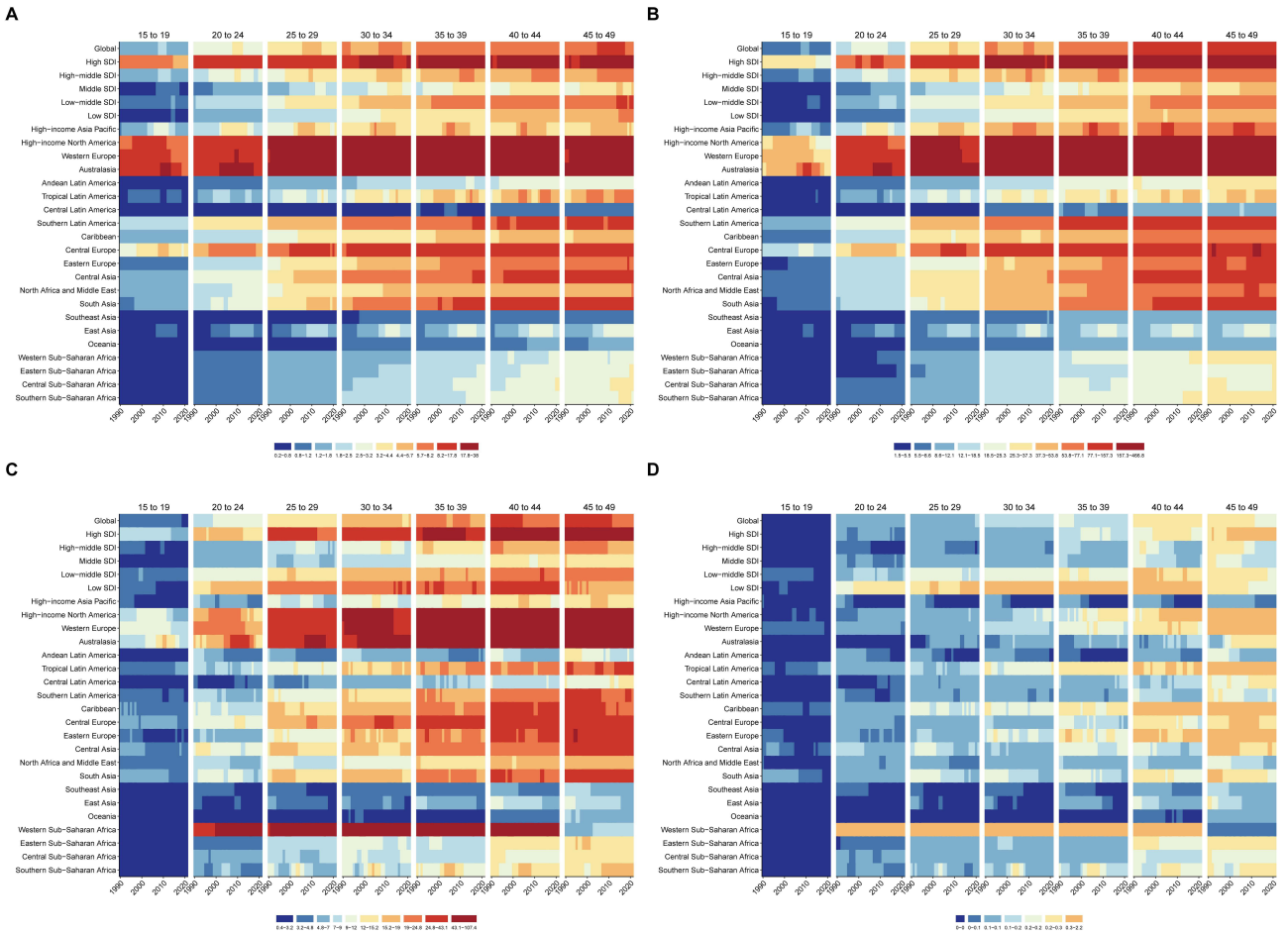


**Figure 4** Age-Specific Trends in Inflammatory Bowel Disease Burden Among Women of Reproductive Age, 1990–2021. (**A**) Global, SDI-specific, and regional trends in age-specific incidence rates. (**B**) Global, SDI-specific, and regional trends in age-specific prevalence rates. (**C**) Global, SDI-specific, and regional trends in age-specific DALY rates. (**D**) Global, SDI-specific, and regional trends in age-specific mortality rates.

showed the largest increase in the 20–24 age group (EAPC: 0.86, 95% CI: 0.75 to 0.97), while the most significant decline occurred in the 45–49 age group (EAPC: −1.24, 95% CI: −1.35 to −1.12)(Figures 4 and 5, Tables 2 and S8–10).

## Age-Specific Patterns in the Regional Burden of Inflammatory Bowel Disease Among Reproductive-Age Women

In the five SDI regions, the burden of IBD increases with age, with the highest disease burden observed in the 40–49 age group in terms of incidence, prevalence, DALYs, and mortality. Notably, in Low SDI regions, the peak incidence occurs earlier, in the 35–39 age group. Compared to 1990, in High SDI regions, the incidence, prevalence, DALYs, and mortality in younger age groups have declined, while higher age groups have seen increases. High-middle SDI regions exhibit similar trends in incidence, prevalence, and DALYs, although mortality only increased in the 45–49 age group, with decreases in other age groups. In Middle SDI regions, both incidence and prevalence have increased, with the growth rate accelerating with age. DALYs and mortality in younger age groups have slightly decreased, while those in older age groups have increased. Both Low SDI and Low-middle SDI regions show an overall increase in the number of IBD cases, with the growth rate higher in Low-middle SDI regions for older age groups. In Low SDI regions, the 40–44 age group has the highest increase in incidence and prevalence, while the greatest increases in DALYs and mortality occur in the 20–24 and 25–29 age groups, respectively (Figures 4 and 5, Tables 2 and S8–10).

In terms of ASR, the burden of disease in all five SDI regions remains concentrated in the 40+ age groups. Notably, in Low SDI regions, the ASDR and ASMR for the 45–49 age group are exceptionally low, second only to the values in the


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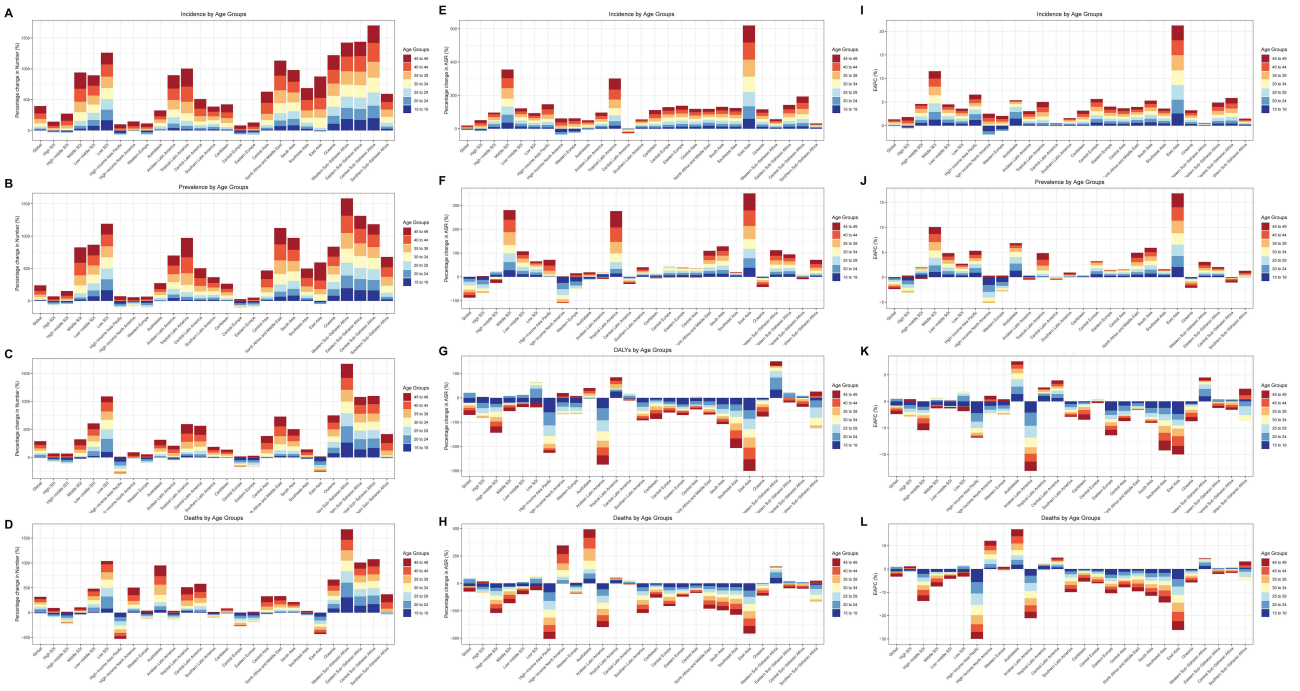

**Figure 5** Age-specific Rates in inflammatory bowel disease burden among women of reproductive age, 1990–2021. (**A**) Global, SDI-specific, and regional changes in age-specific incidence numbers. (**B**) Global, SDI-specific, and regional changes in age-specific prevalence numbers. (**C**) Global, SDI-specific, and regional changes in age-specific DALY numbers. (**D**) Global, SDI-specific, and regional changes in age-specific mortality numbers. (**E**) Global, SDI-specific, and regional changes in age-specific incidence rates. (**F**) Global, SDI-specific, and regional changes in age-specific prevalence rates. (**G**) Global, SDI-specific, and regional changes in age-specific DALY rates. (**H**) Global, SDI-specific, and regional changes in age-specific mortality rates. (**I**) Global, SDI-specific, and regional EAPC in age-specific incidence rates. (**J**) Global, SDI-specific, and regional EAPC in age-specific prevalence rates. (**K**) Global, SDI-specific, and regional EAPC in age-specific DALY rates. (**L**) Global, SDI-specific, and regional EAPC in age-specific mortality rates.

15–19 age group. In terms of trends, the ASIR and ASPR have significantly increased in Low, Low-middle, and Middle SDI regions, with the most pronounced increases observed in the 35–39 age group in Middle SDI regions. In High SDI regions, the ASIR for younger age groups has slightly decreased, though this change is not significant. Except for the 45–49 age group, the ASPR in High SDI regions shows a slight increase, while all other age groups exhibit notable declines. In High-middle SDI regions, the ASIR has increased across all age groups, with the highest growth observed in the 35–39 age group. The changes in ASPR were minimal, with a significant decrease in the 45–49 age group and a notable increase in the 15–19 age group. In High SDI regions, both the ASDR and ASMR for the 40–49 age groups have shown slight increases, while a marked decline is seen in other age groups. In High-middle SDI regions, both ASDR and ASMR have decreased significantly across all age groups, with declines steeper than in other regions. Although there is a decreasing trend in Middle SDI regions, the decline is not significant. In Low-middle SDI regions, the ASDR and ASMR for the 20–24 age group showed an anomalous increase compared to other age groups. Similarly, in Low SDI regions, a significant increase in the 20–24 age group was observed (Figures 4 and 5, Tables 2 and S8–10).

In the analysis of the 21 GBD regions, the greatest reduction in ASIR occurred in the 15–19 age group in High-income North America. East Asia had the highest growth rate across all age groups, with the 35–39 age group showing the highest increase (EAPC = 3.19, 95% CI: 2.63 to 3.76). High-income North America saw the largest decline in ASPR and ASDR in the 15–24 age groups, while East Asia showed the highest increase in ASPR for the 45–49 age group. Additionally, Andean Latin America had the smallest decrease in ASDR (EAPC = −2.48, 95% CI: −2.71 to −2.24). In Western Sub-Saharan Africa, the largest increase in ASDR occurred in the 15–24 age group. In Australasia, the highest increase in ASMR was observed in the older age groups (Figures 4 and 5, Tables 2 and S8–10).

**Table 2** Age-Specific Incidence of Inflammatory Bowel Disease Among Women of Reproductive Age in 1990 and 2021, with Trends in Age Patterns From 1990 to 2021

| Location | Age (Years) | Incidence Cases | | | Incidence Rates | | | |
|---|---|---|---|---|---|---|---|---|
| | | 1990_Cases (95% UI) | 2021_Cases (95% UI) | Percentage Change in Case (100%) | 1990_per100000 (95% UI) | 2021_per100000 (95% UI) | Percentage Change in ASRs (100%) | EAPC (95% CI) |
| Global | 15 to 19 | 3754.52 (3017.72–4809.58) | 4241.75 (3275.26–5577.51) | 0.13 | 1.47 (1.18–1.88) | 1.4 (1.08–1.84) | −0.05 | −0.08 (−0.41 to 0.25) |
| Global | 20 to 24 | 6628.27 (5221.35–8321.85) | 7820.92 (5882.06–10,170.55) | 0.18 | 2.72 (2.14–3.41) | 2.66 (2–3.46) | −0.02 | 0.08 (−0.17 to 0.34) |
| Global | 25 to 29 | 9397.16 (7305.47–11,976.74) | 12,249.33 (9167.64–16,124.92) | 0.30 | 4.27 (3.32–5.44) | 4.21 (3.15–5.54) | −0.01 | 0.21 (0.02 to 0.41) |
| Global | 30 to 34 | 10,823.83 (8185.92–14,197.74) | 16,801.37 (12,444.34–22,444.23) | 0.55 | 5.69 (4.31–7.47) | 5.62 (4.16–7.51) | −0.01 | 0.19 (0.02 to 0.35) |
| Global | 35 to 39 | 11,197.05 (8705.64–14,580.46) | 19,223.7 (14,609.59–25,250.92) | 0.72 | 6.46 (5.02–8.41) | 6.92 (5.26–9.09) | 0.07 | 0.31 (0.2 to 0.41) |
| Global | 40 to 44 | 10,414.26 (8168.88–13,140.31) | 19,517.89 (15,191.7–24,952.17) | 0.87 | 7.43 (5.83–9.37) | 7.87 (6.12–10.06) | 0.06 | 0.27 (0.19 to 0.35) |
| Global | 45 to 49 | 8711.15 (6914.67–10,929.6) | 19,119.6 (14,904.2–24,128.88) | 1.19 | 7.65 (6.08–9.6) | 8.11 (6.32–10.24) | 0.06 | 0.26 (0.16 to 0.35) |
| High SDI | 15 to 19 | 1817.87 (1501.14–2240.67) | 1537.2 (1195.52–2036.18) | −0.15 | 5.7 (4.71–7.03) | 5.28 (4.11–7) | −0.07 | −0.38 (−0.86 to 0.1) |
| High SDI | 20 to 24 | 3524.9 (2850.23–4356.49) | 3096.16 (2368.14–4043.28) | −0.12 | 10.5 (8.49–12.97) | 9.82 (7.51–12.83) | −0.06 | −0.18 (−0.5 to 0.14) |
| High SDI | 25 to 29 | 5224.46 (4201.17–6454.79) | 5018.45 (3802.08–6503.73) | −0.04 | 14.57 (11.72–18.01) | 14.52 (11–18.82) | 0.00 | 0 (−0.19 to 0.18) |
| High SDI | 30 to 34 | 5983.78 (4642.96–7566.23) | 6793.29 (5041.16–8730.2) | 0.14 | 16.86 (13.08–21.32) | 18.15 (13.47–23.32) | 0.08 | 0.16 (0.04 to 0.28) |
| High SDI | 35 to 39 | 5949.67 (4718.9–7454.01) | 7533.45 (5874.78–9481.97) | 0.27 | 17.79 (14.11–22.29) | 19.86 (15.49–25) | 0.12 | 0.35 (0.24 to 0.45) |
| High SDI | 40 to 44 | 5581.26 (4447.45–6926.55) | 7582.84 (5967.15–9463.46) | 0.36 | 17.88 (14.24–22.18) | 20.66 (16.25–25.78) | 0.16 | 0.57 (0.44 to 0.7) |
| High SDI | 45 to 49 | 4441.7 (3575.67–5476.35) | 7350.78 (5845.37–8991.9) | 0.65 | 17.58 (14.15–21.67) | 20.47 (16.28–25.04) | 0.16 | 0.73 (0.6 to 0.86) |
| High-middle SDI | 15 to 19 | 629.24 (497.04–812.6) | 505.13 (392.07–666.77) | −0.20 | 1.33 (1.05–1.72) | 1.47 (1.14–1.94) | 0.10 | 0.58 (0.12 to 1.03) |
| High-middle SDI | 20 to 24 | 1021.33 (787.53–1305.35) | 886.79 (667.1–1155.45) | −0.13 | 2.12 (1.64–2.71) | 2.49 (1.87–3.25) | 0.17 | 0.6 (0.22 to 0.99) |
| High-middle SDI | 25 to 29 | 1390.49 (1058.82–1788.93) | 1420.61 (1053.61–1882) | 0.02 | 3.04 (2.31–3.91) | 3.52 (2.61–4.67) | 0.16 | 0.76 (0.35 to 1.17) |
| High-middle SDI | 30 to 34 | 1631.16 (1234.86–2156.6) | 2161.56 (1597.56–2922.15) | 0.33 | 3.91 (2.96–5.17) | 4.2 (3.1–5.68) | 0.07 | 0.74 (0.36 to 1.13) |
| High-middle SDI | 35 to 39 | 1725.88 (1318.54–2263.05) | 2561.6 (1919.18–3430.92) | 0.48 | 4.37 (3.34–5.73) | 5.17 (3.87–6.92) | 0.18 | 0.89 (0.66 to 1.12) |
| High-middle SDI | 40 to 44 | 1564.2 (1221.64–2012.34) | 2713.61 (2090.63–3539.52) | 0.73 | 5.09 (3.97–6.55) | 5.96 (4.59–7.78) | 0.17 | 0.68 (0.59 to 0.77) |
| High-middle SDI | 45 to 49 | 1326.14 (1047.95–1662.95) | 2859.79 (2190.08–3663.17) | 1.16 | 5.41 (4.27–6.78) | 5.93 (4.54–7.6) | 0.10 | 0.34 (0.23 to 0.44) |
| Middle SDI | 15 to 19 | 542.66 (410.98–704.04) | 702.82 (538.41–916.61) | 0.30 | 0.59 (0.45–0.76) | 0.8 (0.61–1.04) | 0.36 | 1.28 (0.94 to 1.62) |

(*Continued*)

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**Table 2** (Continued).

| Location | Age (Years) | Incidence Cases | | | Incidence Rates | | | |
|---|---|---|---|---|---|---|---|---|
| | | 1990_Cases (95% UI) | 2021_Cases (95% UI) | Percentage Change in Case (100%) | 1990_per100000 (95% UI) | 2021_per100000 (95% UI) | Percentage Change in ASRs (100%) | EAPC (95% CI) |
| Middle SDI | 20 to 24 | 854.76 (628.85–1128.47) | 1239.08 (918.89–1634.42) | 0.45 | 0.97 (0.71–1.28) | 1.43 (1.06–1.89) | 0.48 | 1.63 (1.28 to 1.98) |
| Middle SDI | 25 to 29 | 1107.41 (810.97–1473.6) | 2001.44 (1455.4–2660.82) | 0.81 | 1.48 (1.08–1.97) | 2.21 (1.61–2.94) | 0.49 | 1.81 (1.49 to 2.13) |
| Middle SDI | 30 to 34 | 1218.98 (883.89–1656.41) | 2961.96 (2193.43–4012.79) | 1.43 | 2.03 (1.47–2.76) | 3 (2.22–4.06) | 0.48 | 1.75 (1.48 to 2.02) |
| Middle SDI | 35 to 39 | 1295.49 (960.75–1752.34) | 3489.11 (2574.82–4704.28) | 1.69 | 2.34 (1.73–3.16) | 3.81 (2.81–5.13) | 0.63 | 1.82 (1.63 to 2.01) |
| Middle SDI | 40 to 44 | 1144.73 (877.27–1515.3) | 3541.68 (2710.47–4678.71) | 2.09 | 2.71 (2.08–3.59) | 4.33 (3.31–5.72) | 0.60 | 1.7 (1.56 to 1.85) |
| Middle SDI | 45 to 49 | 993.72 (755.99–1284.88) | 3603.63 (2758.55–4677.5) | 2.63 | 2.93 (2.23–3.79) | 4.44 (3.4–5.77) | 0.52 | 1.56 (1.41 to 1.7) |
| Low-middle SDI | 15 to 19 | 578.46 (441.73–750.97) | 1008.88 (769.06–1319.21) | 0.74 | 0.98 (0.75–1.28) | 1.12 (0.85–1.46) | 0.13 | 0.61 (0.45 to 0.76) |
| Low-middle SDI | 20 to 24 | 941.03 (701.8–1239.3) | 1833.83 (1363.35–2429.47) | 0.95 | 1.8 (1.35–2.38) | 2.11 (1.57–2.79) | 0.17 | 0.68 (0.53 to 0.84) |
| Low-middle SDI | 25 to 29 | 1292.05 (946.55–1710.85) | 2784.69 (2035.29–3749.53) | 1.16 | 2.88 (2.11–3.81) | 3.43 (2.51–4.61) | 0.19 | 0.71 (0.56 to 0.85) |
| Low-middle SDI | 30 to 34 | 1541.93 (1137.34–2089.31) | 3641.87 (2683.66–4938.09) | 1.36 | 4.12 (3.04–5.58) | 4.93 (3.63–6.68) | 0.20 | 0.71 (0.59 to 0.84) |
| Low-middle SDI | 35 to 39 | 1724.64 (1293.26–2307.09) | 4238.52 (3150.56–5728.43) | 1.46 | 5.38 (4.04–7.2) | 6.37 (4.73–8.6) | 0.18 | 0.68 (0.57 to 0.78) |
| Low-middle SDI | 40 to 44 | 1662.16 (1273.67–2200.73) | 4318.07 (3336.64–5706.09) | 1.60 | 6.41 (4.91–8.48) | 7.49 (5.78–9.89) | 0.17 | 0.59 (0.52 to 0.67) |
| Low-middle SDI | 45 to 49 | 1528.98 (1186.78–1976.77) | 4099.34 (3105.3–5286.95) | 1.68 | 7.04 (5.47–9.11) | 8.29 (6.28–10.69) | 0.18 | 0.52 (0.47 to 0.57) |
| Low SDI | 15 to 19 | 181.89 (137.86–238.43) | 484.02 (368.87–641.72) | 1.66 | 0.72 (0.55–0.95) | 0.79 (0.6–1.04) | 0.08 | 0.43 (0.34 to 0.52) |
| Low SDI | 20 to 24 | 279.32 (206.93–368.18) | 758.66 (560.73–1002.97) | 1.72 | 1.29 (0.95–1.7) | 1.44 (1.06–1.9) | 0.12 | 0.49 (0.41 to 0.58) |
| Low SDI | 25 to 29 | 373.64 (272.53–502.27) | 1014.55 (746.09–1358.69) | 1.72 | 2.02 (1.47–2.71) | 2.3 (1.69–3.08) | 0.14 | 0.53 (0.44 to 0.62) |
| Low SDI | 30 to 34 | 437.32 (319.46–594.1) | 1229.98 (905.85–1672.58) | 1.81 | 2.88 (2.1–3.91) | 3.31 (2.44–4.51) | 0.15 | 0.58 (0.49 to 0.67) |
| Low SDI | 35 to 39 | 489.98 (363.26–664.31) | 1386.78 (1020.36–1877.28) | 1.83 | 3.8 (2.82–5.16) | 4.35 (3.2–5.89) | 0.14 | 0.58 (0.51 to 0.65) |
| Low SDI | 40 to 44 | 451.35 (346.12–599.36) | 1346.7 (1032.78–1784.37) | 1.98 | 4.55 (3.49–6.04) | 5.16 (3.95–6.83) | 0.13 | 0.5 (0.44 to 0.56) |
| Low SDI | 45 to 49 | 411.85 (315.68–534.9) | 1191.37 (923.71–1542.88) | 1.89 | 4.96 (3.8–6.44) | 5.74 (4.45–7.43) | 0.16 | 0.49 (0.45 to 0.53) |
| High-income Asia Pacific | 15 to 19 | 89.2 (69.57–115.41) | 52.53 (40.66–68.53) | −0.41 | 1.21 (0.94–1.56) | 1.3 (1–1.69) | 0.07 | 1.2 (0.09 to 2.32) |
| High-income Asia Pacific | 20 to 24 | 133.49 (103.52–174.19) | 105.79 (79–138.98) | −0.21 | 1.97 (1.53–2.57) | 2.27 (1.7–2.98) | 0.15 | 1.24 (0.31 to 2.19) |
| High-income Asia Pacific | 25 to 29 | 175.44 (134.33–230.47) | 159.85 (118.39–212.28) | −0.09 | 2.71 (2.08–3.56) | 3.21 (2.38–4.26) | 0.18 | 0.97 (0.2 to 1.74) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| High-income Asia Pacific | 30 to 34 | 200.26 (150.92–267.88) | 193.38 (139.95–260.47) | −0.03 | 3.22 (2.43–4.31) | 3.8 (2.75–5.12) | 0.18 | 0.7 (0.09 to 1.32) |
| High-income Asia Pacific | 35 to 39 | 211.03 (160.49–280.41) | 240.39 (181.17–321.05) | 0.14 | 3.35 (2.54–4.45) | 4.22 (3.18–5.63) | 0.26 | 0.69 (0.13 to 1.25) |
| High-income Asia Pacific | 40 to 44 | 227.14 (176.59–294.18) | 280.89 (217.69–370.5) | 0.24 | 3.35 (2.6–4.34) | 4.4 (3.41–5.8) | 0.31 | 0.81 (0.28 to 1.35) |
| High-income Asia Pacific | 45 to 49 | 195.53 (151.8–249.53) | 314.35 (237.9–410.6) | 0.61 | 3.37 (2.62–4.3) | 4.38 (3.32–5.72) | 0.30 | 0.96 (0.52 to 1.4) |
| High-income North America | 15 to 19 | 707.68 (578.22–873) | 674.19 (521.5–886.85) | −0.05 | 7.25 (5.92–8.94) | 5.77 (4.46–7.59) | −0.20 | −1.18 (−1.76 to −0.59) |
| High-income North America | 20 to 24 | 1474.71 (1175.44–1834.46) | 1418.69 (1075.07–1856.37) | −0.04 | 13.88 (11.06–17.26) | 12.02 (9.11–15.73) | −0.13 | −0.66 (−1.07 to −0.24) |
| High-income North America | 25 to 29 | 2482.79 (1994.62–3109.23) | 2435.95 (1854.06–3151.74) | −0.02 | 20.6 (16.55–25.79) | 19.73 (15.02–25.53) | −0.04 | −0.15 (−0.41 to 0.11) |
| High-income North America | 30 to 34 | 3139.34 (2427.86–3987.07) | 3409.2 (2545.93–4382.44) | 0.09 | 25.23 (19.52–32.05) | 26.72 (19.95–34.35) | 0.06 | 0.29 (0.12 to 0.45) |
| High-income North America | 35 to 39 | 3181.26 (2537.06–3994.17) | 3923.73 (3082.67–4938.49) | 0.23 | 27.91 (22.26–35.04) | 31.65 (24.87–39.83) | 0.13 | 0.58 (0.47 to 0.7) |
| High-income North America | 40 to 44 | 2930.03 (2333.6–3649.41) | 4063.85 (3243.78–5030.57) | 0.39 | 28.83 (22.96–35.91) | 34.27 (27.36–42.43) | 0.19 | 0.77 (0.67 to 0.88) |
| High-income North America | 45 to 49 | 2265.07 (1818.03–2786.57) | 3938.92 (3173.34–4750.36) | 0.74 | 28.6 (22.95–35.18) | 35.26 (28.41–42.52) | 0.23 | 0.89 (0.78 to 1) |
| Western Europe | 15 to 19 | 1121.13 (936.56–1352.41) | 811.57 (629.42–1068.71) | −0.28 | 8.4 (7.02–10.13) | 7.09 (5.5–9.34) | −0.16 | −0.78 (−1.26 to −0.29) |
| Western Europe | 20 to 24 | 2089.65 (1696.58–2570.6) | 1530.63 (1166.16–2010.25) | −0.27 | 14.02 (11.38–17.24) | 12.88 (9.81–16.92) | −0.08 | −0.32 (−0.72 to 0.09) |
| Western Europe | 25 to 29 | 2729.86 (2209.4–3337.72) | 2282.85 (1715.75–2954.12) | −0.16 | 17.78 (14.39–21.74) | 18.06 (13.57–23.37) | 0.02 | 0.09 (−0.17 to 0.35) |
| Western Europe | 30 to 34 | 2723.23 (2136.65–3404.98) | 2952.15 (2169.38–3844.29) | 0.08 | 19.24 (15.1–24.06) | 21.49 (15.79–27.99) | 0.12 | 0.33 (0.17 to 0.49) |
| Western Europe | 35 to 39 | 2567.72 (2060.65–3179.98) | 3141.69 (2431.65–4049.38) | 0.22 | 19.3 (15.49–23.9) | 22.34 (17.29–28.79) | 0.16 | 0.44 (0.3 to 0.58) |
| Western Europe | 40 to 44 | 2439.07 (1969.43–3010.55) | 3146.72 (2436.52–3976.5) | 0.29 | 18.56 (14.99–22.91) | 21.71 (16.81–27.43) | 0.17 | 0.54 (0.38 to 0.71) |
| Western Europe | 45 to 49 | 2020.62 (1630.35–2487.39) | 3086.75 (2415.01–3832.11) | 0.53 | 17.82 (14.38–21.94) | 20.69 (16.19–25.69) | 0.16 | 0.65 (0.5 to 0.79) |
| Australasia | 15 to 19 | 70.28 (53.98–93.69) | 71.98 (55.29–97.16) | 0.02 | 8.5 (6.53–11.33) | 8.19 (6.29–11.05) | −0.04 | 1.49 (0.38 to 2.62) |
| Australasia | 20 to 24 | 124.24 (94.16–167.64) | 154.38 (115.87–205.65) | 0.24 | 15.59 (11.82–21.03) | 16.12 (12.1–21.47) | 0.03 | 1.42 (0.54 to 2.3) |
| Australasia | 25 to 29 | 189.79 (145.41–251.25) | 266.85 (202.42–354.23) | 0.41 | 22.72 (17.41–30.08) | 24.51 (18.59–32.53) | 0.08 | 1.05 (0.51 to 1.59) |
| Australasia | 30 to 34 | 234.54 (170.88–322.03) | 360.07 (264.59–484.3) | 0.54 | 28.3 (20.62–38.86) | 31.09 (22.84–41.81) | 0.10 | 0.66 (0.39 to 0.93) |
| Australasia | 35 to 39 | 246.26 (186.83–331.56) | 390.68 (299.89–519.38) | 0.59 | 31.62 (23.99–42.58) | 34.78 (26.7–46.24) | 0.10 | 0.39 (0.25 to 0.54) |
| Australasia | 40 to 44 | 243.15 (184.01–324.43) | 364.76 (282.44–480.57) | 0.50 | 33.11 (25.06–44.18) | 36.32 (28.12–47.85) | 0.10 | 0.24 (0.12 to 0.37) |
| Australasia | 45 to 49 | 188.25 (145.83–238.48) | 367.06 (291.44–463.09) | 0.95 | 33.25 (25.76–42.12) | 36.42 (28.92–45.95) | 0.10 | 0.13 (−0.02 to 0.29) |

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**Table 2** (Continued).

| Location | Age (Years) | Incidence Cases | | | Incidence Rates | | | |
|---|---|---|---|---|---|---|---|---|
| | | 1990_Cases (95% UI) | 2021_Cases (95% UI) | Percentage Change in Case (100%) | 1990_per100000 (95% UI) | 2021_per100000 (95% UI) | Percentage Change in ASRs (100%) | EAPC (95% CI) |
| Andean Latin America | 15 to 19 | 11.56 (8.54–15.43) | 16.17 (11.97–21.33) | 0.40 | 0.56 (0.41–0.75) | 0.6 (0.45–0.79) | 0.08 | 0.26 (0.2 to 0.31) |
| Andean Latin America | 20 to 24 | 16.7 (12.01–22.21) | 28.58 (20.72–37.87) | 0.71 | 0.91 (0.66–1.21) | 1 (0.73–1.33) | 0.10 | 0.32 (0.25 to 0.39) |
| Andean Latin America | 25 to 29 | 20.73 (14.64–28.53) | 42.08 (29.73–55.86) | 1.03 | 1.32 (0.93–1.82) | 1.47 (1.04–1.96) | 0.12 | 0.38 (0.31 to 0.46) |
| Andean Latin America | 30 to 34 | 22.88 (16.44–31.58) | 51.96 (37–71.23) | 1.27 | 1.74 (1.25–2.4) | 1.98 (1.41–2.71) | 0.14 | 0.45 (0.37 to 0.53) |
| Andean Latin America | 35 to 39 | 23.29 (16.75–32.31) | 59.05 (42.57–81.44) | 1.53 | 2.12 (1.52–2.93) | 2.46 (1.77–3.39) | 0.16 | 0.51 (0.42 to 0.6) |
| Andean Latin America | 40 to 44 | 21.37 (15.97–29.05) | 61.16 (46.08–83.44) | 1.86 | 2.4 (1.79–3.26) | 2.84 (2.14–3.87) | 0.18 | 0.56 (0.47 to 0.65) |
| Andean Latin America | 45 to 49 | 18.42 (13.64–24.14) | 57.85 (42.8–75.62) | 2.14 | 2.59 (1.92–3.4) | 3.09 (2.29–4.04) | 0.19 | 0.59 (0.51 to 0.67) |
| Tropical Latin America | 15 to 19 | 53.44 (40.67–68.86) | 64.73 (48.97–86.43) | 0.21 | 0.68 (0.52–0.87) | 0.8 (0.61–1.07) | 0.18 | 0.18 (−0.41 to 0.76) |
| Tropical Latin America | 20 to 24 | 82.89 (61.28–110.15) | 127.9 (94.03–171.81) | 0.54 | 1.14 (0.84–1.51) | 1.44 (1.06–1.93) | 0.26 | 0.39 (−0.22 to 1.01) |
| Tropical Latin America | 25 to 29 | 113.44 (83.26–152.23) | 204.9 (148.63–279.36) | 0.81 | 1.69 (1.24–2.26) | 2.28 (1.65–3.1) | 0.35 | 0.6 (−0.01 to 1.22) |
| Tropical Latin America | 30 to 34 | 131.73 (95.96–180.78) | 295.22 (214.9–408.06) | 1.24 | 2.26 (1.65–3.1) | 3.25 (2.37–4.49) | 0.44 | 0.78 (0.18 to 1.38) |
| Tropical Latin America | 35 to 39 | 138.5 (102.43–188.31) | 396.07 (288.76–539.25) | 1.86 | 2.79 (2.06–3.79) | 4.24 (3.09–5.77) | 0.52 | 0.92 (0.34 to 1.5) |
| Tropical Latin America | 40 to 44 | 127.83 (97.56–169.28) | 441.85 (333.88–597.1) | 2.46 | 3.18 (2.43–4.21) | 5.08 (3.84–6.87) | 0.60 | 1.03 (0.47 to 1.59) |
| Tropical Latin America | 45 to 49 | 110.02 (84.2–142.37) | 430.41 (325.59–560.48) | 2.91 | 3.45 (2.64–4.46) | 5.72 (4.33–7.45) | 0.66 | 1.13 (0.61 to 1.65) |
| Central Latin America | 15 to 19 | 23.01 (16.29–31.39) | 26.39 (18.75–35.74) | 0.15 | 0.25 (0.18–0.34) | 0.24 (0.17–0.33) | −0.02 | 0.11 (−0.04 to 0.26) |
| Central Latin America | 20 to 24 | 31.32 (22.48–41.81) | 39.98 (28.94–53.6) | 0.28 | 0.38 (0.27–0.51) | 0.37 (0.27–0.5) | −0.03 | 0.15 (−0.03 to 0.33) |
| Central Latin America | 25 to 29 | 37.91 (26.99–53.6) | 54.68 (39.16–75.14) | 0.44 | 0.54 (0.39–0.77) | 0.52 (0.37–0.71) | −0.04 | 0.07 (−0.11 to 0.25) |
| Central Latin America | 30 to 34 | 41.13 (29.16–55.66) | 66.52 (47.06–91.8) | 0.62 | 0.7 (0.5–0.95) | 0.67 (0.47–0.92) | −0.05 | −0.01 (−0.13 to 0.11) |
| Central Latin America | 35 to 39 | 41.3 (30.01–57.6) | 76.46 (53.87–106.07) | 0.85 | 0.86 (0.62–1.19) | 0.81 (0.57–1.12) | −0.05 | −0.02 (−0.14 to 0.11) |
| Central Latin America | 40 to 44 | 36.96 (27.61–50.84) | 81.44 (58.78–112.27) | 1.20 | 0.97 (0.73–1.34) | 0.93 (0.67–1.28) | −0.04 | −0.04 (−0.19 to 0.1) |
| Central Latin America | 45 to 49 | 30.86 (23.05–40.64) | 78.85 (56.89–106.8) | 1.56 | 1.03 (0.77–1.36) | 0.99 (0.72–1.35) | −0.04 | 0.14 (0.01 to 0.28) |
| Southern Latin America | 15 to 19 | 41.24 (30.97–54.22) | 48.95 (37.09–64.95) | 0.19 | 1.85 (1.39–2.44) | 1.98 (1.5–2.63) | 0.07 | 0.17 (0.14 to 0.19) |
| Southern Latin America | 20 to 24 | 68.35 (50.26–92.36) | 95.05 (70.9–128.49) | 0.39 | 3.38 (2.49–4.57) | 3.65 (2.72–4.93) | 0.08 | 0.2 (0.17 to 0.23) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Southern Latin America | 25 to 29 | 99.15 (70.64–135.82) | 148.99 (107.66–202.22) | 0.50 | 5.1 (3.64–6.99) | 5.54 (4–7.51) | 0.08 | 0.23 (0.2 to 0.26) |
| Southern Latin America | 30 to 34 | 120.24 (86.87–164.86) | 190.81 (138.85–262.94) | 0.59 | 6.64 (4.8–9.11) | 7.23 (5.26–9.96) | 0.09 | 0.26 (0.23 to 0.3) |
| Southern Latin America | 35 to 39 | 126.29 (91.12–173.24) | 207.58 (152.04–290.84) | 0.64 | 7.7 (5.55–10.56) | 8.36 (6.12–11.71) | 0.09 | 0.28 (0.23 to 0.32) |
| Southern Latin America | 40 to 44 | 119.93 (88.72–165.3) | 207.57 (154.2–286.18) | 0.73 | 8.16 (6.03–11.24) | 8.81 (6.54–12.15) | 0.08 | 0.25 (0.2 to 0.3) |
| Southern Latin America | 45 to 49 | 105.14 (78.76–137.74) | 191.33 (142.4–255.96) | 0.82 | 8.19 (6.14–10.73) | 8.75 (6.51–11.71) | 0.07 | 0.2 (0.14 to 0.26) |
| Caribbean | 15 to 19 | 23.91 (18.43–30.95) | 25.52 (19.44–33.75) | 0.07 | 1.29 (1–1.67) | 1.37 (1.05–1.82) | 0.06 | 0.18 (0.12 to 0.25) |
| Caribbean | 20 to 24 | 36.78 (27.77–48.38) | 43.52 (32.23–57.31) | 0.18 | 2.11 (1.59–2.78) | 2.31 (1.71–3.04) | 0.09 | 0.27 (0.21 to 0.34) |
| Caribbean | 25 to 29 | 46.84 (34.39–62.99) | 60.82 (44.76–81.59) | 0.30 | 2.92 (2.14–3.93) | 3.28 (2.42–4.41) | 0.13 | 0.38 (0.32 to 0.44) |
| Caribbean | 30 to 34 | 46.16 (33.78–62.83) | 76.86 (56.71–105.43) | 0.66 | 3.6 (2.63–4.9) | 4.16 (3.07–5.71) | 0.16 | 0.49 (0.43 to 0.54) |
| Caribbean | 35 to 39 | 44.97 (32.97–61.45) | 81.14 (60.24–110.37) | 0.80 | 4.06 (2.98–5.55) | 4.85 (3.6–6.6) | 0.19 | 0.56 (0.52 to 0.61) |
| Caribbean | 40 to 44 | 40.29 (30.66–54.37) | 77.12 (58.64–101.78) | 0.91 | 4.27 (3.25–5.76) | 5.25 (4–6.93) | 0.23 | 0.62 (0.57 to 0.67) |
| Caribbean | 45 to 49 | 33.86 (25.05–45.07) | 77.77 (58.98–99.86) | 1.30 | 4.29 (3.17–5.71) | 5.36 (4.06–6.88) | 0.25 | 0.67 (0.62 to 0.72) |
| Central Europe | 15 to 19 | 142.44 (113.13–184.36) | 91.91 (72.24–119.87) | −0.35 | 2.98 (2.36–3.85) | 3.24 (2.54–4.22) | 0.09 | 0.66 (0.17 to 1.16) |
| Central Europe | 20 to 24 | 213.48 (167.08–273.83) | 163.11 (124.8–213.25) | −0.24 | 4.88 (3.82–6.26) | 5.6 (4.29–7.32) | 0.15 | 0.75 (0.35 to 1.14) |
| Central Europe | 25 to 29 | 287.56 (221.19–372.28) | 268.27 (201.08–350.83) | −0.07 | 6.87 (5.28–8.89) | 8.16 (6.11–10.67) | 0.19 | 0.77 (0.48 to 1.06) |
| Central Europe | 30 to 34 | 385.01 (295.34–503.5) | 382.02 (282.33–506.14) | −0.01 | 7.96 (6.11–10.42) | 9.94 (7.35–13.17) | 0.25 | 0.87 (0.56 to 1.17) |
| Central Europe | 35 to 39 | 444.51 (344.16–577.67) | 453.63 (343.74–598.69) | 0.02 | 9.12 (7.06–11.85) | 10.89 (8.25–14.37) | 0.19 | 0.94 (0.69 to 1.19) |
| Central Europe | 40 to 44 | 414.77 (327.43–527.36) | 522.42 (405.51–664.98) | 0.26 | 9.77 (7.71–12.42) | 11.82 (9.17–15.04) | 0.21 | 0.95 (0.82 to 1.09) |
| Central Europe | 45 to 49 | 342.26 (270.01–426.22) | 522.86 (406.84–655.91) | 0.53 | 10.04 (7.92–12.5) | 12.2 (9.5–15.31) | 0.22 | 0.7 (0.62 to 0.78) |
| Eastern Europe | 15 to 19 | 83.29 (63.62–108.14) | 63.29 (47.97–82.62) | −0.24 | 1.08 (0.82–1.4) | 1.21 (0.92–1.58) | 0.13 | 0.43 (0.39 to 0.47) |
| Eastern Europe | 20 to 24 | 144.21 (107.23–190.58) | 109.38 (81.38–145.58) | −0.24 | 1.96 (1.46–2.59) | 2.28 (1.69–3.03) | 0.16 | 0.51 (0.49 to 0.52) |
| Eastern Europe | 25 to 29 | 273.33 (200.18–365.17) | 207.17 (150.72–279.34) | −0.24 | 3.06 (2.24–4.08) | 3.65 (2.65–4.92) | 0.19 | 0.55 (0.54 to 0.57) |
| Eastern Europe | 30 to 34 | 406.97 (298.51–550.94) | 416.51 (308.99–564.64) | 0.02 | 4.23 (3.1–5.72) | 5.11 (3.79–6.92) | 0.21 | 0.6 (0.58 to 0.62) |
| Eastern Europe | 35 to 39 | 472.59 (351.26–632.41) | 570.57 (418.14–780.07) | 0.21 | 5.29 (3.94–7.08) | 6.47 (4.74–8.84) | 0.22 | 0.64 (0.62 to 0.67) |
| Eastern Europe | 40 to 44 | 429.83 (329.33–570.14) | 599.73 (456.06–805.88) | 0.40 | 6.1 (4.67–8.09) | 7.51 (5.71–10.09) | 0.23 | 0.66 (0.62 to 0.69) |

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**Table 2** (Continued).

| Location | Age (Years) | Incidence Cases | | | Incidence Rates | | | |
|---|---|---|---|---|---|---|---|---|
| | | 1990_Cases (95% UI) | 2021_Cases (95% UI) | Percentage Change in Case (100%) | 1990_per100000 (95% UI) | 2021_per100000 (95% UI) | Percentage Change in ASRs (100%) | EAPC (95% CI) |
| Eastern Europe | 45 to 49 | 375.51 (284.67–485.01) | 620.57 (467.97–801.66) | 0.65 | 6.66 (5.05–8.6) | 8.2 (6.18–10.59) | 0.23 | 0.65 (0.6 to 0.7) |
| Central Asia | 15 to 19 | 47.57 (36.46–61.95) | 55.25 (42.65–73.06) | 0.16 | 1.47 (1.13–1.91) | 1.64 (1.27–2.17) | 0.12 | 0.38 (0.35 to 0.4) |
| Central Asia | 20 to 24 | 81.6 (61.34–106.67) | 104.52 (78.44–136.42) | 0.28 | 2.7 (2.03–3.53) | 3.08 (2.31–4.02) | 0.14 | 0.45 (0.43 to 0.48) |
| Central Asia | 25 to 29 | 133.83 (99.59–176.6) | 191.9 (142.49–256.81) | 0.43 | 4.21 (3.13–5.55) | 4.89 (3.63–6.55) | 0.16 | 0.51 (0.49 to 0.53) |
| Central Asia | 30 to 34 | 155.51 (113.42–208.72) | 282.32 (208.66–382.2) | 0.82 | 5.74 (4.19–7.71) | 6.77 (5–9.17) | 0.18 | 0.56 (0.54 to 0.57) |
| Central Asia | 35 to 39 | 150.83 (113.85–200.59) | 303.53 (229.71–403.67) | 1.01 | 7.04 (5.31–9.36) | 8.39 (6.35–11.16) | 0.19 | 0.59 (0.57 to 0.61) |
| Central Asia | 40 to 44 | 104.82 (80.36–137.01) | 290.34 (222.8–380.65) | 1.77 | 7.95 (6.1–10.39) | 9.53 (7.31–12.49) | 0.20 | 0.61 (0.59 to 0.63) |
| Central Asia | 45 to 49 | 99.48 (76.13–127.5) | 279.52 (212.67–362.8) | 1.81 | 8.5 (6.51–10.9) | 10.18 (7.74–13.21) | 0.20 | 0.59 (0.57 to 0.62) |
| North Africa and Middle East | 15 to 19 | 242.58 (185.48–315.42) | 415.17 (321.08–541.06) | 0.71 | 1.37 (1.05–1.78) | 1.62 (1.25–2.11) | 0.18 | 0.59 (0.54 to 0.64) |
| North Africa and Middle East | 20 to 24 | 339.53 (257.57–440.48) | 644.44 (485.94–848.83) | 0.90 | 2.24 (1.7–2.9) | 2.65 (1.99–3.48) | 0.18 | 0.6 (0.56 to 0.65) |
| North Africa and Middle East | 25 to 29 | 405.65 (303.61–541.61) | 887.12 (653.89–1187.21) | 1.19 | 3.16 (2.36–4.21) | 3.71 (2.73–4.96) | 0.18 | 0.58 (0.54 to 0.62) |
| North Africa and Middle East | 30 to 34 | 425.92 (320.64–569.24) | 1123.67 (828.1–1526.4) | 1.64 | 3.99 (3–5.33) | 4.64 (3.42–6.3) | 0.16 | 0.56 (0.51 to 0.6) |
| North Africa and Middle East | 35 to 39 | 412.03 (312.87–546) | 1270.15 (922.69–1737.15) | 2.08 | 4.63 (3.52–6.14) | 5.35 (3.89–7.32) | 0.16 | 0.54 (0.49 to 0.59) |
| North Africa and Middle East | 40 to 44 | 345.2 (263.68–455.9) | 1166.96 (881.43–1602.11) | 2.38 | 4.91 (3.75–6.48) | 5.68 (4.29–7.8) | 0.16 | 0.53 (0.47 to 0.59) |
| North Africa and Middle East | 45 to 49 | 281.29 (215.07–362.4) | 963.16 (722.91–1266.35) | 2.42 | 4.87 (3.72–6.27) | 5.7 (4.28–7.5) | 0.17 | 0.55 (0.49 to 0.61) |
| South Asia | 15 to 19 | 616 (468.78–803.73) | 1126.09 (856.93–1479.11) | 0.83 | 1.17 (0.89–1.53) | 1.32 (1.01–1.74) | 0.13 | 0.71 (0.48 to 0.93) |
| South Asia | 20 to 24 | 1079.67 (802.64–1426.84) | 2198.64 (1643.71–2927.51) | 1.04 | 2.25 (1.68–2.98) | 2.62 (1.96–3.49) | 0.16 | 0.77 (0.54 to 1) |
| South Asia | 25 to 29 | 1575.9 (1143.55–2106.97) | 3521.21 (2568.83–4745.93) | 1.23 | 3.76 (2.73–5.02) | 4.45 (3.25–6) | 0.18 | 0.81 (0.6 to 1.01) |
| South Asia | 30 to 34 | 1958.72 (1438.13–2652.84) | 4841.8 (3592.97–6540.18) | 1.47 | 5.53 (4.06–7.49) | 6.64 (4.93–8.97) | 0.20 | 0.81 (0.63 to 0.98) |
| South Asia | 35 to 39 | 2251.61 (1682.05–3045.35) | 5851.65 (4347.35–7842.08) | 1.60 | 7.28 (5.44–9.84) | 8.8 (6.54–11.79) | 0.21 | 0.78 (0.64 to 0.92) |
| South Asia | 40 to 44 | 2214.08 (1699.52–2945.12) | 6070.01 (4708–7977.48) | 1.74 | 8.74 (6.71–11.63) | 10.6 (8.22–13.93) | 0.21 | 0.74 (0.64 to 0.84) |
| South Asia | 45 to 49 | 2036.27 (1573.9–2618.01) | 5866.22 (4499.35–7567.63) | 1.88 | 9.82 (7.59–12.63) | 11.91 (9.13–15.36) | 0.21 | 0.69 (0.62 to 0.76) |
| Southeast Asia | 15 to 19 | 89.79 (66.44–119.34) | 112.41 (83.76–149.24) | 0.25 | 0.36 (0.27–0.48) | 0.41 (0.3–0.54) | 0.12 | 0.47 (0.4 to 0.54) |

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|---|---|---|---|---|---|---|---|---|
| Southeast Asia | 20 to 24 | 118.09 (86.93–157.23) | 164.31 (120.37–219.12) | 0.39 | 0.52 (0.38–0.69) | 0.59 (0.44–0.79) | 0.15 | 0.51 (0.46 to 0.57) |
| Southeast Asia | 25 to 29 | 136.36 (98.35–187.1) | 216.84 (156.57–296.29) | 0.59 | 0.66 (0.48–0.9) | 0.77 (0.56–1.06) | 0.17 | 0.53 (0.49 to 0.57) |
| Southeast Asia | 30 to 34 | 136.74 (97.69–187.02) | 251.64 (181.82–346.5) | 0.84 | 0.77 (0.55–1.06) | 0.92 (0.67–1.27) | 0.19 | 0.55 (0.52 to 0.58) |
| Southeast Asia | 35 to 39 | 122.14 (88.63–167.32) | 267.67 (196.13–362.38) | 1.19 | 0.86 (0.62–1.17) | 1.03 (0.76–1.4) | 0.21 | 0.55 (0.51 to 0.59) |
| Southeast Asia | 40 to 44 | 99.64 (75.95–134.95) | 268.39 (202.72–359.18) | 1.69 | 0.91 (0.7–1.24) | 1.1 (0.83–1.47) | 0.20 | 0.52 (0.47 to 0.58) |
| Southeast Asia | 45 to 49 | 86.71 (65.39–114.46) | 251.35 (189.2–328.18) | 1.90 | 0.94 (0.71–1.24) | 1.13 (0.85–1.47) | 0.20 | 0.48 (0.42 to 0.55) |
| East Asia | 15 to 19 | 255.12 (188.04–340.39) | 230.79 (174.75–306.59) | −0.10 | 0.4 (0.3–0.54) | 0.64 (0.49–0.85) | 0.60 | 2.58 (1.67 to 3.5) |
| East Asia | 20 to 24 | 397.73 (291.19–529.55) | 375.26 (276.55–502.14) | −0.06 | 0.6 (0.44–0.8) | 1.04 (0.77–1.4) | 0.74 | 2.92 (2.05 to 3.8) |
| East Asia | 25 to 29 | 442.68 (318.59–600.41) | 635.2 (466.24–852.74) | 0.43 | 0.8 (0.58–1.08) | 1.49 (1.09–2) | 0.86 | 3.1 (2.33 to 3.89) |
| East Asia | 30 to 34 | 431.07 (310.71–591.34) | 1141.22 (828.09–1563.18) | 1.65 | 0.98 (0.71–1.35) | 1.89 (1.38–2.6) | 0.93 | 3.16 (2.5 to 3.83) |
| East Asia | 35 to 39 | 503.85 (369.55–692.81) | 1190.87 (882.98–1615.82) | 1.36 | 1.11 (0.81–1.52) | 2.23 (1.65–3.03) | 1.02 | 3.19 (2.63 to 3.76) |
| East Asia | 40 to 44 | 397.21 (301.4–533.34) | 1130.64 (860.37–1473.03) | 1.85 | 1.2 (0.91–1.61) | 2.43 (1.85–3.17) | 1.02 | 3.17 (2.67 to 3.68) |
| East Asia | 45 to 49 | 320.05 (242.48–419.61) | 1426.39 (1098.57–1837.75) | 3.46 | 1.26 (0.95–1.65) | 2.54 (1.96–3.27) | 1.02 | 3.13 (2.69 to 3.58) |
| Oceania | 15 to 19 | 1.16 (0.84–1.59) | 2.41 (1.77–3.26) | 1.09 | 0.35 (0.25–0.48) | 0.39 (0.29–0.53) | 0.12 | 0.34 (0.32 to 0.36) |
| Oceania | 20 to 24 | 1.56 (1.12–2.11) | 3.56 (2.55–4.79) | 1.28 | 0.52 (0.37–0.7) | 0.59 (0.42–0.8) | 0.14 | 0.41 (0.38 to 0.43) |
| Oceania | 25 to 29 | 1.85 (1.32–2.58) | 4.59 (3.26–6.35) | 1.49 | 0.69 (0.5–0.97) | 0.8 (0.57–1.11) | 0.16 | 0.45 (0.42 to 0.48) |
| Oceania | 30 to 34 | 1.86 (1.33–2.59) | 5.14 (3.6–7.29) | 1.76 | 0.85 (0.61–1.18) | 1 (0.7–1.42) | 0.17 | 0.48 (0.44 to 0.51) |
| Oceania | 35 to 39 | 1.73 (1.25–2.43) | 5.21 (3.85–7.32) | 2.01 | 0.98 (0.71–1.37) | 1.15 (0.85–1.62) | 0.18 | 0.5 (0.45 to 0.54) |
| Oceania | 40 to 44 | 1.52 (1.15–2.09) | 4.91 (3.69–6.75) | 2.22 | 1.06 (0.8–1.45) | 1.26 (0.95–1.73) | 0.19 | 0.52 (0.46 to 0.57) |
| Oceania | 45 to 49 | 1.27 (0.96–1.67) | 4.3 (3.14–5.68) | 2.37 | 1.11 (0.83–1.46) | 1.33 (0.97–1.76) | 0.20 | 0.55 (0.49 to 0.61) |
| Western Sub-Saharan Africa | 15 to 19 | 50.75 (38.5–66.52) | 144.66 (108.76–189.13) | 1.85 | 0.5 (0.38–0.65) | 0.52 (0.39–0.68) | 0.05 | 0.08 (0.04 to 0.13) |
| Western Sub-Saharan Africa | 20 to 24 | 73.35 (54.39–99.05) | 205.76 (152.63–274.68) | 1.81 | 0.83 (0.62–1.12) | 0.89 (0.66–1.18) | 0.07 | 0.1 (0.04 to 0.16) |
| Western Sub-Saharan Africa | 25 to 29 | 91.93 (67.22–122.24) | 260.71 (192.14–346.12) | 1.84 | 1.24 (0.9–1.64) | 1.33 (0.98–1.77) | 0.08 | 0.1 (0.02 to 0.18) |
| Western Sub-Saharan Africa | 30 to 34 | 99.5 (73.06–134.58) | 293.4 (215.68–398.95) | 1.95 | 1.66 (1.22–2.24) | 1.8 (1.33–2.45) | 0.09 | 0.09 (−0.01 to 0.19) |
| Western Sub-Saharan Africa | 35 to 39 | 94.51 (70.36–127.15) | 300.37 (225.24–403.3) | 2.18 | 2.04 (1.52–2.75) | 2.23 (1.67–2.99) | 0.09 | 0.07 (−0.04 to 0.18) |

(*Continued*)

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**Table 2** (Continued).

| Location | Age (Years) | Incidence Cases | | | Incidence Rates | | | |
|---|---|---|---|---|---|---|---|---|
| | | 1990_Cases (95% UI) | 2021_Cases (95% UI) | Percentage Change in Case (100%) | 1990_per100000 (95% UI) | 2021_per100000 (95% UI) | Percentage Change in ASRs (100%) | EAPC (95% CI) |
| Western Sub-Saharan Africa | 40 to 44 | 82.78 (63.43–108.27) | 278.17 (213.56–358.28) | 2.36 | 2.34 (1.79–3.06) | 2.56 (1.96–3.3) | 0.09 | 0.06 (−0.06 to 0.18) |
| Western Sub-Saharan Africa | 45 to 49 | 75.43 (58.06–96.73) | 246.29 (189.78–315.44) | 2.26 | 2.55 (1.96–3.27) | 2.8 (2.16–3.59) | 0.10 | 0.06 (−0.07 to 0.19) |
| Eastern Sub-Saharan Africa | 15 to 19 | 52.01 (38.91–69.2) | 139.69 (105.92–183.64) | 1.69 | 0.51 (0.38–0.67) | 0.57 (0.43–0.75) | 0.12 | 0.45 (0.4 to 0.49) |
| Eastern Sub-Saharan Africa | 20 to 24 | 73.58 (53.76–98.31) | 205.54 (152.71–274.48) | 1.79 | 0.84 (0.62–1.13) | 0.97 (0.72–1.3) | 0.16 | 0.53 (0.48 to 0.58) |
| Eastern Sub-Saharan Africa | 25 to 29 | 91.09 (66.4–121.22) | 258.33 (190.24–343.14) | 1.84 | 1.25 (0.91–1.66) | 1.48 (1.09–1.97) | 0.19 | 0.63 (0.58 to 0.67) |
| Eastern Sub-Saharan Africa | 30 to 34 | 96.52 (70.62–130.94) | 293.2 (217.15–402.58) | 2.04 | 1.67 (1.22–2.27) | 2.03 (1.5–2.78) | 0.21 | 0.72 (0.67 to 0.77) |
| Eastern Sub-Saharan Africa | 35 to 39 | 95.88 (71.44–128.79) | 306.57 (231.04–410.95) | 2.20 | 2.04 (1.52–2.74) | 2.53 (1.9–3.39) | 0.24 | 0.8 (0.74 to 0.85) |
| Eastern Sub-Saharan Africa | 40 to 44 | 81.14 (62.4–105.88) | 287.16 (219.47–374.37) | 2.54 | 2.34 (1.8–3.05) | 2.92 (2.23–3.8) | 0.25 | 0.86 (0.79 to 0.92) |
| Eastern Sub-Saharan Africa | 45 to 49 | 73.14 (56.28–94.13) | 240.92 (185.57–310.72) | 2.29 | 2.54 (1.95–3.27) | 3.2 (2.46–4.12) | 0.26 | 0.9 (0.84 to 0.97) |
| Central Sub-Saharan Africa | 15 to 19 | 15.63 (11.76–21.31) | 46.75 (35.51–62.99) | 1.99 | 0.55 (0.42–0.75) | 0.63 (0.48–0.85) | 0.14 | 0.46 (0.43 to 0.5) |
| Central Sub-Saharan Africa | 20 to 24 | 22.34 (16.34–29.74) | 67.8 (50.61–90.45) | 2.03 | 0.92 (0.67–1.22) | 1.1 (0.82–1.46) | 0.19 | 0.61 (0.58 to 0.65) |
| Central Sub-Saharan Africa | 25 to 29 | 28.06 (20.77–37.69) | 87.91 (64.09–118.26) | 2.13 | 1.34 (1–1.81) | 1.67 (1.22–2.25) | 0.24 | 0.75 (0.72 to 0.78) |
| Central Sub-Saharan Africa | 30 to 34 | 30.04 (21.5–40.48) | 102.73 (74.39–141.59) | 2.42 | 1.77 (1.27–2.39) | 2.28 (1.65–3.14) | 0.29 | 0.86 (0.84 to 0.89) |
| Central Sub-Saharan Africa | 35 to 39 | 29.83 (22.17–40.16) | 106.21 (79.77–144.43) | 2.56 | 2.14 (1.59–2.88) | 2.83 (2.12–3.85) | 0.32 | 0.97 (0.95 to 1) |
| Central Sub-Saharan Africa | 40 to 44 | 24.55 (18.71–32.38) | 100 (77.02–133.3) | 3.07 | 2.39 (1.83–3.16) | 3.25 (2.5–4.33) | 0.36 | 1.07 (1.04 to 1.1) |
| Central Sub-Saharan Africa | 45 to 49 | 22.95 (17.2–29.75) | 87.69 (67.64–113.93) | 2.82 | 2.55 (1.91–3.31) | 3.53 (2.72–4.59) | 0.38 | 1.14 (1.11 to 1.18) |
| Southern Sub-Saharan Africa | 15 to 19 | 16.74 (12.63–21.96) | 21.28 (16.08–28.29) | 0.27 | 0.57 (0.43–0.74) | 0.59 (0.45–0.79) | 0.05 | 0.18 (0.13 to 0.23) |
| Southern Sub-Saharan Africa | 20 to 24 | 24.98 (18.39–33.36) | 34.09 (25.17–46.09) | 0.36 | 0.96 (0.71–1.29) | 1.02 (0.75–1.37) | 0.05 | 0.18 (0.13 to 0.24) |
| Southern Sub-Saharan Africa | 25 to 29 | 32.99 (24.31–44.21) | 53.12 (39.2–70.62) | 0.61 | 1.46 (1.07–1.95) | 1.52 (1.12–2.02) | 0.04 | 0.19 (0.12 to 0.26) |
| Southern Sub-Saharan Africa | 30 to 34 | 36.46 (26.32–50.13) | 71.56 (52.17–96.25) | 0.96 | 1.98 (1.43–2.72) | 2.05 (1.5–2.76) | 0.04 | 0.2 (0.11 to 0.28) |
| Southern Sub-Saharan Africa | 35 to 39 | 36.91 (27.8–49.85) | 80.47 (60.6–108.33) | 1.18 | 2.45 (1.84–3.3) | 2.54 (1.91–3.42) | 0.04 | 0.22 (0.12 to 0.31) |
| Southern Sub-Saharan Africa | 40 to 44 | 32.95 (25.31–43.03) | 73.8 (56.69–95.74) | 1.24 | 2.81 (2.16–3.67) | 2.92 (2.24–3.79) | 0.04 | 0.24 (0.13 to 0.34) |
| Southern Sub-Saharan Africa | 45 to 49 | 29.03 (22.21–37.06) | 67.06 (51.83–85.7) | 1.31 | 3.05 (2.33–3.89) | 3.19 (2.47–4.08) | 0.05 | 0.27 (0.16 to 0.37) |

## Sociodemographic Index and Disease Burden of Inflammatory Bowel Disease Among Women of Reproductive Age

Based on global data from 1990 to 2021, we assessed the relationship between the SDI and the burden of IBD among women of reproductive age (Figure S1). At the regional level, the associations between ASIR and ASPR with SDI were relatively consistent. Both ASIR and ASPR showed modest increases with rising SDI, with a significant acceleration once SDI exceeded 0.65. They reached their peak around an SDI of 0.82, after which they declined rapidly. In contrast, the ASDR and ASMR initially increased as SDI rose above 0.3, but decreased between SDI values of 0.3 to 0.48. Afterward, ASDR showed a slight increase, rising sharply between SDI values of 0.6 and 0.81, and then decreasing again when SDI exceeded 0.81. However, ASMR stabilized once SDI exceeded 0.3, showing a slight decrease when SDI surpassed 0.8. Notably, regions such as Australasia, High-Income North America, and Western Europe consistently had ASIR, ASPR, and ASDR values well above the expected levels, while South Asia exhibited higher-than-expected ASIR and ASPR values. On the other hand, regions like High-Income Asia Pacific, East Asia, Oceania, Southeast Asia, and Andean Latin America consistently had lower-than-expected values for ASIR, ASPR, ASDR, and ASMR (Figure S1A–D).

At the country level, both ASIR and ASPR increased gradually with rising SDI, with a more rapid growth once SDI exceeded 0.7. Conversely, ASDR and ASMR exhibited an upward trend when SDI was below 0.25, followed by a gradual decline once SDI surpassed 0.25. However, when SDI exceeded 0.75, ASDR began to rise again, while ASMR remained relatively stable Canada and the Netherlands consistently had higher-than-expected ASIR and ASPR values, whereas El Salvador, Mexico, and the Philippines had values consistently below expectations. Guinea-Bissau, Mali, and Gambia exhibited higher-than-expected ASDR and ASMR, while the Northern Mariana Islands showed lower-than-expected rates (Figure S1E–H).

## Decomposition Analysis of Inflammatory Bowel Disease Burden Among Women of Reproductive Age

Figure S2 and Table S11 present the relative contributions of aging, population growth, and epidemiological changes to the global burden of IBD among women of reproductive age. On a global scale, population growth contributed the most to the increase in incidence, prevalence, DALYs, and mortality, accounting for 77.32%, 104.84%, 100.16%, and 95.01%, respectively. Aging also made positive contributions to all four indicators, although it was not the dominant factor. Notably, epidemiological changes had a negative impact on prevalence, DALYs, and mortality, but a positive effect on incidence (Figure S2 and Table S11).

The most significant contributions from aging, population growth, and epidemiological changes were observed in DALYs in the High-middle SDI region, with contributions of 698.09%, 394.98%, and −993.07%, respectively. In this region, population growth was no longer the predominant factor driving changes in disease burden, with aging and epidemiological changes becoming more influential. Aging and population growth contributed negatively to mortality, while aging had a larger positive impact on the increase in incidence compared to population growth. In contrast, in the Low SDI region, epidemiological changes contributed positively to all four indicators, and the contribution from aging decreased. In Western Europe, the contributions from aging, population growth, and epidemiological changes to DALYs were particularly notable, with values of −2880.99%, 1062.07%, and 1918.92%, respectively (Figure S2 and Table S11).

## Predictions of Global Inflammatory Bowel Disease Burden Among Women of Reproductive Age Using Eight Machine Learning Algorithms, 2022-2050

Based on our comprehensive evaluation of eight machine learning algorithms, the ARIMA model demonstrated the best performance in predicting the global incidence, prevalence, and DALY rates of IBD among women of reproductive age. The model showed superior performance across multiple evaluation metrics, including the lowest mean squared error (MSE), mean absolute percentage error (MAPE), and the highest coefficient of determination ($R^2$). Overall, the ARIMA model achieves the optimal performance in terms of prediction accuracy, goodness of fit, and robustness, with no critical performance shortcomings. According to the ARIMA model's projections for 2022–2050, the incidence, prevalence, and DALY rates of IBD are expected to decline overall. Specifically, the incidence rate is predicted to slightly increase from 2024 to 2029 before

stabilizing and declining thereafter; the prevalence rate is expected to show a modest increase between 2023 and 2026, followed by a gradual decline; and the DALY rate is projected to continuously decline (Figure S3 and Tables S12-14).

In terms of mortality prediction, the Prophet model stands out the most, as it is significantly superior to other models in terms of robustness, prediction accuracy, and goodness of fit. According to the Prophet model's predictions, the mortality rate for IBD among women of reproductive age is expected to exhibit fluctuating growth from 2022 to 2050. This trend warrants particular attention, as the increasing mortality rate underscores the need for improved healthcare interventions and early detection strategies to mitigate the burden of IBD in this population (Figure S3, Tables S15 and S16).

## Discussion

This study, based on the most recent GBD2021 data, provides a comprehensive analysis of the global burden of IBDamong women of reproductive age from 1990 to 2021. The analysis encompasses incidence, prevalence, mortality, and DALYs across global, five SDI subregions, 21 GBD regions, and 204 countries, with trends and a further exploration of age distribution, burden decomposition analysis, and projections for the next 29 years. Over the past three decades, the global burden of IBD among women of reproductive age has shown a slight upward trend in terms of incidence, prevalence, DALYs, and mortality, indicating an increasing impact of the disease on this population. Decomposition analysis reveals that population growth is a significant factor contributing to this trend. Furthermore, the ongoing urbanization, industrialization, and cultural Westernization in many regions, leading to changes in lifestyle and dietary patterns, may further increase the susceptibility to IBD.[3,4] Although the ASIR has slightly increased, the relative decline in ASPR, ASDR, and ASMR reflects improvements in healthcare. Enhanced diagnostic technologies, treatment options, and disease management may be the main drivers of these changes.[17] However, with the increase in ASIR, it remains crucial to continuously monitor new potential risk factors and implement effective intervention measures.

There are significant differences in the burden of IBD across various SDI regions. High SDI regions continue to bear the heaviest burden of IBD among women of reproductive age, consistent with findings on the burden of IBD across all age groups.[3] Most high SDI countries are Western nations, where IBD originated and was previously considered a Western disease.[18] These regions began with a higher baseline burden and have already entered the third stage of epidemiology (complex prevalence), although they have not yet fully achieved a balanced prevalence.[19] Therefore, optimizing lifestyle, improving environmental factors, and implementing precision medical interventions to reduce the impact of IBD on women of reproductive age remain key issues in these regions. On the other hand, the death burden is more pronounced in lower-middle and low SDI regions, likely due to limited medical resources and lower diagnostic and treatment levels. IBD diagnosis requires colonoscopy, which is often inaccessible to most people living in low-income countries, potentially leading to delayed diagnoses and missed optimal treatment windows.[20] Additionally, emerging IBD treatments, such as targeted adhesion molecule therapies, cytokine inhibitors, stem cell therapy, gut-brain axis regulation, and host-microbiome interactions, while promising, are costly, and some patients in low-income countries may not afford these treatments.[21] This highlights the critical need to improve diagnostic and treatment capabilities and increase health interventions in these regions.

In middle SDI regions, while both incidence and prevalence have risen significantly, mortality and DALY rates show a downward trend. This phenomenon may reflect the dual changes occurring in these countries as they advance through industrialization and urbanization.[22] The widespread adoption of a Western lifestyle, particularly dietary changes, has led to a shift toward diets high in protein, fats, and refined carbohydrates, which may disrupt the gut microbiota and promote the onset and progression of IBD.[23] Furthermore, the transition in lifestyle is associated with reduced physical activity, increased obesity rates, higher psychological stress, sleep disturbances, and widespread unhealthy behaviors like smoking, all of which further increase the risk of IBD onset and relapse.[24] However, the gradual improvement in healthcare and stronger disease management and early intervention measures in these regions have contributed to the reduction in mortality and DALY rates. This positive change is attributed to advances in treatment methods. For instance, since 2016, the US Food and Drug Administration has approved a variety of TNF-α inhibitors for the clinical treatment of IBD.[25] By precisely inhibiting inflammatory pathways, these drugs effectively delay disease progression and reduce complications. Consequently, they not only improve patients' survival rates and quality of life but also significantly alleviate the overall disease burden of IBD. This trend suggests that as healthcare resources and health management improve, the fatality of IBD can be effectively controlled. Based on these findings, future efforts in moderate SDI regions should focus on reducing the incidence of IBD from its source,

lowering prevalence, and implementing effective disease management strategies through policy guidance, lifestyle interventions, and precision medicine to further reduce the overall burden of IBD.

Traditionally, the geographic distribution of IBD was thought to be influenced by racial and regional factors, with a primary impact on Western European populations.[26] However, as globalization accelerates, this geographic difference is diminishing. The incidence and prevalence of IBD in Asian populations have risen significantly.[27,28] Our study finds that South Asia bears the heaviest burden of IBD among reproductive-age women, surpassing that of Western countries. This region has the highest rates of incidence, prevalence, DALYs, and mortality. Additionally, the incidence and prevalence of IBD in East Asia have also seen notable increases. Whether Asian IBD differs from Western IBD in terms of heterogeneity remains a subject of ongoing research. Some studies suggest that compared to the West, the burden of ulcerative colitis (UC) in Asia is higher, and UC patients in Asia tend to have better prognoses.[29,30] The differences in genetic backgrounds across regions also play a crucial role in the disparities in IBD burden. For example, common NOD2 gene mutations in Western IBD patients are not associated with IBD patients in India, China, Korea, and Japan,[31,32] but new genetic mutations have been identified in IBD patients from these Asian countries.[33] Therefore, genetic studies on IBD in Asia and the exploration of new susceptibility genes could provide important insights for developing new treatment methods for the region.

Regarding the age distribution of IBD in women of reproductive age, our results show that the burden of IBD increases with age. Both in terms of absolute numbers and age-standardized rates, the 40–49 age group has the most significant burden. This trend is likely due to the physiological changes associated with aging, such as a decline in immune function, as well as the cumulative effects of prolonged exposure to various environmental and lifestyle factors.[34] For high-risk age groups, implementing more precise screening, timely diagnosis, and personalized treatment plans is crucial to effectively control disease progression and prevent further deterioration. Additionally, the significant rise in ASDR and ASMR in the 20–24 age group warrants attention. Our study suggests that this phenomenon is primarily observed in low and lower-middle SDI regions, where healthcare resources are insufficient and public health awareness is low,[35] resulting in a more pronounced impact of IBD. Furthermore, low SDI regions tend to have higher fertility rates and younger populations, with early marriage and childbearing being common.[36] As 20–24 years is considered the ideal age for marriage, pregnancy can trigger IBD complications, thereby increasing the risk of disability and mortality in this group. Therefore, it is essential to focus on the young female population in these regions and implement targeted disease prevention and health management strategies to identify and address the underlying factors contributing to the increased risk.

Looking ahead to 2050, the machine learning model predictions present a mixed outlook. The overall downward trend in incidence, prevalence, and DALYs predicted by the ARIMA model is optimistic. However, the short-term fluctuations in incidence and prevalence, such as slight increases during specific periods, remind us that the path to reducing the IBD burden may not be linear. These fluctuations may be influenced by emerging factors such as environmental stressors, changes in pathogen prevalence, or healthcare policy shifts.[37] Nevertheless, the steady decline in DALYs indicates that future efforts in disease management and treatment may have a positive impact on reducing the overall harm caused by IBD. Conversely, the predicted increase in mortality, as indicated by the Prophet model, is concerning. This suggests that while disease incidence and prevalence may improve, the ability to prevent severe outcomes and save lives may face challenges. This may be due to the increasing complexity of IBD cases, potential drug resistance, or difficulties in providing timely and appropriate end-of-life care.[38] Therefore, focusing on improving intensive care and developing new treatment strategies to address the rising mortality risk becomes crucial.

## Limitations

This study has several limitations. First, while the GBD data provides a broad overview of global trends, the accuracy of IBD incidence and prevalence estimates may be affected by variations in diagnostic capabilities across regions. In regions with limited healthcare infrastructure, the true burden of IBD may be underreported. Second, the projections are based on historical data and models that may not account for future changes in environmental, dietary, and genetic factors that could influence IBD trends. Finally, the analysis did not include an in-depth exploration of specific risk factors or genetic predispositions, which would be valuable for understanding the drivers behind the observed trends.

## Conclusion

In conclusion, this study provides a comprehensive analysis of the global burden of IBD among women of reproductive age from 1990 to 2021, utilizing GBD2021 data. We observed a steady increase in IBD incidence, prevalence, DALYs, and mortality, with notable regional variations. High SDI regions show improved healthcare outcomes, evidenced by declining mortality and DALYs, while low and lower-middle SDI regions face significant challenges due to limited healthcare access and lower awareness. Our age-specific analysis reveals a higher burden among women aged 40–49, with alarming increases in disability and mortality in the 20–24 age group in low SDI regions. Projections for 2050 suggest a continued decline in incidence and DALYs but a concerning rise in mortality, highlighting the need for targeted prevention, early diagnosis, and better treatment strategies, particularly in resource-limited settings.

## Provenance and Peer Review

Not commissioned, externally peer-reviewed.

## Data Sharing Statement

The data used for the analyses in the study are publicly available at https://ghdx.healthdata.org/gbd-2021.

## Consent for Publication

Agree to publish.

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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 no competing interests in this work.

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