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Original Article

Global, regional, and national burden of inflammatory bowel disease from 1990 to 2021: findings from the Global Burden of Disease 2021

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Abstract

Background: Inflammatory bowel disease (IBD) imposes a significant economic and social burden. We aimed to assess the burden of IBD globally, regionally, and nationally.

Methods: The incidence, mortality, prevalence, and disability-adjusted life year were obtained from Global Burden of Disease 2021. Estimated annual percentage change, average annual percent change, and age-period-cohort model were used to access trends. Associations between age-standardized rate (ASR) and socio-demographic index were explored. Predictions were made using Bayesian age-period-cohort model and Nordpred.

Results: In 2021, IBD affected 3.8 million people, with ASR of incidence and death of 4.4 and 0.5. The global ASR of incidence increased from 1990 to 2021, while ASR of death, prevalence, and disability-adjusted life year decreased. The age-standardized death rate (ASDR) did not show a significant increase from 2019 to 2021 in most regions and countries. High-incidence regions, such as Western Europe, continued to face significant burdens. East Asian, especially China, was experiencing a sharp increase in incidence. ASR of incidence and death increased with rising socio-demographic index. By 2035, the ASR of incidence and death of IBD will gradually decline.

Conclusion: The global burden of IBD remains severe with changing epidemiological trends. Reducing the burden requires changes in public health policies, disease prevention, and healthcare services.

Keywords: inflammatory bowel disease; Global Burden of Disease; age-standardized rate; disease burden

Introduction

Inflammatory bowel disease (IBD) imposes a high incidence and significant societal costs. It may result from an inappropriate immune response of a genetically susceptible host to environmental factors [1]. Although the incidence of IBD appears to be stabilizing in many Western countries, the numbers remain high [2]. It is estimated that the annual treatment cost of IBD in the USA exceeded 10 billion dollars, with indirect costs being even harder to estimate [3]. Compared with patients without IBD, patients with IBD faced over three times the economic burden [4]. Additionally, the emergence of new, increasingly sophisticated drugs and disease management models further exacerbates the financial burden [5]. Proper assessment of global, regional, and national epidemiological trends helps achieve better disease control, management, and prevention, thereby saving medical costs.

The Global Burden of Disease (GBD) study is the most comprehensive global observational epidemiological research, integrating data from 328,938 sources. It serves as an invaluable resource for evaluating health status and trends worldwide. The latest GBD study analyzed data spanning 1990 to 2021, encompassing 204 countries and regions, 371 diseases and injuries, and 88 risk factors [6]. This provides significant data support for health sector leaders, clinicians, and researchers. Different regions and countries experienced different stages of IBD prevalence at different times [7]. Meanwhile, the corona virus disease 2019 (COVID-19) pandemic had also increased the global all-cause mortality (5.1% from 2020 to 2021) [6]. Given the evolving temporal, regional, and developmental variations, along with the impact of the COVID-19 pandemic, a comprehensive analysis of the global burden of IBD is crucial for improving disease assessment, management, and control. We utilized the latest estimates from

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the GBD 2021 study to evaluate the burden and trends of IBD globally, regionally, and nationally, to predict the disease burden in the near future, also to explore the impact of the COVID-19 pandemic on death of IBD. By comprehensively understanding the disease burden and trends in different regions and countries, we aimed to provide effective support for healthcare policy reform, resource allocation, and system improvement to better meet the health needs of the population.

Materials and methods

Study data

The GBD study assessed the impact of diseases, disabilities, and risk factors on population health at global and regional levels to provide comprehensive data supporting and public health decision-making. The GBD Results tool collects information on the incidence, mortality, prevalence, and disability-adjusted life years (DALYs) of IBD annually from 1990 to 2021, categorized by age, sex, region, and country. The data and results are expressed as numbers or rates with 95% uncertainty intervals. DALYs are calculated by adding years lived with disability and years of life lost, serving as an evaluation of disease burden [8]. We classified countries into five categories based on the socio-demographic index (SDI) index (high SDI, high-middle SDI, middle SDI, low-middle SDI, and low SDI) [9]. Additionally, the globe is divided into 21 regions based on geography.

For GBD 2021, IBD was determined according to the 10th revision of the International Classification of Diseases (ICD-10 codes: K50–K52, K52.8–K52.9). Detailed data retrieval methods can be found in the Supplementary Methods. The definition of reference cases included cases diagnosed in patients with appropriate clinical signs and symptoms through endoscopy, imaging studies, or biopsy, or cases identified using an ICD-based case identification algorithm through patient databases (including inpatient and outpatient care). The non-reference datapoints were adjusted toward the reference in GBD 2021, using a meta-regression approach, which were able to bypass compositional bias and adjust non-reference datapoints more accurately (https://www.healthdata.org/gbd/methods-appendices-2021). GBD prevalence estimates extracted from Institute for Health Metrics and Evaluation-processed inpatient discharge and claims data were excluded. Similar to GBD 2019, GBD 2021 used two IBD databases as inputs for two independent, complete DisMod models. Additionally, GBD 2021 incorporated high-quality systematic review and administrative data from Canada that were extracted using a validated algorithm [7, 10].

Statistical analysis

We used age-standardized rates (ASRs) and estimated annual percentage change (EAPC) to quantify trends in the incidence, mortality, prevalence, and DALYs [11]. Additionally, joinpoint regression analysis was used to analyze the annual percentage change (APC) and average annual percent change (AAPC) of incidence, prevalence, mortality, and DALYs along with their corresponding 95% confidence intervals (CIs) [12]. Age standardization facilitates the comparison of different age structures or the same population's age structure at different periods. The ASR (per 100,000 population) calculated by the direct method involves multiplying the age-specific rate of each age group by the weights of the same age group in the selected standard population, summing these products, and then dividing by the total sum of the standard population weights. The standard population used was the GBD 2021 standard population [6]. Total percent change can be directly obtained from the GBD Results tool. We retrieved the total percent change in global, regional, and national disease burden from 1990 to 2021 and from 2019 to 2021 to determine the impact of the COVID-19 pandemic on mortality of IBD.

If the EAPC estimate and its 95% CI >0, the ASR is considered to be increasing, and vice versa. We assessed the association between EAPC and ASR in 1990 and Human Development Index (HDI) in 2021 at the national level. HDI data for each country were sourced from Human Development Reports [13]. We also performed stratified cluster analysis, categorizing countries into four classes based on the EAPC of incidence or death of IBD. We determined the socioeconomic development status of a country or region and its relation to the burden of IBD using the SDI. The SDI ranges from 0 (worst) to 1 (best) and is composed of total fertility rate under 25 years, mean years of schooling for the population aged 15 and over, and per capita income; higher SDI values indicate more developed countries [14].

We used the age-period-cohort model to examine the global trends by age, period, and birth cohort from 1990 to 2021 using the Age-Period Cohort Web Tool. Net drift represents the overall log-linear trend of the population stratified by period and birth cohort, indicating the overall APC in the expected age-adjusted rate, and local drift represents the log-linear trend of each age group stratified by period and birth cohort, indicating the APC over time in the expected age-specific rate [15]. The longitudinal age curve displays the expected age-specific rate in the reference cohort, adjusted for period effects, and the period (or cohort) rate ratio represents the ratio of the age-specific rate in each period (or cohort) relative to the reference rate [15]. Finally, to further predict future trends in IBD based on the latest data, we obtained global population estimates (2017–2100) from the GBD database (https://ghdx.healthdata.org/record/ihme-data/global-population-forecasts-2017-2100). We analyzed using the Bayesian age-period-cohort (BAPC) with nested Laplace approximation. The BAPC model assumes a relationship between incidence or mortality and age structure and population size [16]. The advantage of the BAPC model is that it directly approximates the posterior marginal distribution, does not require convergence diagnostics, and achieves high accuracy. Compared with the generalized additive model, the smooth spline model, the Nordpred model, and Poisson regression, the BAPC model has higher accuracy in predicting the short- and medium-term burden [17]. Nordpred was used for supplementary analysis, considering changes in incidence rates and population structure, to predict sex-specific burden by 2035 [18].

All statistical analyses and graphical representations were conducted using R-4.2.2, Joinpoint Trend Analysis Software (5.0), and GraphPad Prism (9.5.1). A P value of less than 0.05 was considered statistically significant.

Results

Global burden of IBD in 2021

In 2021, the global prevalent cases of IBD were 3,830,119, with 375,140 incident cases and 42,423 deaths, resulting in a cumulative total of 1,510,784 DALYs (Table 1). The global age-standardized incident rate (ASIR) and age-standardized death rate (ASDR) in 2021 were 4.4 (95% uncertainty interval: 3.9–5.2) and 0.5 (95% uncertainty interval: 0.5–0.6), respectively. The highest incident cases occurred in the 35–50 age group, with the highest ASIR in the 60–64 age group (Figure 1A). With increasing age, the global number of IBD deaths and ASDR in 2021 also increased, with the highest ASDR in the 95–99 age group (Figure 1B). The 50–54 age group had the highest prevalence of IBD. As age increased, the age-standardized prevalent rate (ASPR) of both males and females

Table 1. Global, regional, and national burden of IBD from 1990 to 2021[c]

	1990		2021		1990–2021		
Location	**Incident cases (95% UI)**	**ASR per 100,000 (95% UI)**	**Incident cases (95% UI)**	**ASR per 100,000 (95% UI)**	**EAPC (95% CI)**	**AAPC (95% CI)**	**TPC (95% CI)**
Global	199235.9 (174583.8–232676.2)	4.2 (3.7–4.9)	375140 (327686–436925)	4.4 (3.9–5.2)	0.29 (0.20–0.38)	0.16 (0.07–0.24)	0.05 (0.04–0.07)
High SDI	104710.9 (93318.3–120553.5)	10.6 (9.5–12.3)	158046 (139737–180170)	11.6 (10.1–13.4)	0.33 (0.21–0.46)	0.27 (0.22–0.32)	0.09 (0.06–0.11)
High-middle SDI	32333.9 (28390.3–37886.6)	3.0 (2.6–3.5)	53486 (46612–63298)	3.3 (2.8–3.9)	0.48 (0.33–0.64)	0.29 (0.20–0.38)	0.10 (0.07–0.12)
Middle SDI	22846.1 (19540.7–27838.7)	1.6 (1.4–1.9)	64887 (56016–78446)	2.4 (2.0–2.9)	1.54 (1.38–1.7)	1.37 (1.11–1.62)	0.50 (0.48–0.52)
Low-middle SDI	30776.5 (26407.0–37156.7)	3.6 (3.2–4.3)	75380 (64725–91310)	4.3 (3.7–5.1)	0.55 (0.49–0.62)	0.54 (0.45–0.62)	0.18 (0.16–0.20)
Low SDI	8373.3 (7159.3–10141.8)	2.5 (2.2–3.1)	23065 (19690–27960)	3.0 (2.6–3.6)	0.57 (0.54–0.61)	0.52 (0.46–0.58)	0.17 (0.15–0.20)
East Asia	8632.7 (7283.5–10588.2)	0.7 (0.6–0.9)	25532 (22107–30530)	1.4 (1.2–1.7)	2.88 (2.37–3.40)	2.05 (1.49–2.61)	0.87 (0.82–0.92)
China	8315.7 (7018–10181.6)	0.7 (0.6–0.9)	24941 (21583–29821)	1.4 (1.2–1.7)	2.93 (2.41–3.46)	2.09 (1.46–2.72)	0.89 (0.84–0.94)
Location	**Dead cases (95% UI)**	**ASR per 100,000 (95% UI)**	**Dead cases (95% UI)**	**ASR per 100,000 (95% UI)**	**EAPC (95% CI)**	**AAPC (95% CI)**	**TPC (95% CI)**
Global	21417.7 (18422.8–23612.6)	0.6 (0.5–0.7)	42423 (37537–46502)	0.5 (0.5–0.6)	-0.31 (-0.48 to -0.14)	-0.49 (-0.68 to -0.29)	-0.13 (-0.22 to -0.02)
High SDI	7616.8 (7023.7–8006.5)	0.7 (0.7–0.7)	19080 (16203–20658)	0.8 (0.7–0.9)	0.84 (0.52–1.17)	0.39 (0.07–0.70)	0.13 (0.07–0.20)
High-middle SDI	4692.1 (4305.2–5212.5)	0.5 (0.5–0.6)	7445 (6481–8795)	0.4 (0.3–0.5)	-0.99 (-1.09 to -0.89)	-0.82 (-1.17 to -0.47)	-0.24 (-0.32 to -0.13)
Middle SDI	4902.5 (3456.1–5923.3)	0.5 (0.3–0.6)	7911 (6468–9100)	0.3 (0.3–0.4)	-1.67 (-1.80 to -1.53)	-1.48 (-1.71 to -1.26)	-0.36 (-0.49 to -0.14)
Low-middle SDI	2884.3 (2101.7–3511.7)	0.5 (0.3–0.6)	5211 (4305–6489)	0.4 (0.3–0.5)	-0.77 (-0.82 to -0.71)	-0.74 (-0.96 to -0.51)	-0.20 (-0.41 to 0.04)
Low SDI	1300.8 (917.9–1610.7)	0.5 (0.4–0.7)	2741 (1910–3422)	0.5 (0.3–0.6)	-0.42 (-0.49 to -0.35)	-0.41 (-0.56 to -0.25)	-0.12 (-0.26 to 0.05)
Australasia	72.9 (66.6–79.5)	0.3 (0.3–0.4)	449 (370–504)	0.7 (0.6–0.8)	3.54 (2.62–4.46)	2.91 (1.53–4.30)	1.22 (0.96–1.47)
Australia[a]	60.3 (54.9–65.9)	0.3 (0.3–0.4)	420 (345–474)	0.8 (0.7–0.9)	4.00 (3.02–5.00)	2.95 (1.66–4.26)	1.44 (1.14–1.73)
Germany[a]	1060.1 (944.3–1175.0)	0.8 (0.8–0.9)	4456 (3680–4972)	1.9 (1.6–2.1)	4.12 (3.51–4.73)	2.84 (2.08–3.62)	1.27 (1.00–1.57)
Location	**Prevalent cases (95% UI)**	**ASR per 100,000 (95% UI)**	**Prevalent cases (95% UI)**	**ASR per 100,000 (95% UI)**	**EAPC (95% CI)**	**AAPC (95% CI)**	**TPC (95% CI)**
Global	2170243.3 (1892401.8–2522561.3)	48.0 (41.9–55.8)	3830119 (3312834–4511555)	44.9 (38.8–52.9)	-0.13 (-0.25 to 0)	-0.22 (-0.27 to -0.17)	-0.07 (-0.08 to -0.05)
High SDI	1306709.5 (1155692.1–1487814.6)	129.5 (114.4–147.6)	2012478 (1755438–2316531)	132.8 (115.0–154.3)	0.08 (-0.10 to 0.26)	0.06 (0.01–0.11)	0.02 (-0.01 to 0.05)
High-middle SDI	374805.8 (323916.7–442307.8)	35.3 (30.6–41.6)	541766 (462605–647488)	31.6 (27.1–37.9)	-0.15 (-0.31 to 0.02)	-0.37 (-0.46 to -0.28)	-0.10 (-0.12 to -0.08)
Middle SDI	194215.3 (163798.4–235106.1)	14.0 (11.9–16.9)	544518 (460464–659902)	19.6 (16.6–23.8)	1.34 (1.19–1.50)	1.12 (0.82–1.43)	0.40 (0.38–0.42)
Low-middle SDI	228004.4 (192791.1–273562.9)	28.0 (23.7–33.5)	561436 (475598–680836)	32.5 (27.5–39.1)	0.66 (0.58–0.73)	0.47 (0.36–0.58)	0.16 (0.14–0.18)
Low SDI	64105.3 (53897.8–77409.2)	20.7 (17.5–25.0)	166793 (140414–203986)	22.8 (19.4–27.6)	0.41 (0.36–0.46)	0.32 (0.24–0.39)	0.11 (0.07–0.14)
East Asia	64806.6 (54671.1–78247.0)	5.6 (4.8–6.7)	172201 (145043–206864)	9.1 (7.7–10.9)	2.49 (1.87–3.11)	1.57 (1.19–1.95)	0.61 (0.67–0.56)
China	62097.9 (52445.9–75050.2)	5.6 (4.7–6.7)	168077 (141521–201684)	9.2 (7.8–11.0)	2.54 (1.91–3.17)	1.62 (1.10–2.14)	0.64 (0.58–0.70)
Location	**DALYs (95% UI)**	**ASR per 100,000 (95% UI)**	**DALYs (95% UI)**	**ASR per 100,000 (95% UI)**	**EAPC (95% CI)**	**AAPC (95% CI)**	**TPC (95% CI)**
Global	948860.8 (808100.6–1096717.0)	21.5 (18.5–24.8)	1510784 (1308508–1750363)	18.1 (15.7–20.9)	-0.52 (-0.60 to -0.43)	-0.57 (-0.68 to -0.46)	-0.16 (-0.22 to -0.10)
High SDI	343883.2 (283244.4–418649.0)	33.7 (27.6–41.2)	599038 (501803–711056)	35.0 (28.3–43.0)	0.31 (0.10 to 0.51)	0.12 (-0.06 to 0.29)	0.04 (0.01–0.07)
High-middle SDI	194740.7 (169862.5–224657.7)	19.3 (16.9–22.3)	229281 (197044–267170)	13.1 (11.2–15.2)	-1.40 (-1.49 to -1.31)	-1.21 (-1.44 to -0.98)	-0.32 (-0.39 to -0.25)
Middle SDI	205675.2 (155790.4–244159.9)	15.7 (11.7–18.4)	285305 (240198–329976)	10.9 (9.2–12.6)	-1.23 (-1.28 to -1.17)	-1.17 (-1.33 to -1.02)	-0.30 (-0.42 to -0.14)
Low-middle SDI	141892.8 (112360.1–174778.2)	17.6 (13.7–21.3)	257852 (210807–312042)	15.4 (12.6–18.7)	-0.45 (-0.49 to -0.41)	-0.43 (-0.51 to -0.35)	-0.13 (-0.26 to 0.03)
Low SDI	61703.0 (45765.1–79566.2)	19.2 (14.3–23.6)	138076 (98060–170355)	18.0 (13.3–21.8)	-0.25 (-0.30 to -0.20)	-0.21 (-0.30 to -0.13)	-0.06 (-0.21 to 0.10)
Australasia	7705.5 (5513.8–10322.6)	34.5 (24.5–46.1)	18181 (14279–22717)	41.7 (31.9–53.8)	1.08 (0.75–1.41)	0.63 (0.17–1.09)	0.21 (0.12–0.32)
Libya[b]	198.3 (126.0–370.8)	7.1 (4.5–12.5)	708 (467–1009)	10.4 (6.8–15.1)	1.79 (1.55–2.03)	1.22 (1.10–1.35)	0.47 (0.01–1.06)
Germany[b]	50343.3 (40785.8–61613.8)	48.7 (38.6–60.8)	105940 (90224–123046)	70.1 (57.1–85.0)	1.73 (1.37–2.09)	1.20 (0.71–1.68)	0.44 (0.32–0.57)

[a,b] Represents the EAPC being close between two countries.
[c] The countries in the table are the ones with the highest EAPC growth.
ASR = age-standardized rate, CI = confidence interval, EAPC = estimated annual percentage change, AAPC = average annual percent change, TPC = total percentage change, UI = uncertainty interval, IBD = inflammatory bowel disease, SDI = socio-demographic index, DALYs = disability-adjusted life year.

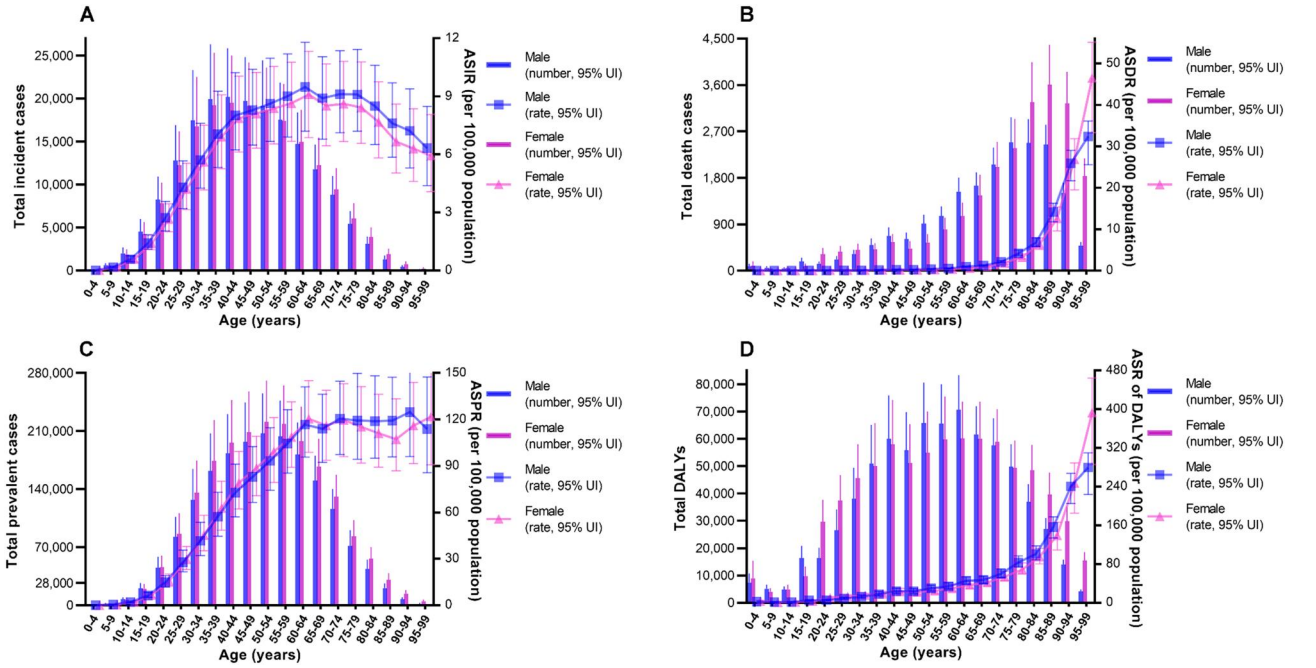

Figure 1. Age patterns by sex in 2021 of number and age-specific rates of incidence (**A**), deaths (**B**), prevalence (**C**), and DALYs (**D**) due to inflammatory bowel disease worldwide. Error bars indicate the 95% UI for the number or age-standardized rates. DALYs = disability-adjusted life years, ASR = age-standardized rate, ASIR = age-standardized incident rate, ASDR = age-standardized death rate, ASPR = age-standardized prevalent rate, UI = uncertainty interval.

increased until age 60 (Figure 1C). DALYs were generally higher in middle-aged and elderly populations, with a significant increase in the ASR of DALYs after the age of 80 (Figure 1D).

Regional and national burden of IBD in 2021

Based on SDI classification, the regions with the highest ASIR, ASDR, ASPR, and ASR of DALYs in 2021 were high-SDI region (Table 1). Based on geographical location, the region and country with the highest ASIR in 2021 were Australasia and Canada (19.7 and 26.8 per 100,000 population, respectively, Tables S1 and S2 and Figure 2A). The region and country with the highest ASDR were Western Europe and the Netherlands (1.1 and 2.2 per 100,000 population, respectively, Tables S3 and S4 and Figure 3A). Australasia and Canada were the regions and countries with the highest ASPR in 2021 (203.3 and 326.6 per 100,000 population, respectively, Tables S5 and S6). For ASR of DALYs, the highest regions and countries in 2021 were High-income North America and the Netherlands (49.6 and 75.0 per 100,000 population, respectively, Tables S7 and S8).

Global burden trends of IBD from 1990 to 2021

From 1990 to 2021, the global ASIR of IBD gradually increased (EAPC: 0.29, 95% CI: 0.20–0.38), while the ASDR, ASPR, and ASR of DALYs significantly decreased (EAPC: -0.31, -0.13, and -0.52, respectively) (Table 1). Between 2019 and 2021, there was no observed upward trend in the global ASDR for IBD (EAPC: -1.56, 95% CI: -1.74 to -1.39, Table S3).

The net drift of global IBD incidence was 0.20% (95% CI: 0.13–0.27). The drift value increased rapidly between the ages of 10 to 30, surpassing 0 at 22.5 years and peaking around 65 years before declining (Figure S1A). The incidence gradually increased with age, stabilizing around 60 years (Figure S1B). Since 2005, the relative incidence risk of IBD had sharply increased until it began to decline after 2010 (Figure S1C). Compared with 1962, the incidence risk for subsequent years had not significantly changed (Figure S1D).

The net drift of global IBD mortality was -0.89% (95% CI: -1.02% to -0.76%). The mortality risk increased with age for those aged 0 to 30 and over 70, but the local drift was greater than 0 only for those over 88 years (Figure S2A).

Mortality risk rose rapidly with age after 65 years, indicating a severe disease burden among the elderly (Figure S2B). Compared with 2005, the recent global mortality rate of IBD had significantly decreased each year (Figure S2C). The mortality risk of IBD had decreased annually with advancements over time, with those under 20 having a lower mortality risk (Figure S2D).

The ASIR for both males and females showed an increasing trend from 1990 to 2021 (AAPC: 0.15 and 0.17, respectively, both $P < 0.05$, Table S9 and Figure 4A). The burden of mortality, prevalence, and DALYs had significantly decreased each year (Table S9 and Figure 4B–D). Moreover, 2010 marked the turning point for the decline in ASIR and ASPR for both sexes (Table S9, Figure S3A–C and Figure S4A–C). After 2003–2004, the ASDR also began to significantly decreased (Table S9 and Figure S3D–F). The burden of DALYs had been significantly declining each year since the late 1990s (Table S9 and Figure S4D–F).

Regional and national burden trend of IBD from 1990 to 2021

The ASIR in all global regions showed an upward trend (Table S1 and Figure 2C), while ASDR and ASR of DALYs mostly showed a downward trend (Tables S3 and S7 and Figure 3C). Compared with other SDI regions, only the high SDI region saw a gradual increase in ASDR (EAPC: 0.84, 95% CI: 0.52–1.17) and ASR of DALYs (EAPC: 0.31, 95% CI: 0.10–0.51) between 1990 and 2021 (Table 1). The most significant increase in incidence was in Equatorial Guinea, and the most significant increase in mortality was in the Northern Mariana Islands (Figures 2B and 3B). The regions and countries with the highest increases in ASIR and ASPR were East

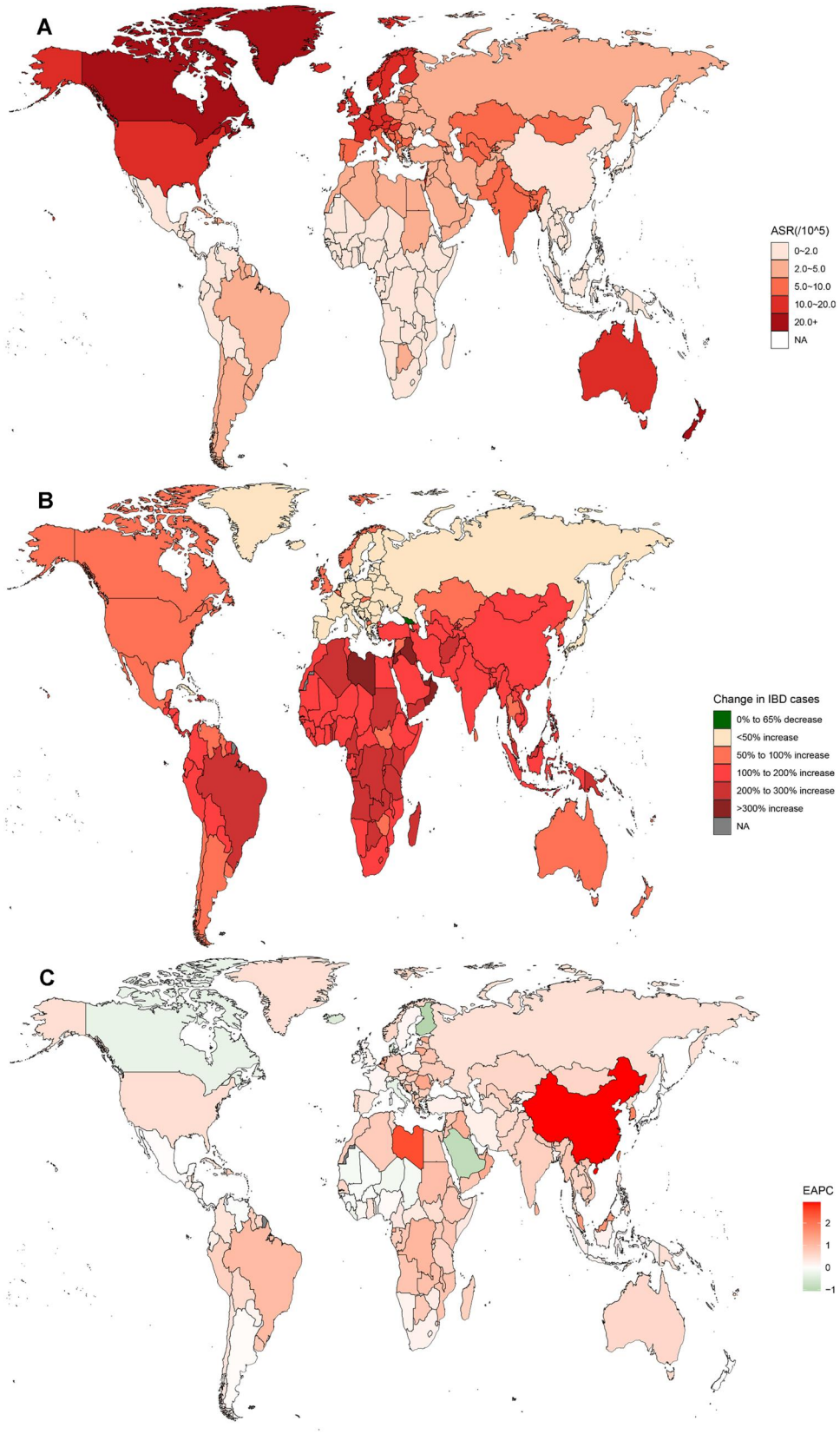

Figure 2. The global disease burden of IBD for both sexes in 2021 based on incidence. (**A**) The ASIR of IBD in 2021. (**B**) The relative change in incident cases of IBD between 1990 and 2021. (**C**) The EAPC of IBD ASIR from 1990 to 2021. ASR = age-standardized rate, ASIR = age-standardized incident rate, EAPC = estimated annual percentage change, IBD = inflammatory bowel disease.

Asia (EAPC of ASIR: 2.88, 95% CI: 2.37–3.40; EAPC of ASPR: 2.49, 95% CI: 1.87–3.11) and China (EAPC of ASIR: 2.93, 95% CI: 2.41–3.46; EAPC of ASPR: 2.54, 95% CI: 1.91–3.17) (Table 1 and Figure 2C). The region with the highest increase in ASDR and ASR of DALYs was Australasia (EAPC of ASDR: 3.54, 95% CI: 2.62–4.46; EAPC of ASR of DALYs: 1.08, 95% CI: 0.75–1.41, Table 1).

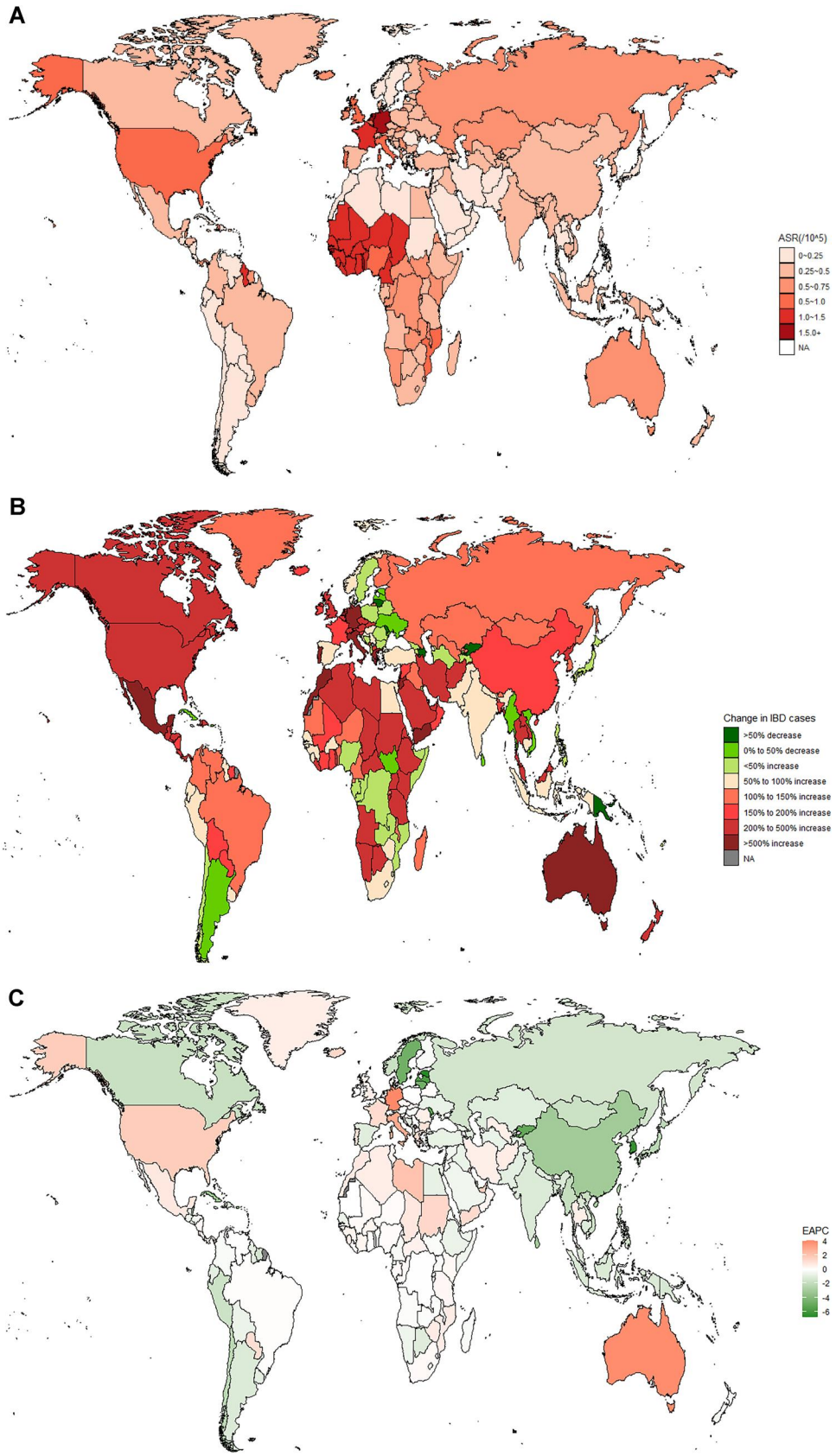

Figure 3. The global disease burden of IBD for both sexes in 2021 based on death. (**A**) The ASDR of IBD in 2021. (**B**) The relative change in death cases of IBD between 1990 and 2021. (**C**) The EAPC of the ASDR of IBD from 1990 to 2021. ASR = age-standardized rate, ASDR = age-standardized death rate, EAPC = estimated annual percentage change, IBD = inflammatory bowel disease.

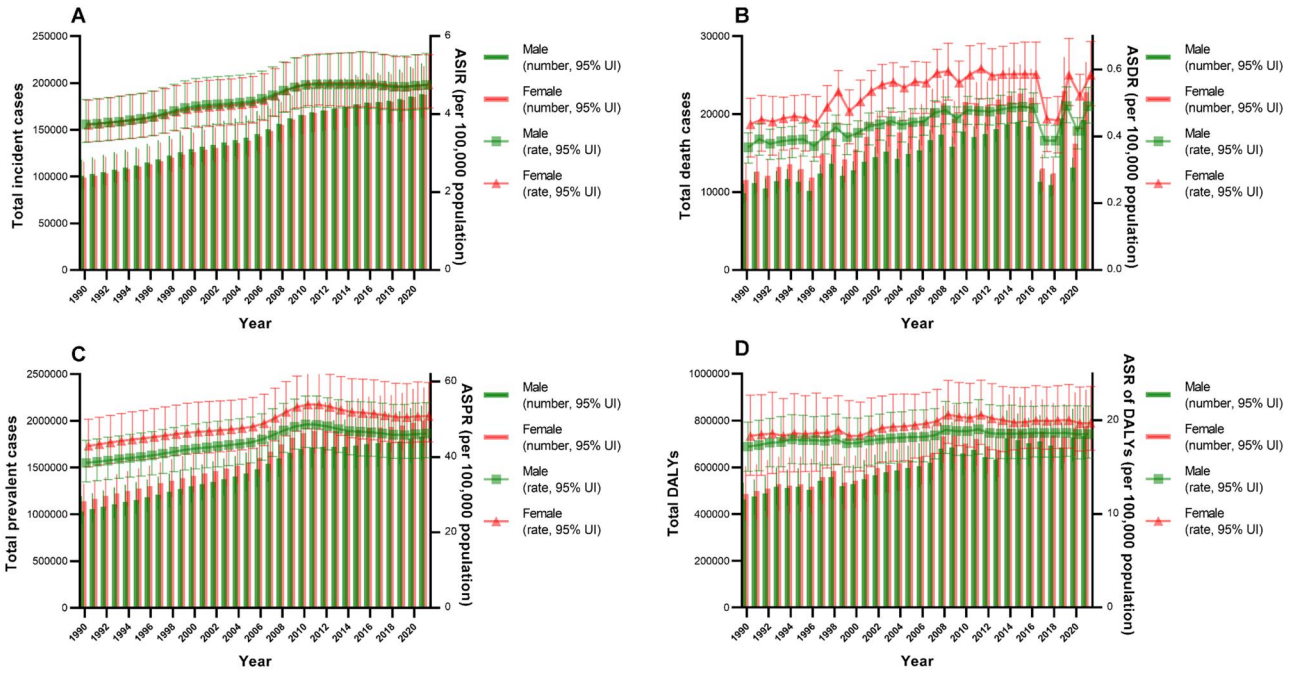

Figure 4. Trends from 1990 to 2021 in number and age-standardized rates of incidence (**A**), deaths (**B**), prevalence (**C**), and DALYs (**D**) of IBD by sex worldwide. 95% UI = 95% uncertainty interval, ASR = age-standardized rate, ASIR = age-standardized incident rate, ASDR = age-standardized death rate, ASPR = age-standardized prevalent rate, DALYs = disability-adjusted life years, IBD = inflammatory bowel disease.

The countries with the most significant increase in mortality and DALYs burden were Australia and Germany, and Libya and Germany, respectively (Table 1 and Figure 3C). Cluster analysis found that China and Libya were countries with a significant increase in ASIR, while Canada, Italy, and 11 other countries showed a significant decrease (Figure S5A). Only Germany was classified as a country with a significant increase in ASDR in the cluster analysis, while Bermuda and American Samoa were classified as having a significant decrease (Figure S5B).

The ASDR showed a declining trend in various regions from 2019 to 2021 (Table S3). At the national level, no significant increase in ASDR was observed between 2019 and 2021 in most countries (96.1%, Table S4).

The impact of HDI and SDI on disease burden

As shown in Figure 5A and B, EAPC was significantly negatively correlated with ASIR and ASDR in 1990 (correlation coefficient = -0.26, -0.40, respectively). However, EAPC of ASIR and ASDR was not associated with HDI in 2021 (Figure 5C and D).

In developed regions such as Australasia, high-income North America, the trend and predicted shape of ASIR changes were similar to those of SDI (Figure S6A). National-level analysis showed that ASIR increased with SDI, especially when SDI is greater than 0.7 (Figure S6B). South Asia closely followed expected trends between ASDR and SDI over the study period (Figure S7A). National-level analysis found good consistency between ASDR and SDI, showing a negative correlation when SDI is less than 0.7, and increasing as SDI rises above 0.75 (Figure S7B). The trend of ASPR positively correlated with SDI (Figure S8A and B). Similarly, the trend of ASR of DALYs and SDI was consistent with the trend of ASDR and SDI (Figure S9A and B).

Prediction of global IBD incidence and death

By 2035, the global incident cases of IBD were expected to reach 456,067, and the death cases was expected to reach 39,338. The ASIR and ASDR were expected to be 4.4 and 0.26 per 100,000 population, respectively. From 2021 to 2035, predictions indicated that ASIR and ASDR will show a significant annual decline (Figure 6A and B and Figure S10A–D). Between 1990 and 2035, the AAPC of ASIR for male and female were both 0.07, respectively (both $P < 0.05$, Table S10). For ASDR, the AAPC for males and females were -0.66 and -0.79, respectively (both $P < 0.05$, Table S10). Additionally, the ASIR peaked in 2010 and then declined significantly each year thereafter (Table S10 and Figure S11A and B). The ASDR started to decline significantly after 2003 (Table S10 and Figure S11C and D). Analyses using the Nordpred also confirmed these results (Figure 6C and D).

Discussion

The burden of IBD remained severe across various global regions, affecting approximately 3.8 million people. Between 1990 and 2021, the global ASIR of IBD gradually increased, while prevalence, mortality, and DALYs decreased. The ASDR did not show a significant increase from 2019 to 2021 in most regions and most countries. Traditional high-incidence regions for IBD continued to face significant disease burdens. Countries in high SDI regions were also facing an increasingly severe burden of deaths and DALYs. In contrast, East Asia was experiencing a sharp increase in IBD incidence risk. By 2035, it is expected that the global ASIR and ASDR will gradually decline.

The changes in the global ASIR of IBD found in this study differ from previous study, while the trends in mortality, prevalence, and DALYs are consistent [2]. The inclusion of systematic reviews and supplementary Canadian administrative data may explain our finding of an increase in ASIR from 1990 to 2021 [7, 10]. Additionally, our findings indicated that East Asia and China exhibited the highest growth rates in ASIR and ASPR among all regions and countries. The rising prevalence in Asian countries may be attributed to increased awareness of the disease and

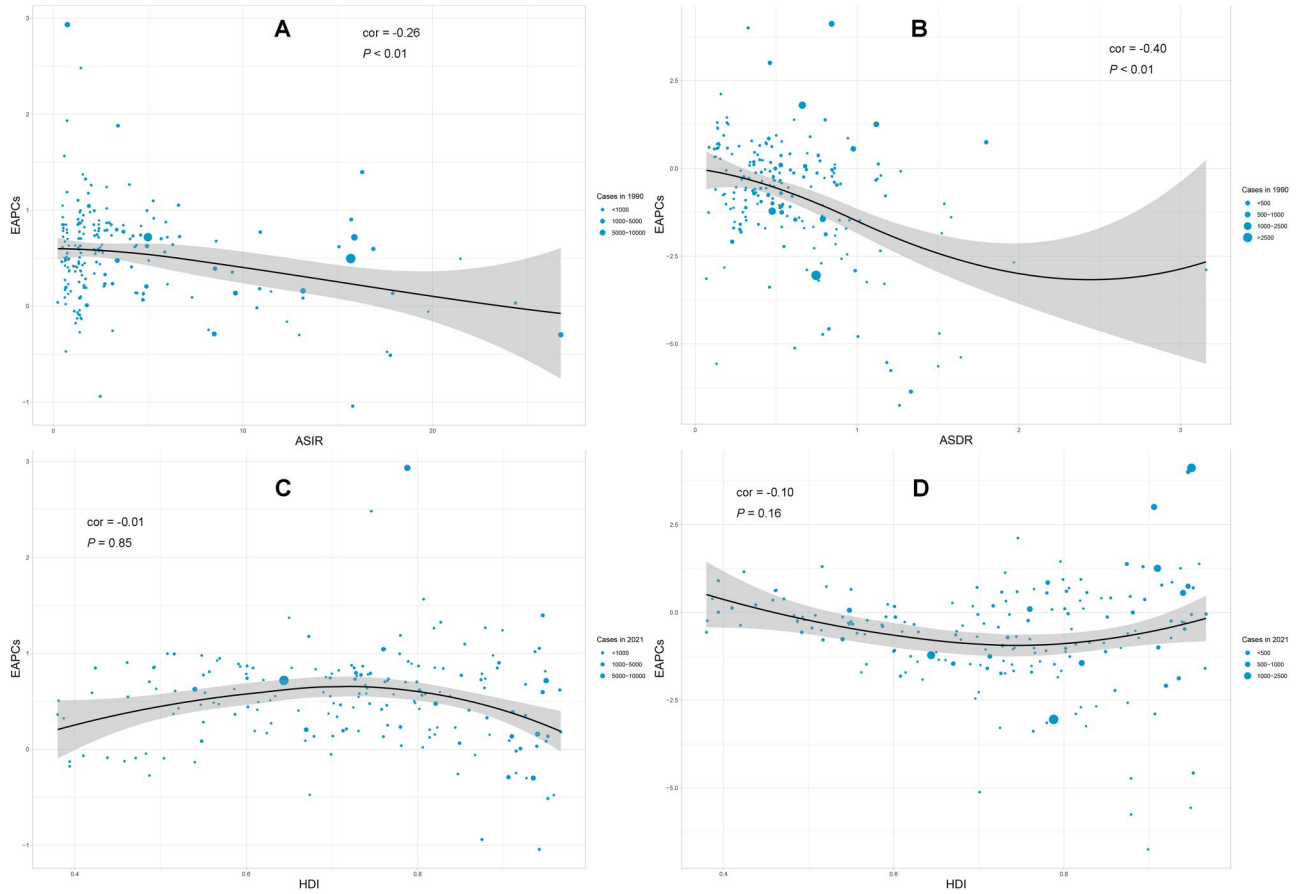

Figure 5. The correlation between EAPC and ASIR and ASDR of IBD in 1990 and HDI in 2021. The correlation between EAPC and ASIR (**A**) and ASDR (**B**) of IBD in 1990. The correlation between EAPC of ASIR (**C**) and ASDR (**D**) and HDI in 2021. EAPC = estimated annual percentage change, ASIR = age-standardized incident rate, ASDR = age-standardized death rate, IBD = inflammatory bowel disease.

improved access to diagnostic tests for IBD. Recent increased awareness of the disease in Asian countries, and possibly better access to IBD diagnostic tests, have led to increased prevalence. With rapid urbanization and dietary changes, the incidence of IBD in China has risen sharply [19]. China, with its large population base and severe aging problem, is facing a rapidly increasing incidence [20]. Studies have found that the ASIR of IBD in urban areas of China were almost on par with that of high-income regions, at a high global level [21]. Advances in medical technology and improvements in healthcare had reduced the mortality while also increasing detection rates. A 20-year study found that the diagnostic interval of IBD in China was significantly decreasing [22]. With the emergence of new therapies and improved disease management systems, the global mortality and DALYs of IBD had significantly declined. The past two decades have undoubtedly been the "biologic era," with a significant increase in the proportion of patients with IBD treated with biologics [23]. The continuous decline in mortality may also be due to the widespread use of biologics, improved cancer monitoring systems, and better surgical techniques [7]. Although the COVID-19 pandemic significantly increased the global all-cause mortality rate, we did not observe an increase in the ASDR of IBD between 2019 and 2021 [6]. COVID-19 may cause some individuals to die prematurely from the virus rather than from IBD. Additionally, IBD population tend to be more health-conscious with a lower prevalence of COVID-19 [24].

High-income regions still bear a greater overall burden compared with other areas [19]. We found that Australasia, particularly Australia, faced a severe burden with significant increases in ASDR and DALYs. Australia is a country with traditionally high IBD incidence rate, and the increasing death burden over the years may be related to regional differences in healthcare. A review of the treatment quality for hospitalized patients across various regions of Australia found that only one out of 71 hospitals met the recognized multidisciplinary IBD care standards, indicating significant differences in care quality [25]. The treatment methods for IBD across Australia also varied greatly and were often provided in a passive and fragmented manner [26]. Against the backdrop of the high incidence and prevalence of IBD in Australia, disparities in healthcare across different regions will increase mortality and the burden of DALYs. Western Europe and high-income North America are facing severe death and DALYs burdens. Many traditional high-incidence IBD countries, such as the USA and the Netherlands, have a large base of patients with IBD, leading to a higher death burden today [27]. Canada currently faces a severe incidence and prevalence burden. In 2023, Canada's prevalence rate was 825, and it is expected that by 2035, 1.1% of the population will have IBD. Canada's total incidence rate for IBD was 30 (per 100,000), which was expected to reach 32.1 by 2035 [28]. Germany has seen the highest growth in death and DALYs burden, which is related to its rapidly aging population structure [29].

We found that countries with a more severe burden of incidence and mortality in 1990 had a smaller EAPC. These countries may have a larger base of affected populations, initiated the diagnosis, treatment, and prevention of IBD earlier, and possess a

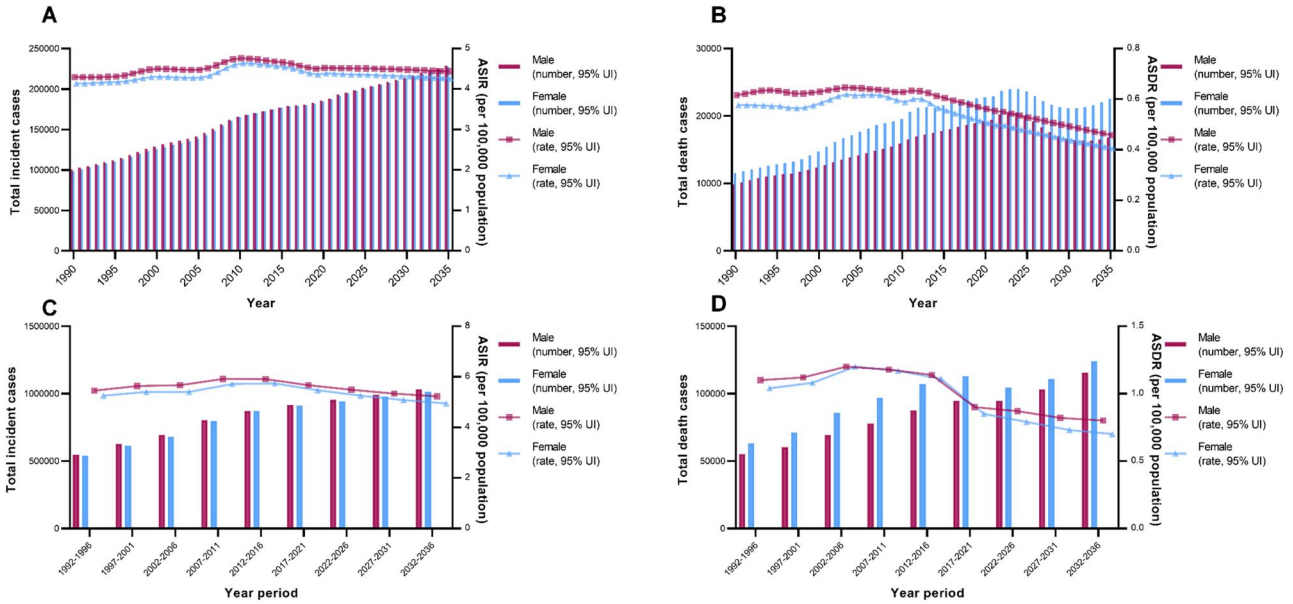

Figure 6. Predictions for total incidence cases, death cases, ASIR and ASDR of inflammatory bowel disease to 2035 by BAPC and Nordpred. Predictions for total incidence cases, ASIR (**A**), death cases, and ASDR (**B**) of inflammatory bowel disease to 2035 by BAPC. Predictions for total incidence cases, ASIR (**C**), death cases, and ASDR (**D**) of inflammatory bowel disease to 2035 by Nordpred. BAPC = Bayesian age-period-cohort, ASIR = age-standardized incident rate, ASDR = age-standardized death rate.

more comprehensive management system. In high SDI regions, higher levels of urbanization, more modernized diets, and better medical conditions and hygiene standards lead to higher IBD detection rates and ASIR. Conversely, in low SDI regions, the detection rate of IBD may be lower due to limited medical technology.

The elderly population faced a more severe burden of morbidity and mortality. The rise in early-onset IBD in the past has led to a longer duration of the disease, more complex conditions in middle and old age, and consequently, a higher risk of complications and treatment-related adverse events [30]. Elderly patients often have complex chronic diseases and tumors, and late-onset patients with IBD experience more frequent complications, related medication use, and hospital treatments, leading to higher surgery and mortality rates [31, 32]. With the accelerating aging process of the population, the incidence of IBD in the elderly is also rising, further exacerbating the disease burden among elderly patients with IBD [33]. The analysis of the elderly population based on GBD 2021 also confirmed that the incidence of IBD in the elderly significantly increased between 1990 and 2021 [34, 35].

The differences in diagnostic and treatment methods across various regions and countries affected the availability and quality of data. In areas with lagging healthcare levels and underdeveloped health systems, data sources are scarce and can only rely on predictive covariates or global trends, which inevitably introduces bias. IBD cases were collected from registry offices where patients belong to the public health system and may receive government medication treatment, which has resulted in many patients not being included. Unfortunately, since the GBD has not yet released data on ulcerative colitis and Crohn's disease, we are unable to conduct separate analyses. GBD 2021 has not yet provided data on risk factors for IBD, such as social determinants of health, antibiotic use, diet, etc., which limits the reliability of our risk assessment. However, GBD 2021 has supplemented disease data from Canada, addressing the shortcomings of GBD 2019 [36].

In conclusion, this study reveals the changing trends and regional differences in the global, regional, and national burden, and the changes in global IBD incidence and mortality in the near future. The COVID-19 pandemic did not lead to an increase in the ASDR of IBD. As the global epidemiological trends of IBD continue to evolve, reducing the global burden of IBD requires parallel efforts in disease prevention and healthcare services to address the changing global IBD burden.

Supplementary data

Supplementary data is available at *Gastroenterology Report* online.

Authors' contributions

G.R. was responsible for investigation and writing and editing the manuscript. Y.S. was responsible for resources management, methodology, and writing and editing the manuscript. Z.Y. was responsible for data curation, resources management, formal analysis, and drafting and revising the manuscript. X.B. was responsible for resource management, methodology, data curation, and conceptualization. H.Y. was responsible for resource management, methodology, investigation, funding acquisition, and supervision. J.Q was responsible for resource management and supervision. All authors have read and approved the final version of the manuscript.

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Conflicts of interest

The authors declare that there is no conflict of interests in this study.

Data availability

Data can be obtained from the Global Health Data Exchange Global Burden of Disease Results Tool (https://vizhub.healthdata.org/gbd-results/). This paper does not report original code.

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