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Trends in the global, regional, and national burden of bladder cancer from 1990 to 2021: an observational study from the global burden of disease study 2021

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To evaluate the changing trend and cross-country inequality of bladder cancer (BC) burden over the past 30 years and further predict the trend until 2036. Based on the Global Burden of Disease (GBD) 2021 study, the global incidence, mortality, and disability-adjusted life years (DALYs) of bladder cancer from 1990 to 2021 were obtained. We described the distribution of BC at global, regional and national levels and overall/local trends. The age-period-cohort analysis, decomposition analysis and inequality analysis related to socio-demographic index (SDI) were conducted. Additionally, we predicted the future trend of BC burden using Bayesian age-period-cohort model. In the GBD 2021, the global incidence number of BC was 540,310, doubling compared to that in 1990. However, the age-standardized rate (ASR) drops from 6.90 to 6.35. The changes in bladder cancer mortality and DALYs are similar. The ratio of ASRs of burden between males and females is approximately 4:1. Interestingly, in regions with middle SDI, low-middle SDI, and low SDI, the ASR of incidence has shown an upward trend to varying degrees in recent 10 years. Central Europe has the highest ASR of DALYs. China bore the heaviest burden of bladder cancer and experienced the greatest increase in the burden of bladder cancer. Globally, population growth, aging, and epidemiological changes accounted for 89.83%, 83.91%, and − 73.74% of the changes in DALYs respectively. The absolute inequality related to the SDI increases significantly. The slope index of inequality for DALYs increases from 79.84 to 115.60, and the concentration index slightly decreases to 0.26 in 2021. The prediction showed that the ASRs of the three indicators of bladder cancer would continue to decline from 2022 to 2036. Despite a downward trend in ASRs from 1990 to 2021, the global bladder cancer burden has generally increased with regional and country variations. The burden growth pattern driven by population growth and aging may potentially increase the burden number in the future. Burden is concentrated in high-SDI countries and there are signs indicating a shift towards lower-SDI countries. These findings highlighted challenges in BC prevention and management.

Keywords Bladder cancer, Global burden of disease, Epidemiology, Disability-adjusted life years, Incidence, Mortality, Urology, Socio-demographic index, Health inequality

Abbreviations

AAPC	average annual percentage change
APC	annual percentage change
ASR	age-standardized rate

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ASDR	age-standardized disability-adjusted life years rate
ASIR	age-standardized incidence rate
ASMR	age-standardized mortality rate
BAPC	Bayesian age-period-cohort
BC	bladder cancer
GBD	Global Burden of Disease
CI	confidence interval
DALYs	disability-adjusted life years
EAPC	estimated annual percentage change
HDI	human development index
INLA	Integrated Nested Laplace Approximation
SDI	socio-demographic index
SII	slope index of inequality
UI	uncertainty interval

Bladder cancer (BC) currently ranks as the tenth most prevalent cancer globally. In the year 2020, it was estimated that there were approximately 573,000 new cases and 213,000 fatalities. Additionally, it serves as the second most common tumor within the urinary system, trailing only behind prostate cancer[1]. It is notably more frequently observed in men. The incidence and mortality rates among men are approximately 3-4 times those of women on a global scale[1,2]. Consequently, in the male population, bladder cancer has emerged as the sixth most prevalent cancer among all malignancies and is the ninth leading cause of cancer-associated mortality[3]. BC is characterized by an extremely high propensity for recurrence and progression. For non-muscle-invasive BC, intensive follow-up monitoring involving repeated cystoscopy and imaging evaluations is essential, along with repeated transurethral resection of bladder tumor for recurrent cases. At the stage of muscle-invasive BC, a greater number of patients will require costly systemic treatments, radiotherapy, and radical cystectomy. Although it is seldom known to the general public, BC is one of the cancers that impose a significant economic burden, placing a heavy strain on both patients and the healthcare system[3,4]. The health-related quality of life of BC patients has been significantly affected. This includes impacts such as those of radiotherapy and chemotherapy on the urinary system and intestinal tract, decreased sexual function, and defects in social interaction, physical activity, and emotional function[5,6]. Therefore, understanding the current global, regional, and national burden change trends, distribution differences, and future change trends of BC can provide crucial reference information for adjusting public health policies and optimizing the allocation of medical resources.

As population aging, social and economic growth, smoking rates, and environmental pollution are expected to increase, the incidence of BC in many countries around the world may rise significantly in the coming decades, potentially bringing an even heavier disease burden[4]. Although several existing studies on the disease burden of BC are available, some utilize relatively old data[7–9], analyze the burden indicators of a specific local region or country[10,11], investigate the burden related to particular risk factors such as smoking[12], or lack predictive analysis of future time trends[13]. Most importantly, the recently released Global Burden of Disease (GBD) 2021 study employs newly available data and improved methods to re-estimate the disease burden indicators of BC for the entire time series, particularly for mortality and years of life lost, thereby providing an updated and comprehensive version of the disease burden[14,15].

Therefore, to better understand the disease burden and epidemiology of BC globally, regionally, and nationally, we used GBD 2021 data to re-evaluate its burden, trends, cross-country inequalities, and future trends. This includes describing burden distribution at different levels, analyzing trends from 1990 to 2021, performing decomposition and inequality analyses, and making future predictions. The results provide references for formulating prevention and control strategies.

Methods

Data source and measurements

The GBD 2021 was released on May 16, 2024. It offers estimated results for 371 diseases and injuries and 88 risk factors, covering 204 countries and territories, 25 age groups, and different sexes from 1990 to 2021[15,16]. With each new GBD data update, the complete time series of the population for all years is re-estimated using the latest available data resources and improved methods, and this process replaces the demographic estimates of all previous versions[14,15]. The GBD 2021 utilized data from various sources such as government websites, statistical yearbooks, demographic compendia, journal literature, survey data, disease registries, and hospital inpatient records to ensure the quality and breadth of relevant analyses[15,17]. Therefore, the results of GBD 2021 are crucial for determining health disparities in the global population and among different countries, and understanding health change trends is essential for national public health policy formulation and research by public health professionals.

The data are publicly accessible at https://vizhub.healthdata.org/gbd-results/, and secondary analysis is carried out accordingly. In our study, the estimated values of BC incidence, mortality, and disability-adjusted life years (DALYs), along with their 95% uncertainty intervals (UIs), including quantities and (ASRs), were extracted from GBD 2021. Data from different sources are standardized using the International Classification of Diseases (ICD) codes to ensure accuracy and comparability, and are estimated with sophisticated modeling tools based on the GBD standard population structure (https://ghdx.healthdata.org/record/ihme-data/gbd-2021-cause-icd-code-mappings). Data processing involves the correction of heterogeneity and bias, as well as uncertainty analysis through 500 Monte Carlo simulations[16,18]. Each of the indicators underwent computational iterations 500 times, wherein the mean value of the estimates was designated as the definitive estimate. The 2.5th and 97.5th percentile values were aggregated to formulate the 95% UI[16]. GBD 2021 uses a Bayesian disease modeling meta-regression tool - Disease Modelling Meta-Regression (version 2.1) to standardize the estimates of incidence and prevalence over time, age, geography, and sex. Additionally, it employs a five-level geographic hierarchy of disease epidemiology data to estimate relevant data for locations with missing data[8,16]. The Cause of Death Ensemble model estimated cause-specific mortality for BC[13]. Relevant studies and official websites have fully explained the detailed processing methods in GBD 2021 (http://ghdx.healthdata.org/)[14–16]. Simultaneously, our study incorporates the socio-demographic index (SDI), a comprehensive indicator of development status strongly correlated with health outcomes. It is the geometric mean of lag-distributed income per capita, educational attainment for those aged 15 years or older, and the total fertility rate of females under 25[18,18]. The SDI ranges from 0 to 1, with a higher value indicating a higher level of regional development, where 1 represents the highest years of education, the highest per capita income and the lowest fertility rate, and 0 represents the contrary. The SDI is divided into high SDI, high-middle SDI, middle SDI, low-middle SDI, and low SDI according to quintiles[18].

Our research strictly adheres to the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER)[19]. No ethical approval and informed consent were necessary for this study, which utilized the GBD database—a publicly available dataset with anonymized participant data. All analyses were done and visualized with R statistical software (version 4.4.0), Joinpoint Trend Analysis Software, and the Age Period Cohort Analysis Web Tool. A P - value less than 0.05 is considered statistically significant.

Descriptive analysis

To comprehensively understand BC's disease burden, descriptive analyses were done globally, in 21 GBD regions, and at 204 countries/territories. First, compare BC incidence, mortality, and DALYs (cases and ASRs) in 1990 and 2019 globally, in GBD regions under 5 SDI levels, and between global males and females. Secondly, compare the top 50 countries ranked by the burden of BC incidence, mortality, and DALYs in 2021 and conduct visualization on a world map. Then, compare the age-related changes of ASRs of overall, male, and female BC burden globally and under five SDI levels.

Trend analysis

When comparing population groups with different age structures at different time points, regions, and between sexes, the trend of change in ASR measured by the estimated annual percentage change (EAPC) is a more accurate and reliable indicator[20]. We calculated the EAPC through the following formula[21]: $Y = \alpha + \beta x + \varepsilon$; $EAPC = 100*(exp(\beta)-1)$. Here, Y is the natural logarithm of ASRs, x corresponds to calendar years, ε represents the error term, and the coefficient β is taken from Y. The EAPC and its 95% confidence interval (CI) are calculated through the subsequent linear regression model. A positive or negative EAPC indicates an upward or downward trend of ASRs, respectively. Visualize the changes in BC burden at the global, regional, and national levels from 1990 to 2021 through world maps and histograms.

Then, we used joinpoint regression analysis to transform the overall trend of BC from 1990 to 2021 into multiple local trends. The joinpoint regression model identifies multiple "joinpoints" in time series data for piecewise regression[22]. These joinpoints indicate significant trend change points. The calculated annual percentage change (APC) and its 95% CI for each sub-period present trend changes in more detail. The average annual percentage change (AAPC) is calculated by the span width weighted average of the regression coefficients of the piecewise interval regression model. Positive or negative APC/AAPC values with their 95% CIs indicate an upward or downward trend. Otherwise, the trend is considered stable[23]. Our study completed joinpoint regression analysis using Joinpoint Trend Analysis Software[24].

Furthermore, we explored the changing trends of BC burden related to age, period, and birth cohort effects. The age effect refers to the variation in the risk of an outcome at different age stages as an individual ages; The period effect pertains to the influence exerted by a specific time point on all age groups simultaneously; The cohort effect denotes the change in outcomes among participants with the same birth cohort due to their different growth experiences. Due to the interaction among these factors, it is difficult for traditional models to estimate their respective effects[25]. The age-period-cohort model based on Poisson distribution and using principal component regression analysis with the intrinsic estimator method investigates temporal changes by incorporating age, time, and birth cohort to estimate their impacts[26,27]. The log-linear regression model is $log(Yi) = \mu + \alpha * agei + \beta * periodi + \gamma * cohorti + \varepsilon$. Yi is the incidence or mortality rate. α, β, γ are coefficients. μ is the intercept. $\varepsilon$is the residual[28]. The Age Period Cohort Analysis Web Tool at https://analysistools.cancer.gov/apc/is used for age- period-cohort analysis[29].

Decomposition analysis

In our study, decomposition analysis was used to analyze the influencing factors of BC burden across different sexes and SDI levels. The change in disease burden was divided into three components: population age structure, total population growth, and epidemiological changes (potential age- and population-adjusted mortality and morbidity)[30]. This method quantifies the temporal evolution of BC burden into the relative impacts of demographic and disease-specific factors.

Cross-country health inequality analysis

Health inequality refers to unfair differences in health status, healthcare access, and social determinants among different populations, potentially caused by socioeconomic status differences. Pearson's correlation analysis is employed to ascertain the correlation between the SDI and the disease burden in 21 GBD regions as well as 204 countries/territories. The slope index of inequality (SII) and the concentration index are used to assess absolute and relative inequalities in BC burden among countries with different SDI levels[31]. The SII, which is the slope of the regression line, is calculated by performing linear regression of the ASRs of disease burden and the weighted position ranking related to SDI for each country[25,32]. It reflects health differences between the lowest and highest SDI groups. The Lorenz concentration curve is obtained by fitting the cumulative proportion of BC burden and the cumulative relative distribution of the population sorted by SDI. The concentration index is obtained by calculating the size of the area under the curve through integration operations, and its range is from − 1 to 1[25]. A Lorenz curve below the diagonal line means the burden of health indicators is concentrated in high-SDI countries and the concentration index is positive; conversely, it's negative. An absolute value of the concentration index between 0.2 and 0.3 indicates a relatively high degree of relative inequality[33].

Predictive analysis

To conduct more accurate prediction and exploration of BC burden in the next 15 years, we use the Bayesian age-period-cohort (BAPC) analysis model with Integrated Nested Laplace Approximation (INLA) to predict the global burden in 2036. The reason for adopting this model lies in the fact that a study has compared the five prediction models, namely age-period-cohort model, BAPC model, Nordpred model, nature-spline model and Joinpoint model, and found that the BAPC model has a relatively low error rate[34]. This model has unique advantages and can accurately estimate future disease burden considering age, period, and cohort effects[35]. The BAPC model's advantage is that INLA can efficiently approximate the marginal posterior distribution, avoiding problems caused by traditional Markov chain Monte Carlo sampling[36]. Due to its advantages, this model is applicable to long-span disease burden prediction and has been widely used and recognized. In particular, it is widely used in GBD studies involving changes in age composition and complex cohort effects[35,37].

Results

Disease burden of bladder cancer at global, regional, and National levels in 2021

Globally, between 1990 and 2021, the number of cases of BC incidence, deaths, and DALYs exhibited a sharp increase, whereas the ASRs of these three indicators demonstrated a downward trend. The burden on males is considerably higher than that on females, and the gap is widening (Table 1; Figure S1, S2, and S3). Additionally, from the perspective of SDI grouping, in 2021, the number of cases of BC incidence, deaths, and DALYs gradually decreased from high SDI regions to low SDI regions. However, the ASRs in low SDI regions are not the lowest (Fig. 1). The number of cases and ASRs of BC incidence, deaths, and DALYs in 1990 and 2021 are presented in detail in Table 1. The regions with the highest ASRs of the three indicators are Central Europe, High-income North America, and Western Europe (Table 1). At the national level, China has the highest burden of BC incidence, deaths, and DALYs, followed by the United States and the countries with the highest ASRs of incidence, deaths, and DALYs are Lebanon, Mali, and Malawi respectively. There are significant differences in the quantity and ASRs of BC burden among different countries (Table S1; Fig. 1). In terms of age distribution, the crude rate of BC burden emerges from the age of 15 and reaches its highest point in people over 85 years old as age advances (Figure S4).

Overall change trends in bladder cancer burden from 1990 to 2021

The EAPC values of global BC age-standardized incidence rate (ASIR), age-standardized mortality rate (ASMR), and age-standardized DALYs rate (ASDR) calculated from 1990 to 2021 are − 0.36 (95% CI: −0.41, −0.3), −0.98 (95% CI: −1.03, −0.94), and − 1.19 (95% CI: −1.24, −1.13), respectively. At the same time, regardless of sex and SDI level, the EAPC values of these three indicators are all negative (except for ASIR in middle SDI regions) (Table 1). Among the 21 GBD regions, bladder cancer ASIR increased most significantly in Central Europe and decreased most significantly in Australasia. ASMR and ASDR increased most significantly in Oceania and decreased most significantly in East Asia (Table 1; Fig. 2). At the national level, the top countries with the largest increase in the number of BC incidence, deaths, and DALYs are China (Fig. 3A, C and E). The countries with a relatively large increase in bladder cancer ASIR, ASMR, and ASDR are Cape Verde, Northern Mariana Islands, and American Samoa (Fig. 3). The country with the largest decrease in ASIR and ASMR is Mongolia, while the country with the most significant decrease in ASDR is Egypt (Fig. 3B, D and F).

Local trends in bladder cancer burden using joinpoint analysis

For the ASIR of bladder cancer, globally, it showed an upward trend from 1990 to 1996, and then continuously declined from 1996 to 2003, from 2003 to 2010, and from 2010 to 2021, with a total of three obvious joinpoints (Table S2; Figure S5). The time-varying trends of ASIR in global males and global females are similar (Table S3; Figure S7). Similarly, the changes in ASMR of bladder cancer on a global scale and in global males and global females are similar to those of ASDR. Globally, ASMR declined the fastest from 2001 to 2007, experiencing four joinpoints in total (Table S2 and S3; Figure S6 and S7). For the ASR of DALYs, there is an obvious downward trend overall from 1990 to 2021. Globally, the ASDR was declining in all periods after remaining stable from 1990 to 1994, with the fastest decline occurring from 2001 to 2007 during which there were four joinpoints (Table S2; Fig. 4). The temporal trends of ASIR, ASMR, and ASDR in different SDI regions have their own characteristics. In particular, in regions with middle SDI, low-middle SDI, and low SDI, the ASIR has shown an upward trend to varying degrees in recent 10 years (Fig. 4, S5, S6 and S7; Table S2 and S3).

Age-period-cohort analysis of bladder cancer burden

As demonstrated in Fig. 5, Figure S8, Figure S9 and Table S4, the age effect has a significant impact on the risk of bladder cancer incidence and deaths. The relative risks of incidence and mortality are at their lowest in the 15–19 age group and then increase as age advances. The relative risks of incidence and mortality reach their respective peaks at 85–89 years old and above 95 years old. It was found that the period effect had a significant impact on bladder burden risk. The period effects on the relative risks of incidence and mortality exhibited a continuous

Location	1990		2021			1990		2021			1990		2021		
	Incidence cases	ASIR	Incidence cases	ASIR		Mortality cases	ASMR	Mortality cases	ASMR		DALYs cases	ASDR	DALYs cases	ASDR	
	(95% UI)	Per 100,000 (95%UI)	(95% UI)	Per 100,000 (95%UI)	EAPC of ASIR (95% CI)	(95% UI)	Per 100,000 (95%UI)	(95% UI)	Per 100,000 (95%UI)	EAPC of ASMR (95% CI)	(95% UI)	Per 100,000 (95%UI)	(95% UI)	Per 100,000 (95%UI)	EAPC of ASDR (95% CI)
Global	260,142 (242823 ,272207)	6.90 (6.46,7.23)	540,310 (494721, 582579)	6.35 (5.80,6.85)	−0.36 (−0.41,−0.3)	123,125 (113327, 129807)	3.51 (3.23,3.70)	221,888 (200567, 242326)	2.68 (2.42,2.93)	−0.98 (−1.03,−0.94)	2,733,041 (2471963, 2894497)	71.05 (64.72,75.17)	4,397,067 (4063657, 4813655)	51.58 (47.56,56.42)	−1.19 (−1.24,−1.13)
Sex															
Male	195,874 (178072, 207081)	11.89 (10.92,12.57)	417,706 (384652, 456195)	10.92 (10.04,11.91)	−0.35 (−0.4,−0.29)	89,314 (78995, 95880)	6.1 (5.48,6.53)	164,624 (149887, 182252)	4.67 (4.22,5.16)	−0.97 (−1.01,−0.93)	2,029,729 (1764128,2190171)	119.24 (104.92, 128.18)	3,321,536 (3031701, 3697557)	86.31 (78.87,95.94)	−1.18 (−1.23,−1.13)
Female	64,267 (59327, 67658)	3.11 (2.86,3.28)	122,604 (108167, 133928)	2.64 (2.34,2.89)	−0.66 (−0.72,−0.59)	33,812 (30883, 35994)	1.71 (1.55,1.82)	57,264 (49417, 62933)	1.22 (1.06,1.34)	−1.25 (−1.32,−1.18)	703,313 (648020, 757679)	33.58 (30.78, 36.07)	1,075,531 (968389, 1175823)	23.29 (20.99,25.45)	−1.37 (−1.44,−1.3)
SDI															
High SDI	125,715 (119992, 129784)	11.20 (10.70,11.56)	228,789 (208294, 241263)	10.60 (9.78,11.14)	−0.19 (−0.27,−0.11)	49,166 (46073, 50950)	4.35 (4.07,4.52)	81,404 (71733, 87086)	3.40 (3.03,3.61)	−0.83 (−0.86,−0.8)	982,175 (938044, 1018190)	87.92 (83.98,91.16)	1,414,897 (1292421, 1499950)	65.07 (60.13,68.71)	−1 (−1.02,−0.98)
High-middle SDI	82,003 (75054, 87377)	8.43 (7.74,8.98)	163,503 (149326, 181563)	8.24 (7.53,9.15)	−0.17 (−0.26,−0.07)	39,306 (35371, 42142)	4.32 (3.90,4.63)	63,715 (57640, 70588)	3.25 (2.94,3.60)	−1.08 (−1.18,−0.99)	892,249 (794563, 960753)	90.85 (81.08,97.72)	1,264,525 (1156998, 1402051)	63.84 (58.43,70.77)	−1.34 (−1.44,−1.25)
Middle SDI	31,194 (25823, 34676)	3.23 (2.71,3.58)	97,202 (84405, 114122)	3.72 (3.24,4.35)	0.31 (0.23,0.39)	19,970 (16818, 22138)	2.32 (1.99,2.56)	45,814 (40125, 53201)	1.89 (1.65,2.20)	−0.88 (−0.97,−0.79)	491,786 (404754, 549709)	48.57 (40.70,53.98)	988,368 (866839, 1149633)	37.63 (33.12,43.70)	−1.04 (−1.13,−0.94)
Low-middle SDI	14,878 (12259, 16660)	2.58 (2.18,2.89)	36,486 (32090, 48079)	2.64 (2.32,3.49)	−0.25 (−0.39,−0.1)	9947 (8524, 11177)	1.93 (1.67,2.17)	21,326 (18789, 27826)	1.68 (1.48,2.21)	−0.65 (−0.76,−0.55)	250,075 (208099, 279837)	41.49 (35.19,46.52)	497,431 (438363, 640209)	35.18 (30.99,45.55)	−0.8 (−0.92,−0.67)
Low SDI	6025 (5105, 6973)	2.97 (2.49,3.44)	13,659 (11797, 15874)	2.95 (2.57,3.42)	−0.18 (−0.29,−0.08)	4562 (3870, 5271)	2.49 (2.11,2.87)	9320 (8098, 10810)	2.26 (1.97,2.63)	−0.45 (−0.54,−0.35)	112,918 (96566, 130515)	51.93 (44.13,59.85)	225,725 (194591, 264190)	45.96 (39.78,53.53)	−0.56 (−0.64,−0.47)
Region															
Andean Latin America	406 (355, 472)	2.10 (1.83,2.45)	1440 (1154, 1799)	2.49 (1.99,3.10)	0.47 (0.31,0.64)	305 (266, 353)	1.67 (1.46,1.93)	858 (696, 1058)	1.52 (1.23,1.87)	−0.35 (−0.51,−0.2)	6556 (5732, 7523)	32.83 (28.71,37.94)	17,114 (13804, 21142)	29.34 (23.63,36.18)	−0.46 (−0.61,−0.3)
Australasia	2391 (2239, 2530)	10.05 (9.42,10.65)	4130 (3727, 4486)	7.39 (6.69,7.99)	−1.03 (−1.14,−0.92)	924 (861, 976)	3.94 (3.66,4.18)	1686 (1480, 1846)	2.78 (2.47,3.04)	−1.15 (−1.24,−1.05)	18,523 (17444, 19528)	78.17 (73.64,82.28)	27,777 (25053, 30266)	49.59 (45.19,53.91)	−1.5 (−1.59,−1.4)
Caribbean	1161 (1101, 1219)	4.60 (4.34,4.82)	2785 (2433, 3093)	5.16 (4.51,5.72)	0.62 (0.5,0.75)	724 (681, 763)	3.00 (2.81,3.15)	1528 (1348, 1699)	2.81 (2.48,3.13)	0.06 (−0.07,0.19)	14,847 (14013, 15669)	58.23 (54.99,61.37)	30,243 (26704, 33818)	55.98 (49.43,62.58)	0.14 (0.02,0.26)
Central Asia	1724 (1537, 1928)	3.65 (3.26,4.08)	2894 (2539, 3233)	3.62 (3.19,4.03)	−0.27 (−0.43,−0.12)	977 (871, 1096)	2.18 (1.94,2.46)	1464 (1293, 1636)	2.01 (1.79,2.23)	−0.47 (−0.64,−0.3)	25,194 (22535, 28167)	52.7 (47.15,59.06)	36,014 (31556, 40440)	44.37 (39.02,49.71)	−0.87 (−1.07,−0.66)
Central Europe	12,315 (11800, 12831)	8.17 (7.81,8.52)	27,508 (25173, 29630)	12.20 (11.17,13.11)	1.25 (1.12,1.38)	6778 (6495, 7060)	4.65 (4.44,4.85)	12,772 (11735, 13696)	5.40 (4.97,5.79)	0.4 (0.32,0.49)	153,477 (147182, 159807)	101.44 (97.30,105.76)	252,538 (232786, 272926)	112.00 (103.07,121.02)	0.24 (0.15,0.33)
Central Latin America	1827 (1764, 1883)	2.32 (2.23,2.40)	5964 (5292, 6621)	2.42 (2.14,2.68)	0.01 (−0.09,0.12)	1213 (1164, 1252)	1.67 (1.59,1.73)	3299 (2923, 3646)	1.38 (1.22,1.52)	−0.67 (−0.77,−0.57)	27,292 (26506, 28127)	33.49 (32.38,34.55)	70,151 (62693, 77656)	28.24 (25.22,31.21)	−0.63 (−0.74,−0.52)
Continued															

Location	1990		2021		EAPC of ASIR (95% CI)	1990		2021		EAPC of ASMR (95% CI)	1990		2021		EAPC of ASDR (95% CI)
	Incidence cases	ASIR	Incidence cases	ASIR		Mortality cases	ASMR	Mortality cases	ASMR		DALYs cases	ASDR	DALYs cases	ASDR	
	(95% UI)	Per 100,000 (95%UI)	(95% UI)	Per 100,000 (95%UI)		(95% UI)	Per 100,000 (95%UI)	(95% UI)	Per 100,000 (95%UI)		(95% UI)	Per 100,000 (95%UI)	(95% UI)	Per 100,000 (95%UI)	
Central Sub-Saharan Africa	650 (527, 801)	3.36 (2.69,4.14)	1642 (1269, 2103)	3.36 (2.61,4.29)	−0.05 (−0.25,0.15)	489 (397, 607)	2.89 (2.29,3.60)	1115 (860, 1424)	2.64 (2.04,3.41)	−0.33 (−0.48,−0.17)	12,692 (10328, 15891)	59.79 (48.31,73.73)	29,085 (22348, 37303)	54.88 (42.29,70.31)	−0.31 (−0.46,−0.15)
East Asia	37,487 (27255, 43835)	4.71 (3.49,5.45)	110,689 (88380, 141591)	5.20 (4.17,6.61)	0.12 (0.04,0.21)	23,567 (17543, 27239)	3.42 (2.59,3.90)	47,061 (38147, 59317)	2.35 (1.91,2.93)	−1.56 (−1.69,−1.42)	581,802 (421586, 679520)	69.66 (51.40,80.75)	970,160 (775288, 1223553)	45.62 (36.68,57.34)	−1.7 (−1.84,−1.57)
Eastern Europe	16,138 (15289, 17352)	5.69 (5.39,6.10)	23,152 (20869, 25273)	6.52 (5.88,7.11)	0.13 (−0.09,0.34)	8500 (8063, 9087)	3.07 (2.92,3.28)	10,334 (9387, 11259)	2.86 (2.60,3.12)	−0.61 (−0.9,−0.31)	204,045 (193026 ,219347)	71.68 (67.89,77.00)	226,527 (204386, 248278)	63.86 (57.69,70.02)	−0.82 (−1.14,−0.5)
Eastern Sub-Saharan Africa	2348 (2002, 2799)	3.48 (2.96,4.12)	5191 (4248, 6475)	3.41 (2.83,4.20)	−0.24 (−0.32,−0.17)	1815 (1545, 2167)	2.96 (2.51,3.52)	3631 (3001, 4479)	2.68 (2.24,3.26)	−0.47 (−0.53,−0.41)	45,606 (39028, 54284)	62.57 (53.36,74.48)	88,982 (72601, 111594)	54.45 (44.88,67.50)	−0.62 (−0.69,−0.56)
High-income Asia Pacific	12,701 (11974, 13267)	6.47 (6.06,6.76)	34,957 (30457, 38140)	6.95 (6.24,7.51)	0.29 (0.22,0.37)	4682 (4364, 4920)	2.54 (2.35,2.68)	13,561 (11269, 15000)	2.18 (1.88,2.39)	−0.46 (−0.53,−0.4)	94,646 (88968, 99521)	48.26 (45.12,50.79)	203,369 (177720, 222129)	39.27 (35.51,42.42)	−0.63 (−0.69,−0.57)
High-income North America	49,650 (47093, 51381)	13.92 (13.24,14.39)	93,310 (85909, 97760)	13.98 (12.96,14.61)	0.03 (−0.15,0.2)	13,512 (12500, 14113)	3.67 (3.40,3.83)	24,227 (21460, 25836)	3.41 (3.04,3.62)	−0.17 (−0.25,−0.08)	275,188 (260230, 288096)	77.34 (73.36,81.00)	452,463 (413941, 480775)	67.31 (62.04,71.53)	−0.4 (−0.51,−0.3)
North Africa and Middle East	11,388 (8681, 13426)	6.96 (5.45,8.21)	35,647 (30169, 43385)	8.22 (6.95,9.95)	0.4 (0.32,0.48)	5928 (4689, 6935)	4.10 (3.32,4.79)	12,291 (10467, 14961)	3.24 (2.75,3.91)	−0.9 (−0.99,−0.81)	153,002 (116039, 178611)	90.38 (70.44,105.26)	287,848 (243734, 352581)	66.27 (56.58,80.57)	−1.23 (−1.33,−1.12)
Oceania	49 (32, 65)	1.70 (1.16,2.23)	160 (101, 218)	2.13 (1.37,2.86)	0.85 (0.8,0.89)	30 (20, 39)	1.23 (0.84,1.63)	87 (56, 120)	1.38 (0.91,1.86)	0.54 (0.48,0.6)	840 (547, 1133)	27.86 (18.65,36.91)	2453 (1537, 3406)	31.41 (20.31,43.08)	0.56 (0.5,0.63)
South Asia	10,182 (8347, 11809)	1.98 (1.62,2.29)	30,709 (26740, 37487)	2.19 (1.91,2.68)	0.04 (−0.06,0.14)	7504 (6122, 8705)	1.62 (1.32,1.89)	19,574 (16998, 24116)	1.51 (1.31,1.88)	−0.49 (−0.58,−0.4)	182,390 (151569, 211358)	33.37 (27.27,38.65)	444,205 (385193, 547312)	30.84 (26.73,38.03)	−0.53 (−0.62,−0.44)
Southeast Asia	4705 (4150, 5310)	1.96 (1.73,2.21)	16,060 (13707, 19974)	2.55 (2.17,3.19)	0.69 (0.64,0.74)	3035 (2701, 3443)	1.42 (1.25,1.62)	7857 (6688, 10162)	1.40 (1.19,1.80)	−0.21 (−0.26,−0.17)	74,638 (66487, 84309)	29.91 (26.63,33.94)	182,243 (155288, 231923)	28.60 (24.36,36.72)	−0.29 (−0.34,−0.25)

Continued

Location	1990		2021		EAPC of ASIR (95% CI)	1990		2021		EAPC of ASMR (95% CI)	1990		2021		EAPC of ASDR (95% CI)
	Incidence cases	ASIR	Incidence cases	ASIR		Mortality cases	ASMR	Mortality cases	ASMR		DALYs cases	ASDR	DALYs cases	ASDR	
	(95% UI)	Per 100,000 (95%UI)	(95% UI)	Per 100,000 (95%UI)		(95% UI)	Per 100,000 (95%UI)	(95% UI)	Per 100,000 (95%UI)		(95% UI)	Per 100,000 (95%UI)	(95% UI)	Per 100,000 (95%UI)	
Southern Latin America	3409 (3196, 3579)	7.43 (6.97,7.81)	5173 (4781, 5538)	5.85 (5.41,6.26)	−0.66 (−0.76,−0.57)	2055 (1927, 2157)	4.63 (4.34,4.85)	2663 (2458, 2856)	2.94 (2.72,3.15)	−1.27 (−1.36,−1.19)	43,377 (41008, 45530)	94.02 (88.93,98.57)	51,950 (48352,55707)	58.97 (54.88,63.14)	−1.35 (−1.43,−1.27)
Southern Sub-Saharan Africa	991 (815, 1193)	3.72 (3.04,4.51)	2426 (2149, 2726)	4.29 (3.82,4.76)	0.39 (0.21,0.58)	649 (532, 784)	2.68 (2.18,3.24)	1468 (1301, 1648)	2.86 (2.55,3.18)	0.19 (−0.05,0.42)	16,250 (13473, 19501)	58.54 (48.23,70.74)	37,246 (32344, 42426)	63.23 (55.53,71.44)	0.25 (0.02,0.49)
Tropical Latin America	3125 (2979, 3247)	3.65 (3.45,3.81)	10,073 (9306, 10634)	3.97 (3.66,4.20)	0.29 (0.22,0.37)	2052 (1939, 2139)	2.62 (2.45,2.74)	5898 (5350, 6249)	2.38 (2.15,2.52)	−0.2 (−0.25,−0.14)	46,837 (44824, 48758)	52.96 (50.42,55.24)	120,415 (111690, 126673)	47.22 (43.72,49.70)	−0.33 (−0.39,−0.27)
Western Europe	85,721 (81644, 88526)	14.54 (13.89,14.99)	122,151 (110741, 130258)	12.59 (11.57,13.40)	−0.46 (−0.54,−0.38)	37,027 (34802, 38304)	6.09 (5.72,6.30)	47,609 (42249, 51152)	4.29 (3.87,4.58)	−1.13 (−1.19,−1.08)	723,581 (692471, 748257)	123.29 (118.13,127.53)	795,692 (722821, 850695)	81.34 (74.89,86.68)	−1.34 (−1.38,−1.3)
Western Sub-Saharan Africa	1775 (1498, 2048)	2.20 (1.88,2.52)	4248 (3548, 5113)	2.37 (1.99,2.84)	0.2 (0.15,0.25)	1359 (1161, 1564)	1.84 (1.58,2.09)	2907 (2438, 3484)	1.83 (1.54,2.22)	−0.02 (−0.07,0.03)	32,258 (27128, 37344)	37.65 (31.94,43.26)	70,593 (58743, 85738)	36.83 (30.85,44.15)	−0.1 (−0.16,−0.04)

Table 1. Numbers and ASRs of bladder cancer burden and their Temporal trend from 1990 to 2019. ***ASIR***, age-standardized incidence rate; ***ASMR***, age-standardized mortality rate; ***ASDR***, age-standardized disability-adjusted life years rate; ***EAPC***, estimated annual percentage change; ***UI***, uncertainty interval; ***CI***, confidence interval; ***SDI***, socio-demographic index.

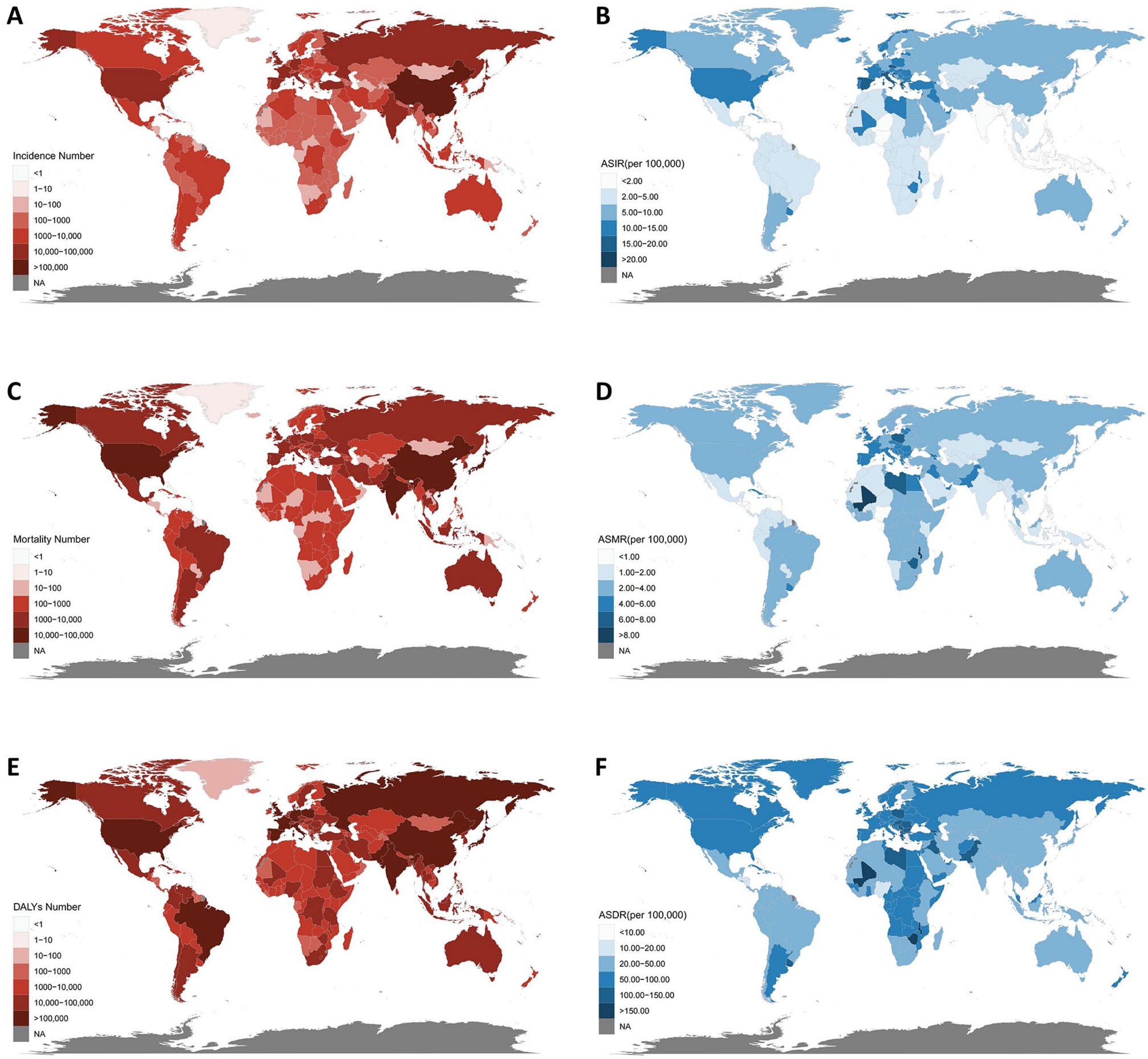

Fig. 1. The global burden of bladder cancer in 204 countries or territories in 2021. (**A**) The incidence number of bladder cancer. (**B**) The age-standardized incidence rate of bladder cancer. (**C**) The mortality number of bladder cancer. (**D**) The age-standardized mortality rate of bladder cancer. (**E**) The DALYs number of bladder cancer. (**F**) The age-standardized DALYs rate of bladder cancer. ASIR, age-standardized incidence rate; ASMR, age-standardized mortality rate; ASDR, age-standardized DALYs rate; DALYs, disability-adjusted life years.

downward trend. In comparison with the period from 1992 to 1996, the relative risks of incidence and mortality in 2016–2021 decreased by 10.5% and 30.5% respectively (Fig. 5C and D, S8 and S9; Table S4). The birth cohort effect has a significant impact on the risk of BC burden. In early cohorts, there is an increased relative risk of disease burden. The relative risks of incidence and mortality respectively reach their peaks in the period from 1922 to 1931 and 1912 to 1916 and then continuously decrease (Fig. 5E and F, S8 and S9; Table S4).

Decomposition analysis of bladder cancer burden

As shown in Fig. 6 and Table S5, globally from 1990 to 2021, aging, population growth, and epidemiological changes contributed to BC incidence increase by 59.40%, 53.78%, and − 13.17% respectively; to mortality increase by 67.22%, 84.46%, and − 51.68%; and to DALYs increase by 89.83%, 83.91%, and − 73.74%. The impact of epidemiological changes on these three indicators was negative in all SDI regions (except for incidence in middle SDI and low-middle SDI regions). Based on the analysis of SDI regions, we found that for the growth of BC burden in any sex, population aging played the most significant role in high SDI, high-middle SDI, and middle SDI regions, while population growth became the most significant factor in low-middle SDI and low SDI regions (Fig. 6; Table S5).

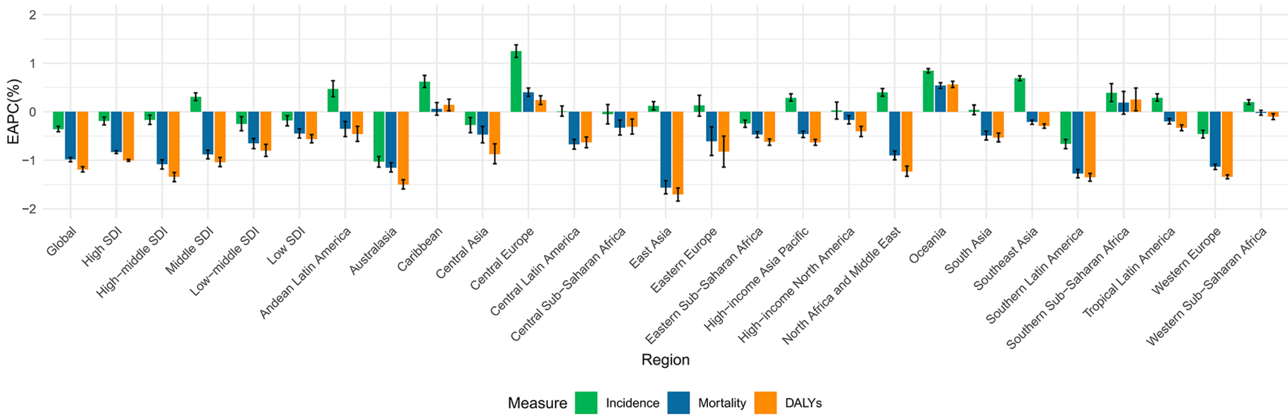

Fig. 2. The EAPC of age-standardized rate of bladder cancer burden at the global and regional levels. EAPC, estimated annual percentage change; SDI, socio-demographic index.

Health inequality analysis of bladder cancer burden

The ASIR of bladder cancer continuously increases with the increase in the SDI level (Figure S10B). The ASMR and ASDR reach their peaks approximately at SDI = 0.78 and then decrease slightly and significantly respectively with the increase in SDI (Figure S10D and S10F). We found that the burden of BC in terms of incidence, mortality, and DALYs is predominantly concentrated in countries with a high level of socio-demographic development. Regarding the absolute inequality of BC burden, in 2021, the SIIs for BC incidence, mortality, and DALYs were 16.98, 6.60, and 115.60 respectively. These values showed a significant increase compared to those in 1990 (Fig. 7A, C and E). However, in 2021, the concentration indices for disease burden stood at 0.40, 0.31, and 0.26 respectively. Although there was a minor decrease compared to 1990, it still suggests that there exists a significant imbalance in the distribution of disease burden among countries with varying levels of SDI. (Figure 7B, D and F).

Predictive analysis on bladder cancer burden from 2022 to 2036

The Bayesian age-period-cohort model results are presented in Fig. 8 and Table S6. It is anticipated that the ASIR, ASMR, and ASDR of bladder cancer for both male and female globally will continue to decline. Specifically, it is projected that by 2036, the male ASIR, ASMR, and ASDR will respectively decrease to 10.10 per 100,000 (95% Crl: 7.05–13.16)), 4.06 per 100,000 (95% Crl: 2.79–5.33), and 78.53 per 100,000 (95% Crl: 52.41–104.65). Meanwhile, for females, the ASIR, ASMR, and ASDR will respectively drop to 2.42 per 100,000 (95% Crl: 1.61–3.23), 1.08 per 100,000 (95% Crl: 0.74–1.42), and 21.13 per 100,000 (95% Crl: 14.42–27.84).

Discussion

This study employed GBD 2021 data to analyze the most recent data on bladder cancer incidence, mortality, and DALYs at the global, regional, and national levels from 1990 to 2021. It further conducted a comprehensive assessment covering time trends, decomposition analysis, health inequalities, and future predictions. From 1990 to 2021, the global burden of BC in terms of incidence, mortality, and DALYs generally exhibited an upward trend, yet there were disparities among different regions, countries, sexes, and SDI levels. Simultaneously, the ASRs of these three indicators showed a downward trend globally. Decomposition analysis revealed that population growth and aging are the main drivers of changes in the burden of BC, while epidemiological change factors contribute to reducing the disease burden. Health inequality analysis indicated that the disease burden of BC is disproportionately concentrated in countries with a higher SDI level. Although the relative inequality related to SDI has decreased over time, this difference remains highly evident. According to predictions by the BAPC model, from 2022 to 2036, the ASRs of incidence, mortality, and DALYs will decline slightly each year. However, considering population aging and the growth of the world population, the disease burden of BC will continue to increase. This demonstrates that in the coming decades, the prevention and management of BC will still face enormous challenges.

In 2021, the global incidence of BC amounted to 0.26 million cases, with the number of deaths standing at 0.12 million, and the number of DALYs cases reaching 2.73 million. Among these, the burden of BC in males is significantly higher than that in females. The numerical ratio is approximately 3:1, while the ratio in terms of ASRs is close to 4:1. The ASRs of the global BC burden that are showing a downward trend are inconsistent with previous studies, which may be related to the update of GBD 2021 data[8,12]. Regarding the ASR of bladder cancer burden, high-income North America has the highest ASIR, whereas Central Europe has the highest ASMR and ASDR. Regions with the most significant increase over the past decades, such as Central Europe which has had the largest increase in the ASR of incidence and Oceania which has witnessed the largest increase in the ASRs of deaths and DALYs, are of concern and demand extra attention. At the level of 204 countries or territories, the differences and changing trends of the complex burden of BC make it necessary to formulate personalized public health policies to strengthen the control of the burden of BC. In 2021, Lebanon had the highest ASR of bladder cancer incidence, Mali had the highest ASR of mortality, and Malawi had the highest ASR of DALYs. However,

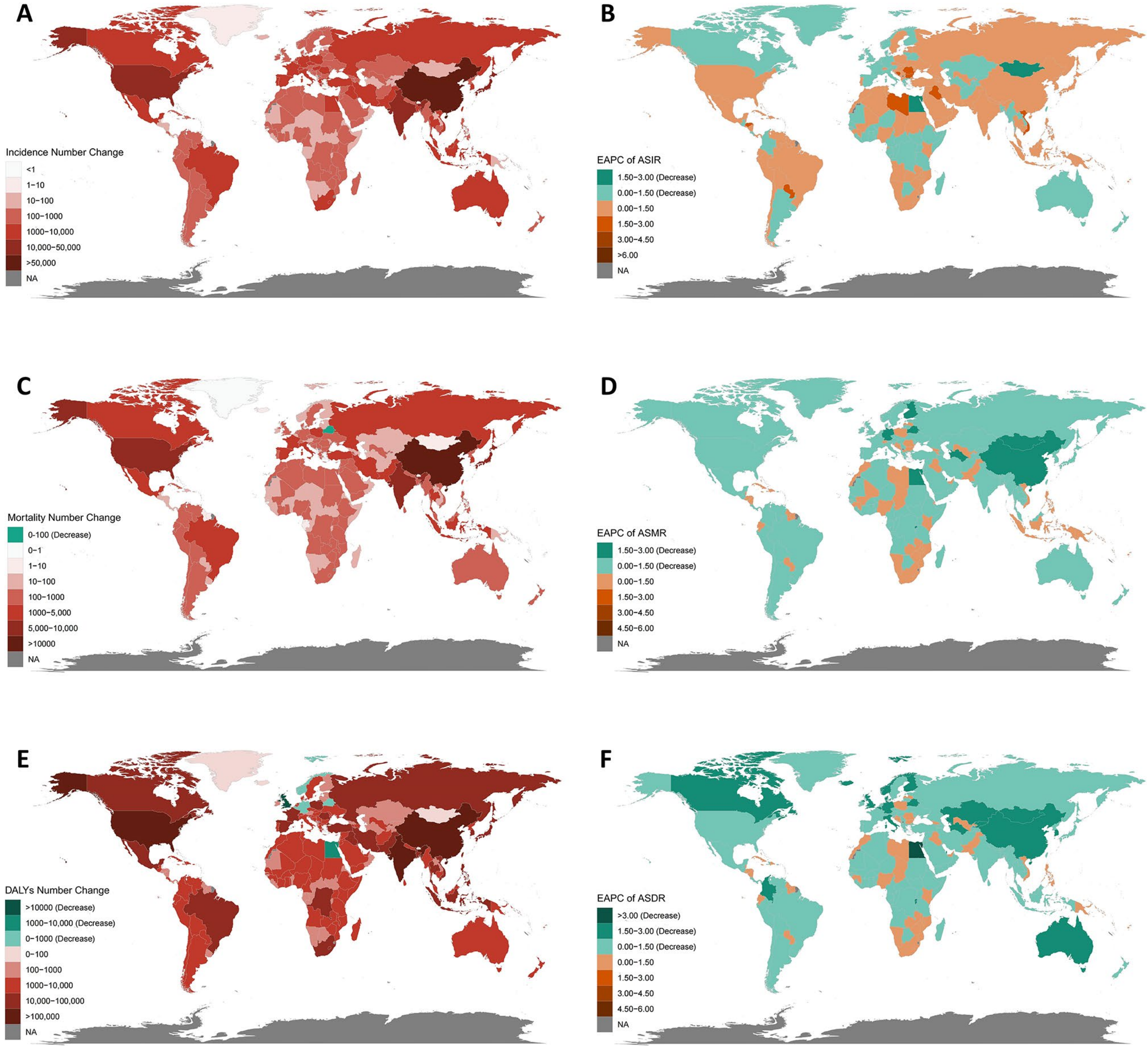

Fig. 3. The global burden changes of bladder cancer in 204 countries or territories from 1990 to 2021. (**A**) The incidence number change of bladder cancer. (**B**) The EAPC of age-standardized incidence rate of bladder cancer. (**C**) The mortality number change of bladder cancer. (**D**) The EAPC of age-standardized mortality rate of bladder cancer. (**E**) The DALYs number change of bladder cancer. (**F**) The EAPC of age-standardized DALYs rate of bladder cancer. ASIR, age-standardized incidence rate; ASMR, age-standardized mortality rate; ASDR, age-standardized DALYs rate; DALYs, disability-adjusted life years; EAPC, estimated annual percentage change.

in 2021, China had the highest number of BC incidence, deaths, and DALYs in the world, as well as the highest increase in the number of disease burden from 1990 to 2021. The United States was the second country in terms of the number of BC burden in 2021, and its increase in disease burden is also among the top. Although China does not possess the highest ASR of bladder cancer burden, it undeniably shoulders the greatest BC burden, a situation likely attributed to its massive population size. Likewise, the United States, boasting a significant population and a relatively high ASIR, also endures a remarkably heavy BC burden. From 1990 to 2021, in China, the ASIR of bladder cancer showed a slight upward trend, while ASMR and ASDR exhibited a relatively obvious downward trend. In the United States, the ASIR and ASMR of bladder cancer remained stable, and the ASDR showed a slight downward trend. A previous study predicted that from 2017 to 2030, the incidence of BC in countries with middle SDI would increase significantly while the mortality rate would decline, and China's situation is in line with this[38]. The reasons for the increase in ASIR of bladder cancer in China may be related to factors such as increased life expectancy, the implementation of early disease screening, increased smoking, and changes in lifestyle[11]. The substantial burden of BC in China, along with the uneven distribution of medical resources, may jointly present a formidable challenge to the management of BC[25]. The ASIR, ASMR, and ASDR of

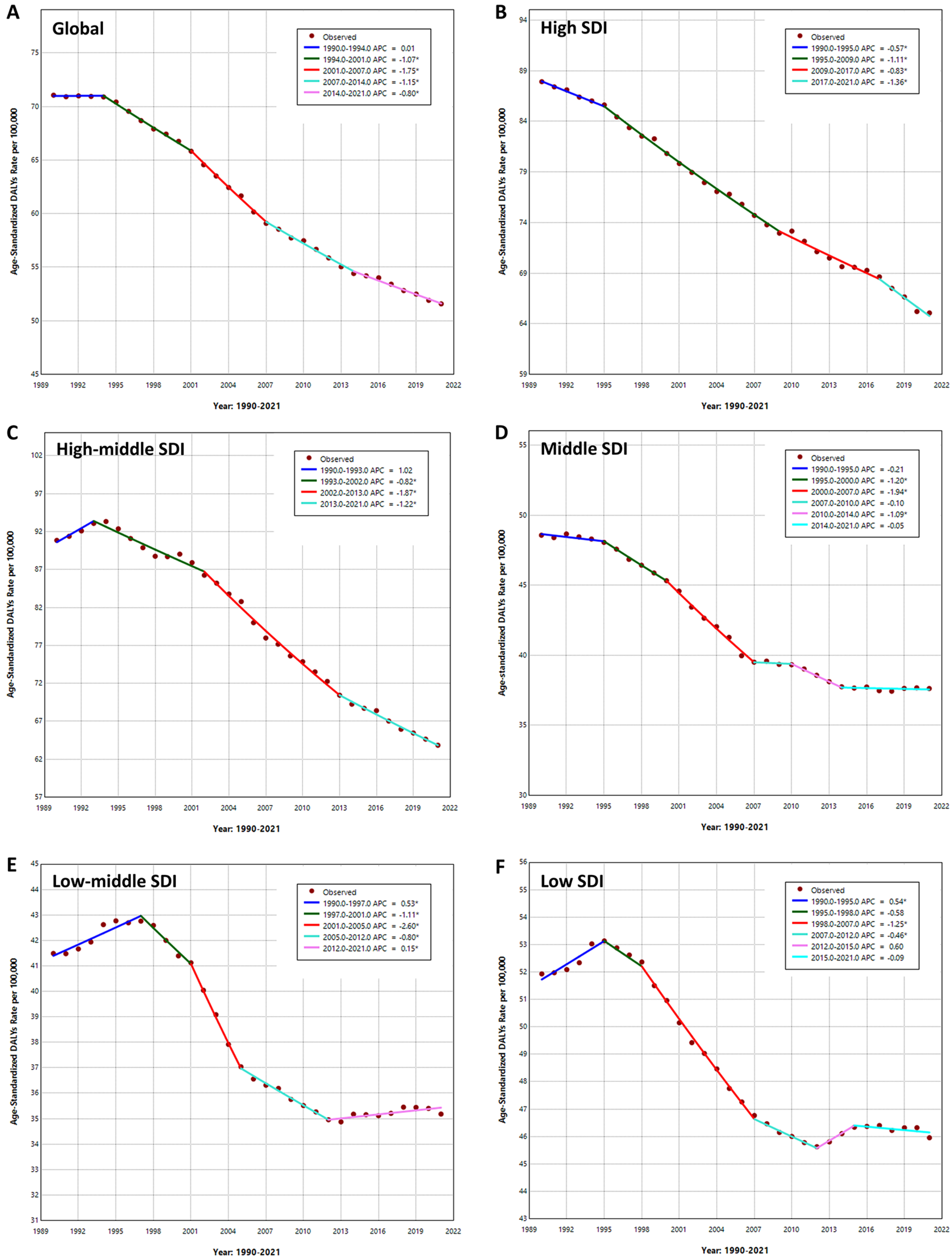

Fig. 4. The joinpoint analysis of age-standardized DALYs rate of bladder cancer from 1990 to 2021. (**A**) The age-standardized DALYs rate change of bladder cancer globally. (**B**) The age-standardized DALYs rate change of bladder cancer in high SDI region. (**C**) The age-standardized DALYs rate change of bladder cancer in high-middle SDI region. (**D**) The age-standardized DALYs rate change of bladder cancer in middle SDI region. (**E**) The age-standardized DALYs rate change of bladder cancer in low-middle SDI region. (**F**) The age-standardized DALYs rate change of bladder cancer in low SDI region. APC, annual percentage change; DALYs, disability-adjusted life years; SDI, socio-demographic index.

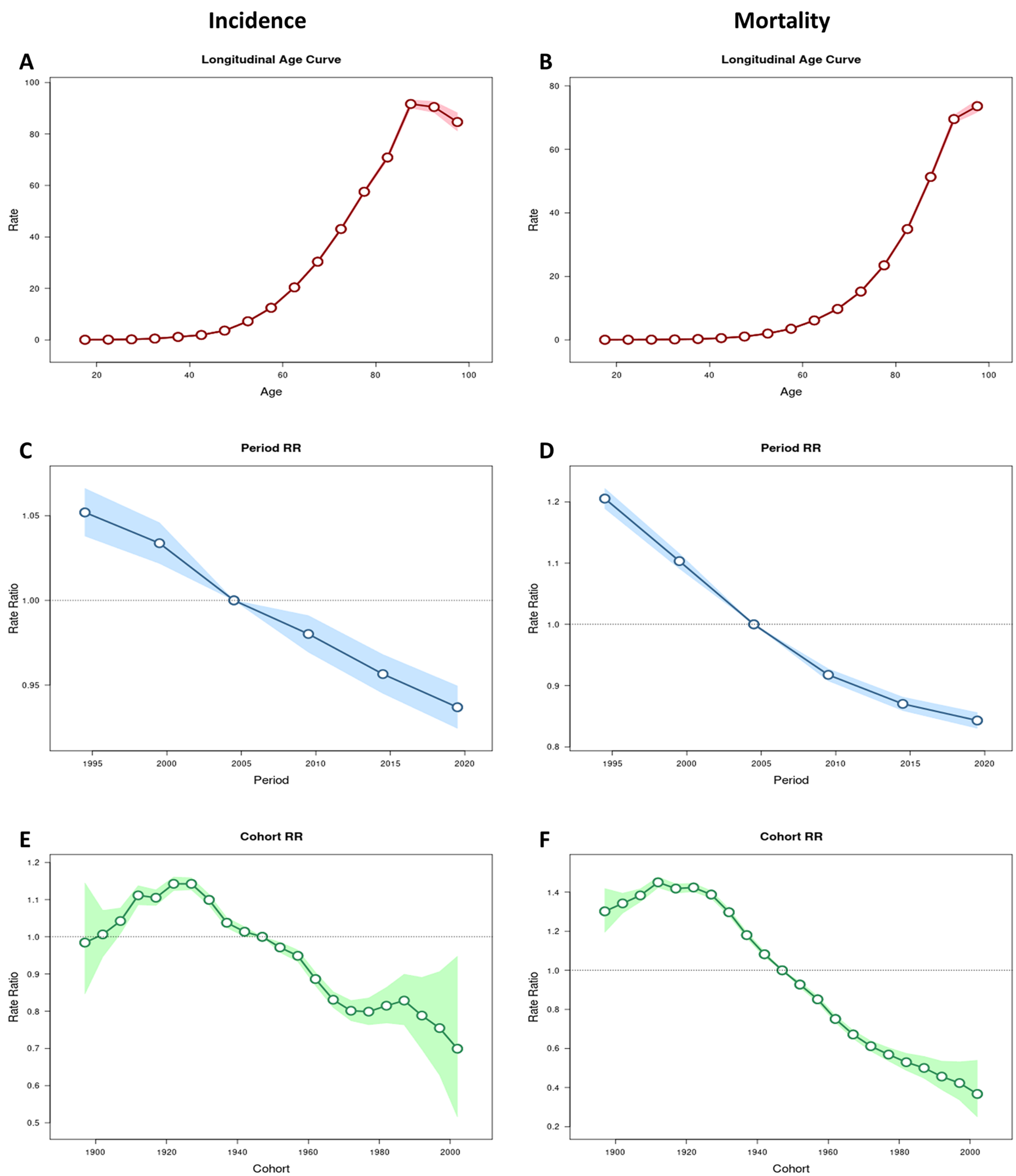

Fig. 5. The effects of age, period, and cohort on the risk of bladder cancer burden globally. (**A**) The age effect of relative incidence risk of bladder cancer. (**B**) The age effect of relative mortality risk of bladder cancer. (**C**) The period effect of relative incidence risk of bladder cancer. (**D**) The period effect of relative mortality risk of bladder cancer. (**E**) The birth cohort effect of relative incidence risk of bladder cancer. (**F**) The birth cohort effect of relative mortality risk of bladder cancer. RR, relative risk.

bladder cancer in Cape Verde, the Northern Mariana Islands, and American Samoa showed the most significant growth, suggesting that they should take more measures in the control of BC. Similar to previous studies, our research observed an increase in the number of incidence, deaths, and DALYs of bladder cancer, indicating that the burden of BC has increased globally over time[9]. Given that BC is prone to recurrence and metastasis by nature, it incurs direct economic losses (such as cystoscopy and imaging reexaminations, drug treatment, radiotherapy, and surgical treatment), indirect economic losses (including absenteeism and premature death), as well as intangible personal costs (such as emotional distress, fatigue, and activity limitations)[4]. Bladder cancer

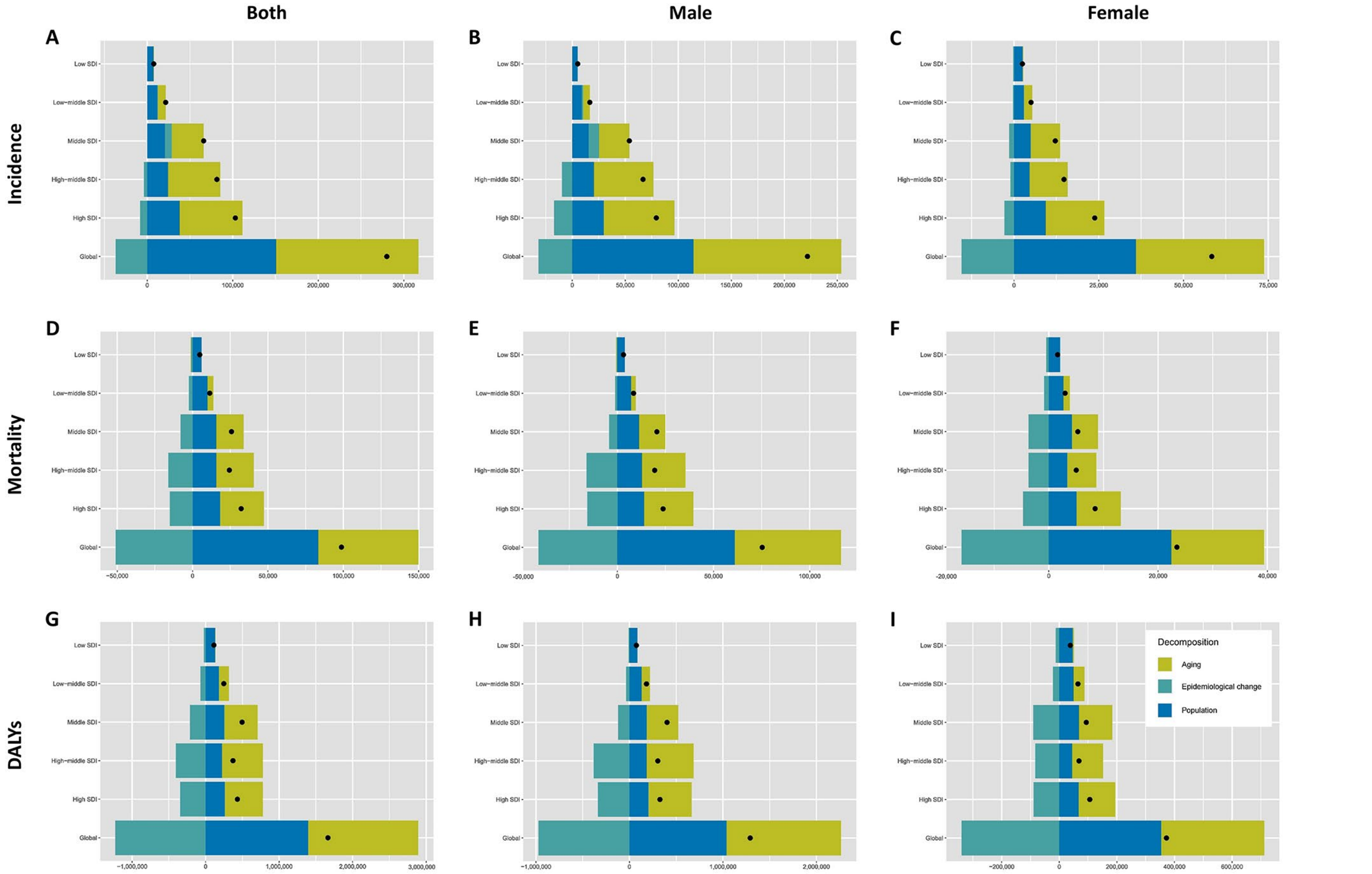

Fig. 6. The decomposition analysis of the burden of bladder cancer from 1990 to 2021. (**A**) The decomposition analysis of incidence number change in overall sexes. (**B**) The decomposition analysis of incidence number change in male. (**C**) The decomposition analysis of incidence number change in female. (**D**) The decomposition analysis of deaths number change in overall sexes. (**E**) The decomposition analysis of deaths number change in male. (**F**) The decomposition analysis of deaths number change in female. (**G**) The decomposition analysis of DALYs number change in overall sexes. (**H**) The decomposition analysis of DALYs number change in male. (**I**) The decomposition analysis of DALYs number change in female. The black dot denotes the overall value of the change resulting from all three components. For each component, the magnitude of a positive value suggests a corresponding increase in burden attributed to the component; the magnitude of a negative value suggests a corresponding decrease in burden attributed to the component. DALYs, disability-adjusted life-years; SDI, sociodemographic index.

is the tumor with the highest lifetime treatment cost for patients among all cancers[39]. It is estimated that the total related cost in the United States was as high as 3.98 billion US dollars in 2010. It is expected to cause economic losses of nearly 4.9 billion euros in Europe in 2012[40,41]. Nowadays, the economic burden caused by BC is incalculable globally. Therefore, developing prevention strategies for bladder cancer, enhancing management measures, and discovering effective treatments are particularly crucial.

When dividing bladder cancer ASIR, ASMR, and ASDR trends into sub-periods, we find that from 1990 to 1996, ASIR showed an upward trend. From 1990 to 1994, there was no significant change in ASMR and ASDR. Later, these three global BC indicators continued to decline. This trend of increased disease burden number but decreased age-standardized rate is similar to previous studies[4,9,12]. The early increase in the ASIR of BC that has been observed might not necessarily signify a genuine elevation in the risk of BC occurrence. Instead, it could potentially reflect the growing prevalence and enhancement of physical examination screening, early detection, and diagnostic techniques such as urine cytology, cystoscopy, and CT scan[13,42]. Of course, there are also reasons such as the increased prevalence of risk factors for BC (including smoking, obesity, alcohol consumption, and consumption of red meat) due to the previously rapidly developing world economy, as well as higher exposure to occupational and environmental carcinogens, or the lag in tobacco control[42]. This requires more detailed epidemiological studies for elaboration, even down to the level of individual countries or risk factors.

The observed downward change in the ASR of the bladder cancer burden globally seems to reflect the geographical distribution differences and changes of risk factors prevalence. Studies have found that economic development level has a significant impact on the BC. The results show that 55% of BC cases and 43% of BC deaths occur in countries with a high human development index (HDI), while only 5% of the BC occurs in countries with a low HDI, which is disproportionate to the population[2]. Simultaneously, this research also observed a

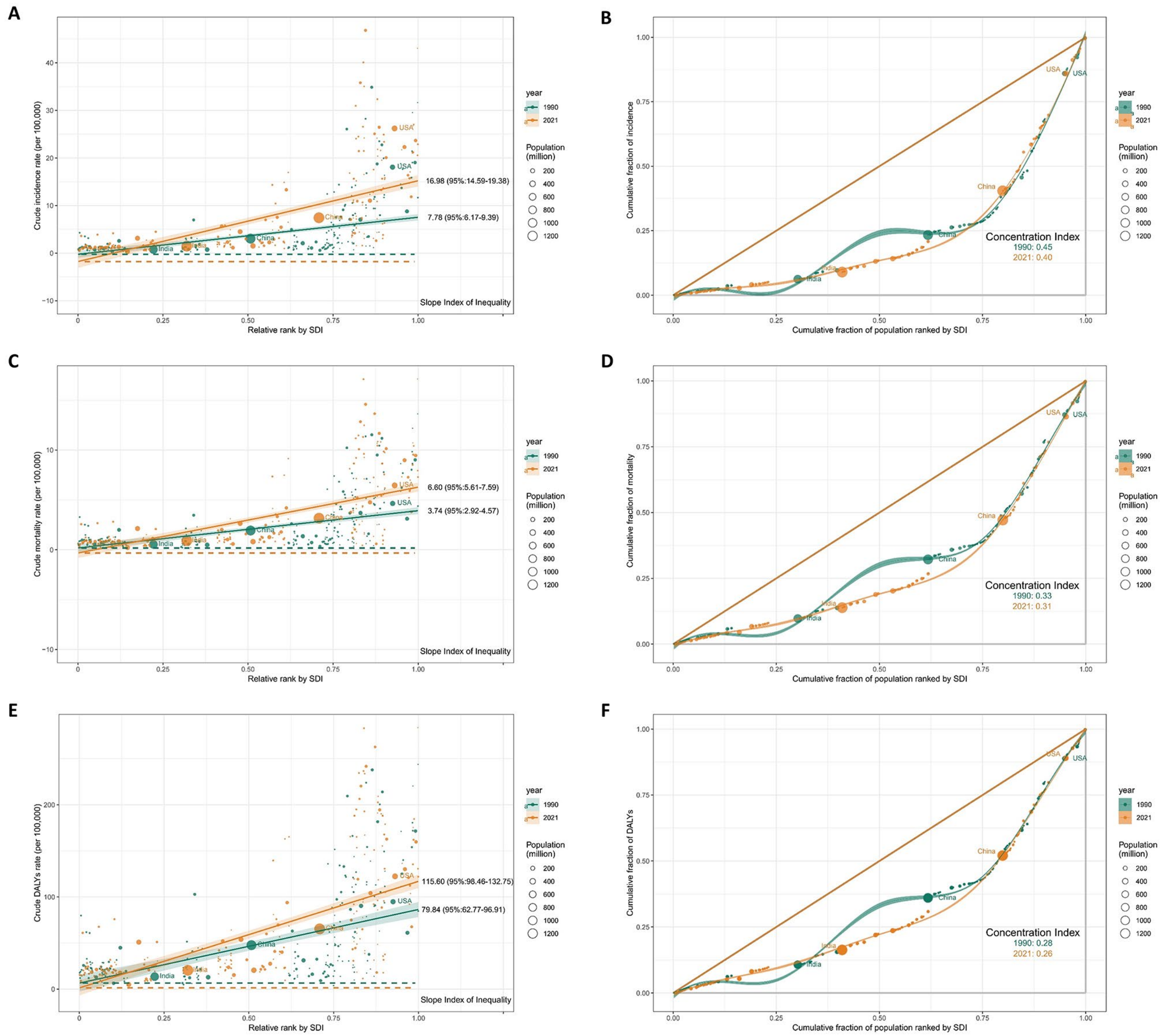

Fig. 7. The SDI-related health inequality analysis for the burden of bladder in 1990 and 2021, globally. (**A**) The SDI-related health inequality regression for incidence of bladder cancer. (**B**) The concentration curves for incidence of bladder cancer. (**C**) The SDI-related health inequality regression for mortality of bladder cancer. (**D**) The concentration curves for mortality of bladder cancer. (**E**) The SDI-related health inequality regression for DALYs of bladder cancer. (**F**) The concentration curves for DALYs of bladder cancer. DALYs, disability-adjusted life-years; SDI, sociodemographic index.

reduction in the incidence and mortality rates of BC in regions such as Western Europe, North America, and Oceania in recent years[2]. Our study additionally detected a continuous decline in ASIR and ASMR in areas with high SDI and high-middle SDI as well as in the aforementioned regions. This might drive down the ASR of the global BC burden. Smoking is the most important risk factor for BC, accounting for about 50% of cases[3]. Thus, the trends in the incidence and mortality rates of BC are partly influenced by the manifestations of tobacco prevalence. Marie Ng and her collaborators found that from 1980 to 2012, at the global level, the estimated prevalence of daily smoking among men and women has significantly decreased[43]. However, the decades-long lag of tobacco control on the risk of BC incidence must be considered[44]. Particularly in the past few decades, the significant decline in the male smoking rate in regions with high HDI levels such as North America and many European countries may explain the reasons for the observed decline in the incidence and mortality rates of BC in these areas[2,39]. The attributable risk analysis of BC deaths also verifies that the proportion of bladder cancer deaths and DALYs caused by smoking in 2021 was significantly lower than that in 1990[13]. In addition, in the past few decades, exposure to occupational carcinogens in the European Union still exists but has been controlled and significantly improved. Due to the long latency period of BC, occupation-related BC may continue to decrease in the coming decades. At the same time, there is still much room for improvement in occupational health in low- and middle-income countries to reduce the burden of bladder cancer[4]. The improvement of

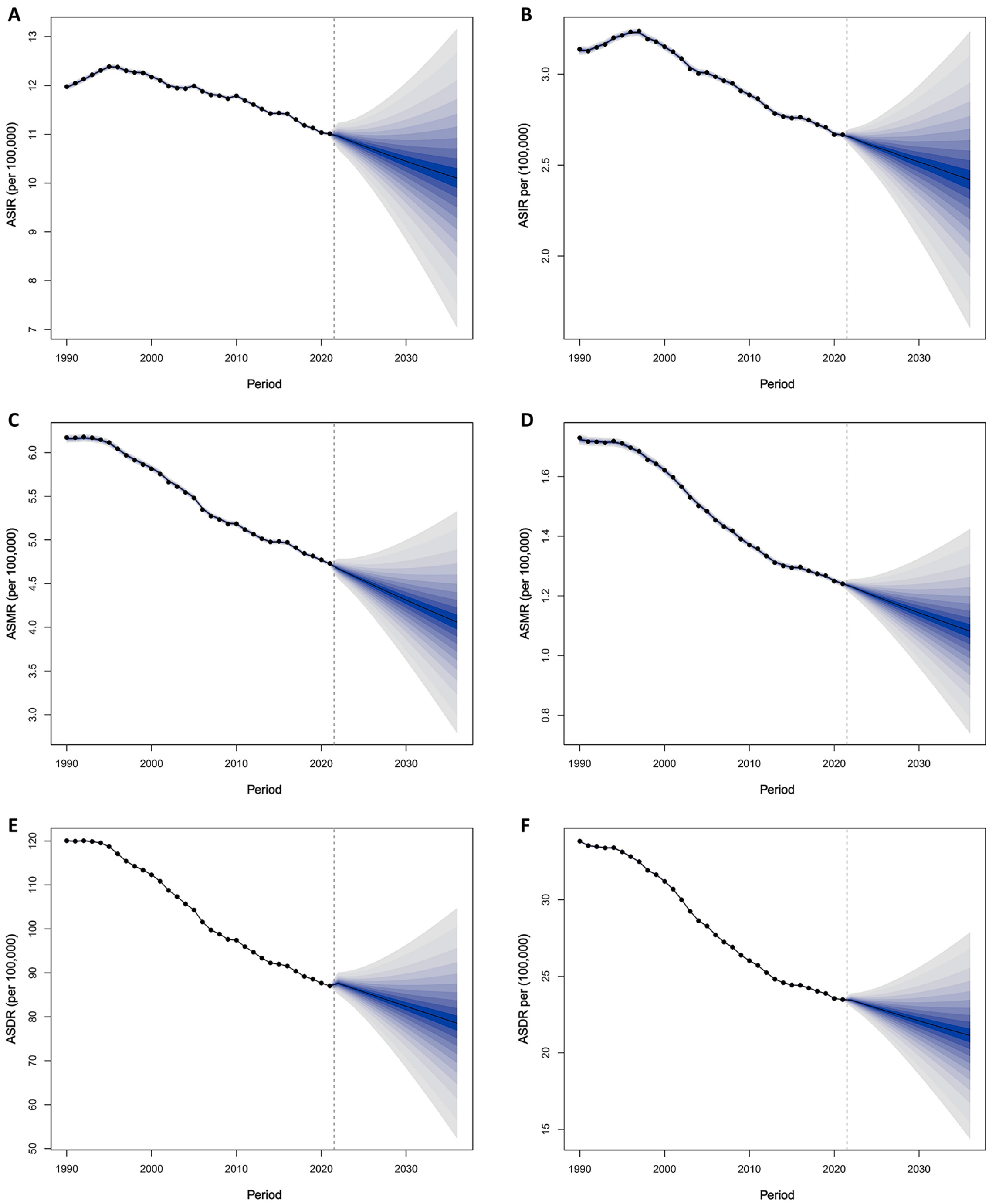

Fig. 8. The predicted age-standardized rate of bladder cancer burden from 2022 to 2036 by sexes globally. (**A**) The predicted ASIR from 2022 to 2036 in male. (**B**) The predicted ASIR from 2022 to 2036 in female. (**C**) The predicted ASMR from 2022 to 2036 in male. (**D**) The predicted ASMR from 2022 to 2036 in female. (**E**) The predicted ASDR from 2022 to 2036 in male. (**F**) The predicted ASDR from 2022 to 2036 in female. ASIR, age-standardized incidence rate; ASMR, age-standardized mortality rate; ASDR, age-standardized DALYs rate; DALYs, disability-adjusted life-years.

environmental factors may also be one of the reasons for the reduction of the burden of BC. Although the relationship between arsenic and chlorine in drinking water and the risk of BC occurrence has been clearly defined at present, unfortunately, there is currently no evidence to show how reducing environmental exposure affects the risk of BC occurrence[3]. Schistosomiasis is an endemic disease affecting hundreds of millions of people in sub-Saharan Africa and parts of the Middle East. Schistosomiasis plus the chronic inflammatory infection it causes significantly increases the risk of squamous cell BC. Taking Egypt as an example, through the extensive use of the effective anthelmintic drug praziquantel for treatment and the improvement of water supply and sanitation conditions, the incidence of BC caused by schistosomiasis in Egypt has significantly decreased[45]. However, the prevention and management of bladder cancer are not as optimistic as imagined. A study has revealed that tobacco consumption in developing countries is increasing and has surpassed that in developed countries where the prevalence of tobacco consumption has commenced to decline[43]. For instance, in some countries in Central America, South America, Central and Eastern Europe, the smoking rate has only recently begun to decline or is even still on the rise[2]. The growth in smoking prevalence, environmental pollution, and aging, along with the ascent of the HDI, may result in an upsurge in the incidence of BC in these regions with low SDI levels in the coming decades[4]. This is in accordance with the upward trend of ASIR in regions with middle SDI, low- middle SDI, and low SDI that we have detected in the past ten years. This inevitably leads us to worry that the burden of bladder cancer is gradually being transferred to regions with lower SDI levels.

Age-period-cohort analysis observed that the relative risks of BC incidence and mortality showed an increasing trend with age. The relative risks increased significantly after the ages of 50 and 65 respectively. In fact, aging is undoubtedly the most important factor in the burden of BC. This may be attributed to the cumulative exposure to a large number of risk factors throughout life and the decline in physical function[4,46]. For the period effect, it is detected that the relative incidence and mortality risk decrease as the period progresses. This may be related to the gradual reduction of risk factors for bladder cancer. In particular, smoking prevalence has gradually decreased as global smoking cessation control is implemented[43]. Regarding the birth cohort effect, the relative risks of incidence and mortality show a trend of first rising and then falling with the increase in birth cohorts, which means that individuals born earlier exhibit a higher risk of BC than those born later. For one thing, for individuals born at an earlier time, the longer the period they have gone through industrialization and social development, the greater the cumulative total of risk factors to which they have been exposed. For another, the decline in smoking, occupational exposure and other risk factors, as well as the improvement of screening and treatment measures, are the results of efforts in recent decades. This has a lagging effect on the effect of BC burden[4].

Our decomposition analysis results show that population aging and growth are important factors contributing to the increased global burden of BC. This is consistent with previous studies that have emphasized the role of population size and structural changes in driving BC burden[8,39]. Interestingly, we also discovered disparities in the impacts of population aging and population growth in regions with varying SDI levels. This underscores the significance of the need for customized prevention and early detection strategies in different countries. The role of epidemiological changes is in line with previous results and generally exhibits a reducing effect on the growth of the burden of BC. However, it is worth noting that the epidemiological changes in male in regions with lower SDI have a positive contribution to the incidence of BC, indicating that these regions should increase investment in preventive measures for male BC.

It is observed that a disproportionate burden of BC is concentrated in countries with higher SDI, which is similar to previous studies[8,47]. The countries with high SDI levels always inevitably have an aging population, better detection rates and the prevalence of risk factors such as smoking and occupational exposure, thus promoting the occurrence of BC. With the further increase of SDI level, the adequacy of medical resources in developed countries enhances the treatment level of BC, thereby reducing the mortality rate and DALYs of BC in countries with the highest SDI level. This may be the reason why the ASMR and ASDR reach their peaks when the SDI is 0.78, unlike the ASIR which continues to rise. Countries with a lower SDI are faced with the challenges of population growth, insufficient medical resources and changes in the prevalence of risk factors. This indicates that with the improvement of the social and demographic development level, the prevention, management and treatment of BC should be strengthened, especially for modifiable risk factors such as smoking, schistosomiasis and occupational exposure. Regarding the control of schistosomiasis, the new WHO guidelines in 2022 recommend expanding the preventive chemotherapy regimen from only school-aged children to the entire community. Meanwhile, it is suggested to adjust the frequency of the preventive chemotherapy regimen according to the community prevalence and to prioritize additional interventions for it, including improving water, sanitation and personal hygiene[48]. This recommendation indicates that low- and middle-income countries, mainly those in sub-Saharan Africa, need to make their prevention and control measures for schistosomiasis more refined and comprehensive. Controlling smoking is of crucial significance in mitigating the impact of smoking on bladder cancer, with Australia and Singapore serving as exemplary cases. In Australia, a series of measures including the imposition of progressive tobacco taxes, the launch of public health campaigns and the implementation of plain packaging laws have been adopted; similarly, Singapore has stipulated smoke-free zones in public places and on transportation, prohibited tobacco advertising, promotion and sponsorship, and elevated the minimum legal age for consuming traditional cigarettes[12,49]. These combined efforts in both countries are worthy of being learned and referenced by those regions and countries that are struggling with slow progress in reducing the smoking-related burden of bladder cancer. The exposure to certain dyes, aromatic amines, rubber products, as well as paint and leather work, associated with industrialization, is linked to an increased risk of bladder cancer[50]. This suggests that developing countries should strengthen environmental protection and occupational exposure safeguards during their economic development to avoid the significant harm to human health that occurred during industrialization in many developed countries.

Although predicted declines in bladder cancer ASRs of incidence, prevalence, and DALYs until 2036, decomposition analysis shows that the increase in global BC burden over the past three decades is mainly due to population growth and aging. Thus, BC control and management are not promising, still facing heavy burdens and challenges. The global population aging problem is severe, and it is expected that by 2050, the world's population over 60 years old will reach 2.1 billion, accounting for 22% of the total population, with the number of people aged 80 or above being as high as 426 million[51]. In developing countries, population growth and the prevalence of disease risk factors brought about by social and economic development will also increase the burden of BC[4]. Therefore, countries around the world should improve their medical policies according to the characteristics of their own population changes and be fully prepared for the increase in disease burden brought about by this demographic transition.

The findings of this study hold significant implications for bladder cancer public health and clinical practice. Firstly, this study investigates the spatiotemporal changing trends of incidence, mortality, and DALYs of bladder cancer on a global scale over the past three decades. Secondly, from 1990 to 2021, driven by population growth and aging, the burden quantity of bladder cancer has increased markedly. In contrast, the ASRs have gradually decreased, and this trend is expected to continue in the future. Thirdly, in countries with a high SDI, the burden of bladder cancer is highly concentrated. Nevertheless, the ASIR in regions with a lower SDI has been on a continuous rise in the past ten years, indicating signs of a transfer of burden. However, several limitations should be noted. Firstly, in some countries with insufficient medical resources, potential misdiagnosis, missed diagnosis, and literature loss reduce the quality and availability of data. Although the application of data processing and statistical modeling methods by GBD collaborators can effectively help address this issue, it introduces uncertainty to the data analysis results. Secondly, it should be noted that there is a delay in GBD data update. The burden of BC is calculated using data from 1990 to 2021 and cannot fully reflect the current situation. Thirdly, our research mainly analyzes the epidemiology of BC and lacks an analysis of disease risk factors, which limits the conclusion of causal inference. Finally, since GBD data focuses on the overall situation of diseases and lacks more detailed information on diseases, we cannot further discuss the situation of specific subtypes of diseases.

Conclusion
In conclusion, bladder cancer is a prominent public health concern. Despite the downward trend of ASRs of incidence, mortality, and DALYs from 1990 to 2021, the global burden of BC has generally increased, with significant variations among regions and countries/territories. The changes in this burden are mainly driven by population growth and aging, potentially resulting in an increase in predicted bladder cancer cases in the next 15 years. The burden is still disproportionately concentrated in high-SDI countries, but there are signs of a shift towards regions with lower SDI levels. These findings jointly highlight the substantial challenges in BC prevention, control, and management, including the increasing number of cases and regional distribution differences.

Data availability
The datasets supporting the conclusions of this article is available in the Global Burden of Disease 2021 study repository (http://ghdx.healthdata.org).

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Author contributions

LX, XH, and XS conceived the study and were responsible for its design. XS performed statistical analysis and developed the methodology. YT and FC interpreted the results and drafted the original manuscript. FC collected the data. YT and XH revised the manuscript. LX completed critical review and oversaw the research activity. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate

Our research is based on and strictly adheres to the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER). No ethical approval and informed consent were necessary for this study, which utilized the GBD database—a publicly available dataset with anonymized participant data.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Additional information

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