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FULL RESEARCH PAPER
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Global magnitude and temporal trend of infective endocarditis, 1990–2019: results from the Global Burden of Disease Study

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Aims To estimate the spatiotemporal patterns in infective endocarditis (IE) burden along with its attributable risk factors at the national, regional, and global levels, which is essential to optimize the targeted prevention, clinical practice, and research.

Methods and results Based on all available data sources, the incidence, mortality, and disability-adjusted life years (DALYs) of IE in 204 countries and regions from 1990 to 2019 were reconstructed by Global Burden of Disease Study 2019 using the Cause of Death Ensemble model, spatiotemporal Gaussian process regression, and DisMod-MR 2.1. We depicted the epidemiological characteristics of IE in detail by gender, region, and age. Globally, 1 090 527 incident cases, 66 322 deaths, and 1 723 594 DALYs of IE were estimated in 2019. The age-standardized incidence rate (ASIR) and age-standardized mortality rate (ASMR) increased from 9.91 and 0.73 to 13.80 and 0.87 per 100 000 person-years over the past 30 years, respectively. ASIR were consistently more pronounced in higher socio-demographic index (SDI) regions. The leading ASMR in 2019 appeared in the High SDI region, with the largest increase in the past three decades. The age-specific burden rate of IE among people over 25 years old usually increased with age, and the annual increasing trend was more obvious for people over 60 years of age, especially in higher SDI regions.

Conclusion The incidence and mortality of IE have continued to rise in the past 30 years, especially in higher SDI regions. The patient population was gradually shifting from the young to the elderly.

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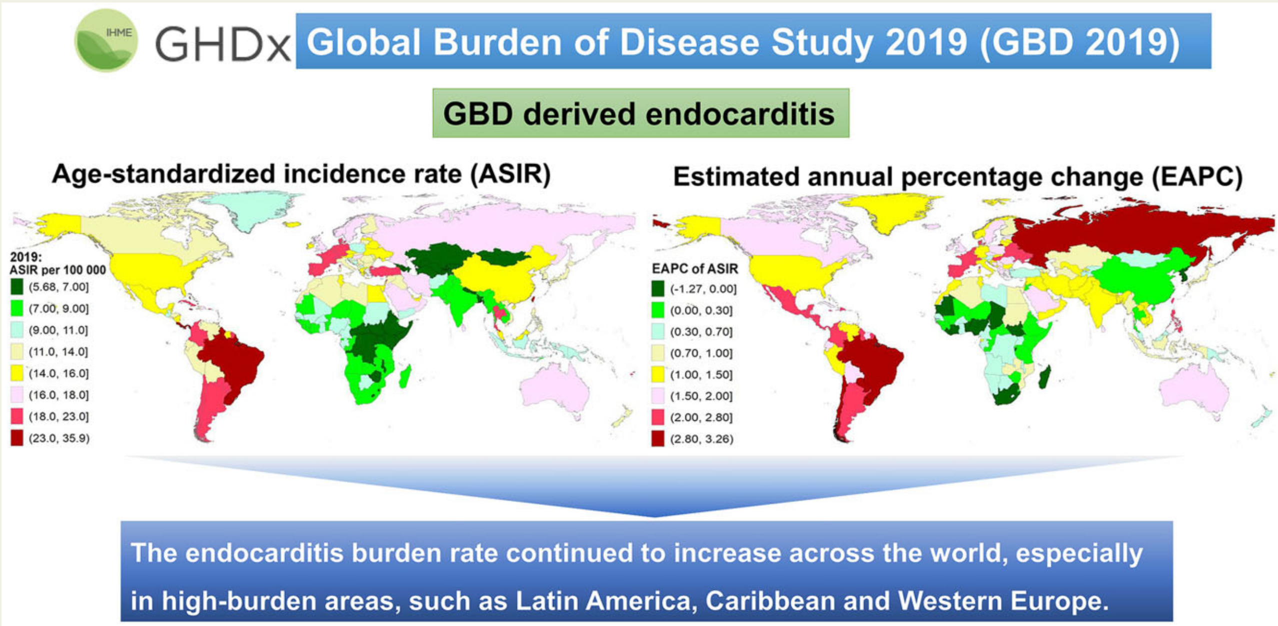
Graphical Abstract



Keywords Infective endocarditis • Global burden • Temporal trend • Risk factors • Disparity • Systematic analysis

Introduction

Infective endocarditis (IE) is a rare but frightening disease in the field of cardiology. It is heterogeneous in aetiology, clinical manifestations, and course of disease.[1–4] Ten years ago, the global annual incidence of IE was estimated to be 3–10 per 100 000 people.[5,6] Epidemiological studies have shown that the incidence of IE continues to increase in many countries.[7,8]

Despite improvements in diagnosis and treatment, IE is still associated with high mortality, up to 22% in hospitals and up to 40% in 5 years.[9–12] In the past few decades, due to the ageing of the population, the increase in the use of cardiac implantable electronic devices (CIEDs), the increase in the number of patients receiving haemodialysis for end-stage renal disease, and more congenital heart disease patients surviving to adulthood, the population at risk of IE has increased.[6,13,14] The changes in the national guidelines on the use of antibiotics to prevent IE are also related to the significant increase in the incidence of IE.[15–18]

There are little data on the global scale and long-term trends of IE and its risk factors, especially in recent years. Comprehensive national and regional information of IE burden is a basic prerequisite for policymakers to rationally allocate finite resources and make policies. The global burden of disease (GBD) 2019 study is a systematic global epidemiological study that quantifies the incidence, mortality, disability, and 87 risk factors of 369 diseases by location, gender, age, and year.[19,20] This research, based on the GBD 2019 study, summarized the incidence, mortality, disability-adjusted life years (DALYs), and the long-term tendency of IE by age and gender group in 204 countries from 1990 to 2019. Our research will help to develop targeted strategies for the intervention and prevention of IE based on the specific characteristics of different countries and regions.

Methods

Data source

The detailed original data introduction and analysis methods of the GBD 2019 study have been described in previous researches.[19–21] The analysis process and reproducible statistical codes of the estimated IE can be collected from the following website: http://ghdx.healthdata.org/gbd-2019/code/cod-4. Here, we briefly introduce methods specific to IE estimation. Each step used to analyse the GBD database in the current study complied with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) statement[22] (Supplementary material online, Report Checklist). For the GBD 2019 assessment, IE was defined as a clinical diagnosis of IE, as described in the previous studies,[20,23] which could be claimed by the following codes I33–I33.9, I38–I39.9 for ICD-10, and 074.22, 421–421.9 for ICD-9 in vital databases. We collected data on the burden of IE by gender and 5-year age group in 204 countries and territories from 1990 to 2019 from the Institute for Health Metrics and Evaluation (http://ghdx.healthdata.org/gbd-resultstool). In order to describe the disease burden of IE in different geographic units, 204 countries and territories are divided into five regions based on their socio-demographic index (SDI, a composite indicator of income per person, years of education, and fertility), namely, Low, Low-middle, Middle, High-middle, and High SDI regions. In addition, the world was further divided geographically into 21 GBD regions such as high-income Asia-Pacific, Central

Latin America, and Central Europe, which were also simplified into 7 super GBD regions such as high-income regions. The risk factors of diseases in the GBD study were identified based on the World Cancer Research Fund grades of convincing or probable evidence, and high systolic blood pressure, diet high in sodium and lead exposure were judged to have sufficient evidence to prove a causal relationship for IE occurrence among 87 behavioural, environmental and occupational, and metabolic risk factors.[19] The disease burden attributable to risk factors was estimated through a comparative risk assessment framework, which includes the estimation of risk outcome pairs, relative risks, theoretical minimum risk exposure level, and population attributable fractions.[19]

Statistical analysis

Based on the world population standard age structure by WHO 2001, the age-standardized incidence rate (ASIR), age-standardized mortality rate (ASMR), and age-standardized DALYs rate (ASDR) were used to assess the differences in the burden of IE by historical periods, genders, and locations, to avoid differences caused by the age composition of the population. The 95% uncertainty intervals (UIs) of every metric in the GBD study were estimated based on the 25th and 975th ordered values of random 1000 draws of the posterior distribution. We further computed the estimated annual percentage change (EAPC) to depict the secular trend in various age-standardized rates (ASRs) of IE burden[24–26] based on a regression model by fitting the natural logarithm of the ASR with the calendar year, namely, $\ln(\text{ASR}) = \alpha + \beta \times \text{calendar year} + \varepsilon$. The EAPC and its 95% confidence interval (CI) were estimated based on the formula of $100 \times (\exp(\beta) - 1)$. The age-standardized indicator was recognized to be in an increasing trend when the EAPCs and the lower boundary of the 95% CI were positive; conversely, to be a decreasing trend when EAPCs and the upper boundary of the 95% CI were negative. For exploring the potential factors of changing trends, we applied the Spearman rank correlation (ρ indicates the correlation coefficient) to estimate the relationship between the EAPCs in IE burden and the baseline burden in 1990 and the SDI in 2019 in 204 countries and territories considering the non-normal distribution. The ASRs of IE in 1990 could reflect the baseline disease reservoir, and the SDI in 2019 could denote the availability and level of healthcare of every country. All statistical analyses in this study were conducted using R program version 4.0.3 (https://www.Rproject.org/), and the two-sided *P*-value <0.05 was considered statistically significant.

Results

Global burden and temporal trend of infective endocarditis

Globally, the number of incident cases of IE increased by 128.41% from 478 002 (95% UI 393 388–572 422) in 1990 to 1 090 527 (95% UI 913 497–1 296 291) in 2019. Besides, the ASIR increased from 9.91 (95% UI 8.24–11.84) to 13.8 (95% UI 11.59–16.34) per 100 000 person-years over the past 30 years, with an EAPC of 1.20 (95% CI 1.16–1.24) (*Table 1* and Supplementary material online, *Figure S1A*). Meanwhile, the global deaths caused by IE were 66 322 (95% UI 46 209–75 862) in 2019, increasing from 28 754 (95% UI 24 370–35 698) deaths in 1990, with an increasing EAPC in ASMR of 0.71 (95% CI 0.44–0.98) from 0.73 (95% UI 0.63–0.93) in 1990 to 0.87 (95% UI 0.59–1) per 100 000 person-years in 2019 (Supplementary material online, *Table S1* and *Figure S1B*). Globally, there were 1.72 (95% UI 1.36–1.94) million DALYs due to IE in 2019, which was 1.5 times increase from 1.12 (95% UI 0.84–1.32) million DALYs in 1990. But the ASDR decreased from 22.78 (95% UI 17.98–26.97) in 1990 to 21.93 (95% UI 17.17–24.60) per 100 000 person-years in 2019, with an EAPC of –0.21 (95% CI –0.35 to –0.08) (Supplementary material online, *Table S2* and *Figure S1C*).

Variation in infective endocarditis burden at regional and national level

The ASIR of IE was highest in the High-middle/High SDI regions across all years from 1990 to 2019: 11.34/11.01 per 100 000 person-years in 1990 and 15.86/15.85 per 100 000 person-years in 2019 (*Table 1*). Low SDI had the lowest ASIR of 7.39 per 100 000 person-years in 2019. The ASIR significantly increased in all SDI regions from 1990 to 2019, especially in the Low-middle, High-middle, and High SDI regions (all EAPCs >1.25) (*Table 1*). The leading ASMR in 2019 was observed in High SDI region of 1.16 per 100 000 person-years and Low SDI ranked second at 0.79 per 100 000 person-years. The Middle SDI region had the lowest rates of 0.62 per 100 000 person-years in 2019 (Supplementary material online, *Table S1*). The largest increase in ASMR was observed in High SDI region (EAPC = 2.01), followed by High-middle region (EAPC = 0.62), whereas Middle SDI and Low SDI region presented a downward trend in the ASMRs (lowest EAPC = –0.62 in Middle SDI region). The largest ASDR in 2019 was observed in Low SDI with 1.16 per 100 000 person-years. Except for High SDI region (EAPC = 1.32), the ASDR in the other four SDI regions all dropped over the past three decades, especially in the Middle SDI region (EAPC = –1.20) (Supplementary material online, *Table S2*).

Regarding GBD regions, Tropical Latin America, Southern Latin America, and Caribbean were among the top three regions for the highest ASIR in 2019, from 18.72 to 24.25 per 100 000 person-years (*Table 1*). On the contrary, the top three GBD regions with the lowest ASIR in 2019 were Central Asia, Eastern Sub-Saharan Africa, and Central Sub-Saharan Africa, from 6.35 to 6.89 per 100 000 person-years (*Table 1*). Moreover, except for Southern and Western Sub-Saharan Africa, the ASIR of IE increased across all GBD regions from 1990 to 2019, which was pronounced usually in high-burden regions, such as Tropical Latin America (EAPC = 3.25) (*Table 1*).

Different from the overall increase of ASIR, ASMR showed an obvious downward trend in many GBD regions from 1990 to 2019, including East Asia, Western Sub-Saharan Africa, and Southern Sub-Saharan Africa. Southern Latin America, Oceania, and High-income North America were the top three GBD regions for highest ASMR in 2019 (>1.35), where the ASMR of IE all rose over the past 30 years (Supplementary material online, *Table S1*). The lowest ASMR was found in East Asia (0.29), followed by Central Asia and Central Europe. The distribution pattern of ASDR of IE in GBD regions was similar to that of ASMR overall, and the downward trend of ASDR was slightly larger than that of ASMR (Supplementary material online, *Table S2*).

In 2019, the difference in ASIR of IE was nearly seven times around the world, with Saint Lucia being the highest (35.83/100 000) and Kyrgyzstan the lowest (5.69/100 000). Other nine countries with an ASIR exceeding 25/100 000 were Grenada, Barbados, Virgin Islands US, Costa Rica, Monaco, Bermuda, Bahamas, Uruguay, and Jamaica (*Figure 1A* and Supplementary material online, *Table S3*). On the

Table 1 **Incidence and age-standardized incidence rate per 100 000 people of endocarditis in 1990 and 2019, and its estimated annual percentage change from 1990 to 2019**

Characteristics	**1990**		**2019**		**EAPC of ASIR (95% CI) from 1990 to 2019**
	ASIR/100 000 (95% UI)	**Incident cases (95% UI)**	**ASIR/100 000 (95% UI)**	**Incident cases (95% UI)**	
Global	9.91 (8.24–11.84)	478 002 (393 388–572 422)	13.8 (11.59–16.34)	1 090 527 (913 497–1 296 291)	1.20 (1.16–1.24)
Male	11.04 (9.28–13.11)	260 804 (215 666–310 473)	16.2 (13.75–18.98)	610 096 (514 073–719 322)	1.40 (1.36–1.45)
Female	8.84 (7.31–10.63)	217 198 (178 415–262 261)	11.62 (9.67–13.83)	48 0431 (401 558–575 145)	0.96 (0.93–1.00)
SDI region					
High SDI	11.01 (9.14–13.37)	100 544 (83 614–121 959)	15.85 (13.56–18.53)	251 565 (214 996–296 056)	1.25 (1.09–1.41)
High-middle SDI	11.34 (9.44–13.59)	124 759 (102 740–150 520)	15.86 (13.24–18.93)	283 709 (235 850–341 808)	1.26 (1.21–1.31)
Middle SDI	10.5 (8.75–12.5)	159 199 (130 193–190 998)	13.22 (11.01–15.77)	314 022 (260 095–379 414)	0.99 (0.89–1.09)
Low-middle SDI	6.47 (5.31–7.78)	62 645 (50 326–76 485)	9.33 (7.79–11.16)	144 051 (117 963–174 198)	1.31 (1.19–1.43)
Low SDI	6.29 (5.23–7.5)	30 593 (24 430–38 073)	7.39 (6.13–8.8)	72 747 (58 016–89 542)	0.81 (0.65–0.97)
GBD region					
High-income Asia-Pacific	10.22 (8.39–12.44)	18 732 (15 262–23 102)	12.54 (10.35–15.15)	43 464 (36 124–52 584)	0.60 (0.45–0.74)
High-income North America	10.11 (8.32–12.27)	31 034 (25 650–37 687)	14.31 (12.38–16.5)	77 032 (66 356–89 252)	1.11 (0.85–1.38)
Western Europe	11.29 (9.29–13.75)	53 685 (44 464–65 371)	18.06 (15.32–21.34)	136 272 (115 897–159 916)	1.72 (1.60–1.84)
Australasia	11.24 (9.32–13.52)	2504 (2064–3007)	16.46 (13.78–19.51)	7171 (5977–8490)	1.38 (1.24–1.51)
Southern Latin America	9.83 (8.41–11.43)	4520 (3834–5288)	20.55 (17.67–23.68)	16 025 (13 776–18 546)	2.62 (2.50–2.75)
Andean Latin America	8.79 (7.43–10.39)	2509 (2105–2963)	13.58 (11.31–16.12)	8009 (6652–9531)	1.46 (1.37–1.55)
Tropical Latin America	8.42 (7.04–10.04)	10 368 (8450–12 520)	24.25 (19.88–29.56)	57 437 (46 772–70 212)	3.25 (3.13–3.38)
Central Latin America	8.48 (6.97–10.39)	10 793 (8634–13 305)	16.93 (14.03–20.44)	40 493 (33 485–49 464)	2.22 (2.03–2.41)
Caribbean	11.14 (9.42–13.09)	3484 (2935–4103)	18.72 (16.06–21.74)	9208 (7883–10 686)	1.80 (1.65–1.95)
Eastern Europe	8.49 (6.91–10.37)	21 128 (17 157–26 027)	15.46 (12.88–18.32)	41 867 (34 665–50 424)	2.71 (2.51–2.92)
Central Europe	8.15 (6.59–10.05)	10 813 (8778–13 359)	12.28 (10.21–14.68)	21 032 (17 443–25 377)	1.63 (1.52–1.74)
Central Asia	5.19 (4.11–6.47)	3116 (2432–3909)	6.35 (5.12–7.83)	5422 (4255–6793)	0.76 (0.71–0.81)
North Africa and Middle East	11.47 (9.62–13.59)	33 371 (27 157–40 600)	15.35 (12.89–18.2)	81 527 (67 013–97 905)	0.96 (0.92–1.00)
South Asia	5.02 (4.07–6.12)	44 695 (34 841–56 225)	7.11 (5.79–8.64)	115 826 (92 253–142 605)	1.25 (1.12–1.38)
Southeast Asia	9.6 (8.2–11.17)	33 534 (27 925–39 870)	12.84 (10.96–14.86)	80 202 (67 560–93 770)	0.96 (0.91–1.01)
East Asia	13.93 (11.51–16.57)	157 039 (128 238–188 455)	14.94 (12.35–18.11)	268 456 (218 125–336 021)	0.25 (0.13–0.36)
Oceania	9.8 (8.32–11.39)	468 (384–561)	11.86 (10.27–13.62)	1166 (987–1363)	0.72 (0.68–0.75)
Western Sub-Saharan Africa	9.25 (7.71–10.95)	20 069 (15 870–25 039)	9.24 (7.68–11.04)	44 276 (35 153–55 809)	−0.11 (−0.16 to −0.05)
Eastern Sub-Saharan Africa	6.33 (5.32–7.48)	9800 (7863–12 200)	6.77 (5.59–8.06)	22 591 (17 683–28 258)	0.18 (0.06–0.30)
Central Sub-Saharan Africa	6.13 (5.15–7.26)	2851 (2279–3595)	6.89 (5.75–8.2)	7356 (5783–9162)	0.40 (0.29–0.51)
Southern Sub-Saharan Africa	7.83 (6.52–9.28)	3488 (2798–4241)	8.09 (6.65–9.69)	5693 (4588–6909)	−0.12 (−0.22 to −0.02)

ASIR, age-standardized incidence rate; CI, confidence interval; EAPC, estimated annual percentage change; SDI, socio-demographic index; UI, uncertainty interval.

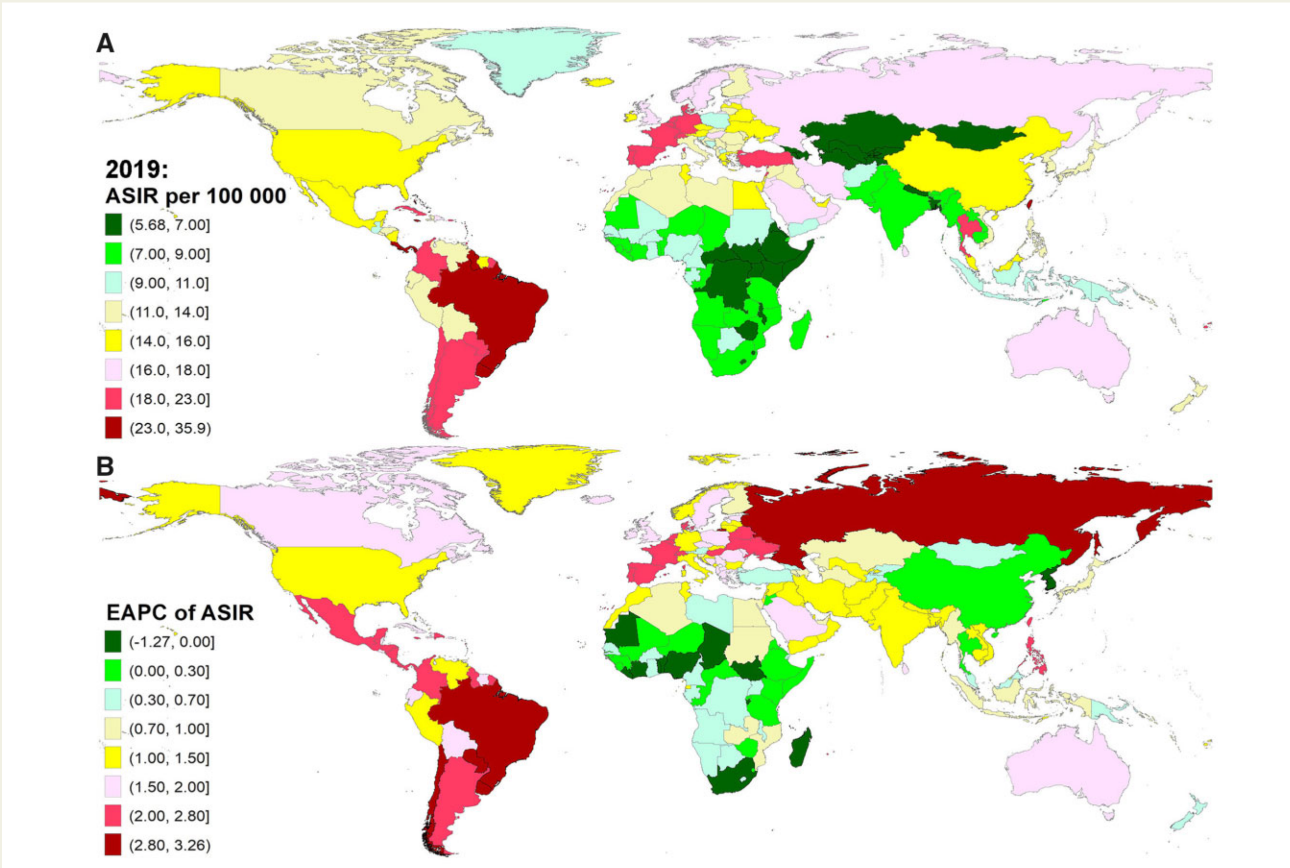


Figure 1 The global incidence of endocarditis for both sexes in 204 countries and territories. (*A*) The age-standardized incidence rate of endocarditis in 2019 and (*B*) the estimated annual percentage change in age-standardized incidence rate of endocarditis from 1990 to 2019. ASIR, age-standardized incidence rate; EAPC, estimated annual percentage change.

contrary, 10 countries including Kyrgyzstan, Azerbaijan, and Turkmenistan have ASIR lower than 6.5/100 000 in 2019 (*Figure 1A* and Supplementary material online, *Table S4*). The highest ASMR in 2019 was observed in Kiribati (5.46/100 000), followed by Fiji, American Samoa, Switzerland, Micronesia, and Marshall Islands (Supplementary material online, *Figure S2A*). Armenia had the lowest ASMR (0.24/100 000) in 2019, followed by Azerbaijan, China, Croatia, Slovenia, and Kyrgyzstan (Supplementary material online, *Figure S2A*). The geographical distributions of ASDR and ASMR were highly consistent in 2019 (Supplementary material online, *Figure S2B*).

From 1990 to 2019, ASIR was rising in 181 out of 204 countries. The largest annualized growth of ASIR was in Brazil [EAPC = 3.26 (95% CI 3.13–3.39)] and the EAPC of ASIR in other 10 countries and territories including Chile, Russia, Uruguay, Paraguay, and Colombia exceeded 2.50 (Supplementary material online, *Table S5* and *Figure 1B*). Conversely, the fastest decline in ASIR was in South Korea [EAPC in ASIR = –1.26 (95% CI –1.48 to –1.05)], while the EAPC of ASIR in other eight countries and territories was <–0.2, including Burundi, South Sudan, Nigeria, Liberia, Chad, Madagascar, Mauritania, and South Africa (Supplementary material online, *Table S6* and *Figure 1B*).

The EAPCs in both ASMR and ASDR were highest in Taiwan [EAPC = 8.10 and 6.48, respectively] and lowest in South Korea [EAPC = –5.94 and –6.22, respectively] from 1990 to 2019. The EAPC of ASMR exceeding 3.00 was observed in other 12 countries and territories, such as Italy, Switzerland, UK, Philippines, Uzbekistan, etc. (Supplementary material online, *Table S7* and *Figure S2C*), and the EAPC of ASMR <–1.5 was found in other 18 countries and territories, including China, Liberia, Jordan, Mauritania, Nigeria, etc. The annualized percentage change in ASDR followed a very similar pattern as ASMR (Supplementary material online, *Table S8* and *Figure S2D*).

Variation in infective endocarditis burden in both genders and 5-year-old age groups

The ASIR of IE among males was slightly higher than that of females (16.20/100 000 vs. 11.62/100 000 in 2019) (*Table 1*), and the male–female difference in ASMR and ASDR were close to that in ASIR. But, notably, the decreases in ASDR from 1990 to 2019 were greater among females than that of males at the global level. The age-specific burden rate gradually increased with age among the population aged over 25 years for both sexes in 2019 at the global level, especially among the population aged over 60 years (*Figure 2*).

From 1990 to 2019, the absolute age-specific incident cases were steadily rising in all SDI regions across most age groups, except for

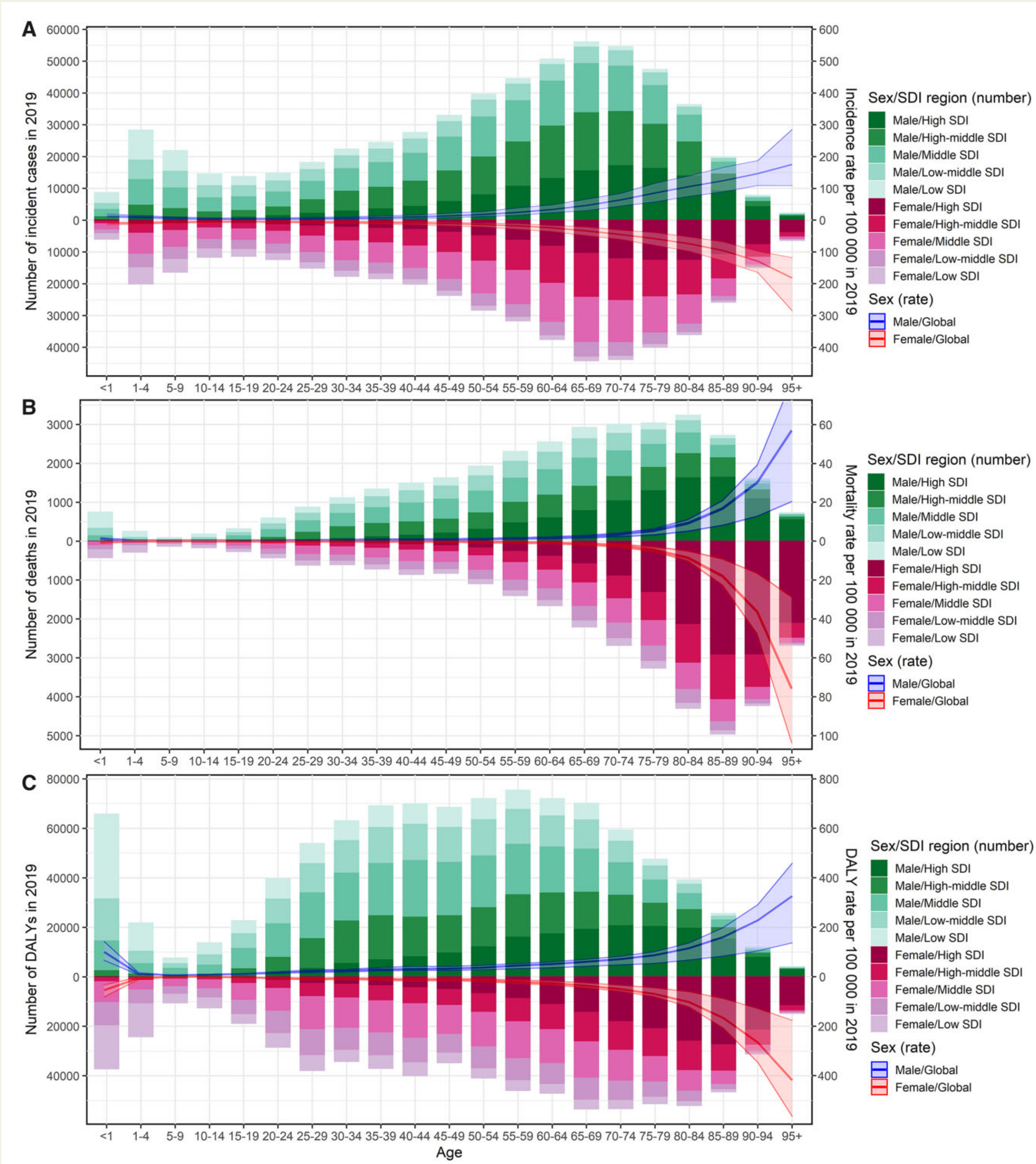


Figure 2 Age-specific counts and rates of endocarditis burden by sex, 2019. (*A*) Incidence; (*B*) mortality; and (*C*) disability-adjusted life years. DALYs, disability-adjusted life years; SDI, socio-demographic index.

among children and young adults in the higher SDI regions (*Figure 3A*). Meanwhile, the age-specific incidence rate increased in all SDI regions among the population over 30 years old, especially among the population over 50 years old (*Figure 3B and C*). However, except for Low SDI and Low-middle region, the incidence was declining among people under 25 years of age, which was more pronounced in the younger population (*Figure 3B and C*). In High-middle and High SDI regions, the EAPC in ASMR and ASDR across all age groups presented a very similar pattern with the changing of ASIR. However, in the other three SDI regions, the EAPC in ASMR and

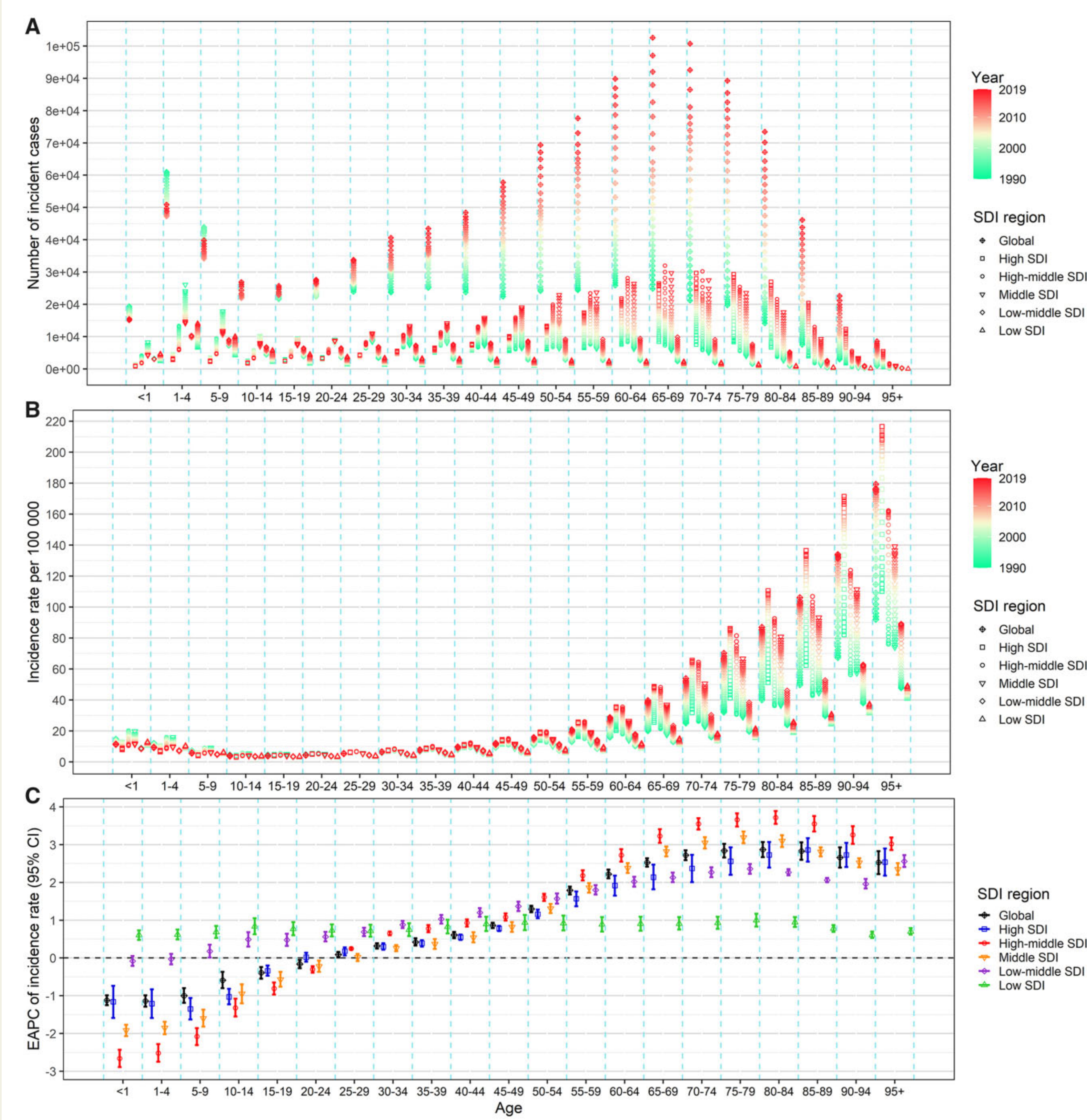


Figure 3 The change in incidence of endocarditis across all age groups, both sexes, from 1990 to 2019. (*A*) Number of incident cases; (*B*) age-specific incidence rate; and (*C*) estimated annual percentage change in age-specific incidence rate. EAPC, estimated annual percentage change.

ASDR among the population over 25 years old have not changed much from 1990 to 2019. In all SDI regions, the EAPC in ASMR and ASDR among the population under 25 years old dropped significantly during the past 30 years (Supplementary material online, *Figures S3 and S4*).

The potential factors of changing trends

In overall the increasing trend of ASIR was relatively pronounced in the countries and territories with high ASIR in 1990 (Spearman rank correlation: $\rho = 0.220$, $P = 0.0015$) (Supplementary material online, *Figure S5A*) or high SDI in 2019 (Spearman rank correlation: $\rho = 0.479$, $P = 4.4\text{e}{-13}$) (Supplementary material online, *Figure S5B*). The annual ASIR and SDI across the 21 GBD regions from 1990 to 2019 presented that except for the four Sub-Saharan Africa Regions and East Asia, the ASIR in most GBD regions continued to climb obviously, especially in higher SDI regions (Supplementary material online, *Figure S5C*). However, the decreasing trend of ASMR/ASDR from 1990 to 2019 was relatively more obvious in the countries and territories with higher baseline ASMR/ASDR in 1990 (Spearman rank correlation: $\rho = -0.382$, $P = 1.7e{-}08$; $\rho = -0.467$, $P = 1.9e{-}12$) or lower SDI in 2019 (Spearman rank correlation: $\rho = 0.385$, $P = 1.3e{-}08$; $\rho = 0.368$, $P = 1.5e{-}07$) (Supplementary material online, *Figures S6 and S7*). The ASMR and ASDR in most GBD regions showed a trend of increasing first and then decreasing, except Central Sub-Saharan Africa, Eastern Sub-Saharan Africa, Western Sub-Saharan Africa, and North Africa and Middle East kept falling, and except Central Latin America, Caribbean, and Central Europe kept climbing (Supplementary material online, *Figures S6 and S7*).

The infective endocarditis burden attributable to risk factors

Globally, in 2019, 30.44% (95% UI 24.55–36.63) of age-standardized DALYs of IE were attributable to high systolic blood pressure, compared with 25.33% (18.17–33.25) for both sexes combined in 1990. Likewise, 4.25% (0.87–10.23) and 1.55% (0.71–2.69) of age-standardized DALYs of IE were attributable to diet high in sodium and lead exposure, compared with 4.40% (1.19–10.02) and 1.97% (0.99–3.27) for both sexes combined in 1990. In 2019, the proportion of age-standardized DALYs of IE attributable to high systolic blood pressure was highest in Eastern Europe (45.09% of age-standardized DALYs of IE) and Central Europe (40.96%) (Supplementary material online, *Figure S8A*). The proportion of age-standardized DALY attributable to high systolic blood pressure is higher than 25% in all age groups from 25 to 95 years old, and higher than 40% in the 45–69 age group (Supplementary material online, *Figure S8B*).

Discussion

This study provides a comprehensive assessment of the global burden of IE. From 1990 to 2019, the number of IE cases and deaths globally increased by 2.3 times for both men and women, which reflected the population growth and the increase in incidence and mortality. The improvement of living standards and the availability of streptococcal antibiotics have reduced the prevalence of rheumatic heart disease in most areas.[27,28] However, degenerative valvular diseases, CIEDs, intravenous medication, congenital heart disease, diabetes, and cancer have replaced rheumatic heart disease as the main risk factors for IE. Healthcare-associated IE accounts for an increasing proportion of cases, and the affected patients are older and more severely ill than in the past, usually accompanied by many comorbidities.[29] Hypervirulent *Staphylococcus* is usually resistant to many antibiotics and has gradually replaced penicillin-sensitive *Streptococcus* as the most common cause.[10,30] It can be seen that, due to changes in risk factors and infectious organisms, advances in medical and sanitation have not had a beneficial impact on IE. Our results are consistent with several published reports on the increase in IE incidence in specific regions.[31–34]

During the past three decades, ASIR has been higher in High-middle and High SDI regions and lower in Low SDI regions. The high incidence of IE in the High-middle and High SDI regions may be related to population ageing and the burgeoned prosthetic valve replacement, CIED, haemodialysis, intravenous catheters, immunosuppression, cancer, diabetes, and intravenous drugs.[1–3,7,10,13,35] The reason for the low incidence in Low SDI region is that the prevalence of rheumatic heart disease gradually decreases with the increase of SDI, and on the other hand, the diagnosis rate is insufficient since the clinical manifestations of IE are complex and changeable and its diagnosis requires multidisciplinary cooperation. The highest ASMR in 2019 was in High SDI region, and this region had the largest increase in ASMR in the past three decades. This is because the incidence of IE in High SDI region has remained high; second, IE patients in High SDI region are often older and weaker, with more complications; third, *Staphylococcus aureus* is the most frequently isolated IE-related microorganisms which tends to acquire antibiotic resistance.[36] Although the incidence of Low SDI region is low, its ASMR level is higher. Delayed diagnosis and inaccessible medical care are the main reasons for high mortality. We further explored the relationship between ASRs of IE in 1990 and the corresponding EAPC. Results showed that the ASIR IE in some countries with high baseline kept rising in the past 30 years, especially in Saint Lucia, France, Spain, and Taiwan of China, etc., suggesting that these countries and territories need to pay more attention to seek an effective strategy to reduce the ASIR of IE.

At the national level, the high ASRs of Western European countries are very eye-catching, such as Monaco and Switzerland. The high proportion of elderly people, better diagnostic procedures, and more healthcare-associated IE all accounted for the high ASIR. Many small countries in the Caribbean, such as Bermuda and Barbados, also exhibited high IE ASIR, but the reasons are different from Western Europe. The small population of these countries may be an important reason for the high ASIR. The ASIRs of uncommon diseases in countries with small population sizes were relatively unstable, because a few more people diagnosed would have a big impact on the overall ASIR. Moreover, the GBD estimation of IE disease is reconstructed through mathematical models based on a huge number of varying quality data sources, which may to some extent deviate from the actual data, particularly in some underdeveloped areas where a priori information is extremely scarce.

In 2019, the global age-specific burden rate of the population over 25 years old gradually increased with age, and the growth trend of the population over 60 years old became more obvious. This significant increase in the elderly is multi-factorial and probably reflects the rise in the incidence of degenerative heart valve disease, the augment in the survival rate of patients with multiple comorbidities, and the increase in invasive treatment interventions including implants cardiac devices (pacemakers, defibrillators, closure devices, and percutaneous valve technology) and haemodialysis, as well as more extensive research on frail elderly patients.[37–39]

The incidence of IE in the population under 25 years of age in the Middle to High SDI regions gradually decreased, and the incidence of IE in the Low and Low-middle SDI regions remained unchanged. Rheumatic heart disease and congenital heart disease are the main risk factors for IE in young people.[40] The infection is mainly caused by community-acquired penicillin-sensitive *Streptococcus*. The development of antibiotics, the reduction of rheumatic heart disease, prenatal screening for the prevention of congenital heart disease, and advances in medicine have significantly reduced the incidence of young people in the Middle to High SDI regions. However, the above improvements have not been implemented well in Low SDI regions. Our results showed that elevated systolic blood pressure, diet high in sodium and lead exposure are risk factors for IE in 2019. However, these factors might be confounded by other variables or exposures, such as cardiac device implantation for heart failure, haemodialysis for renal failure, or socioeconomic conditions.

This study has several limitations. First of all, the GBD estimation of IE disease is reconstructed through mathematical models based on a huge number of varying quality data sources, which may to some extent deviate from the actual data, particularly in some underdeveloped areas where a priori information is extremely scarce, such as Caribbean, South Asia, and Africa.[20] Second, because of the high rate of missed diagnosis of IE in developing countries, estimates of the burden on IE are inevitably biased. Third, we did not analyse the burden of IE attributable to other potential risk factors, for example, prosthetic valve replacement, the presence of CIED, haemodialysis, intravenous catheters, immunosuppression, cancer, diabetes, and intravenous drugs. Finally, the study lacks relevant data on the microbiology and antibiotic treatment of IE. The lack of information on prosthetic valve IE, device-related IE, and microbiological data is particularly important, because one of the most controversial claims is the proposed relationship between the increase in IE over the past few decades and the increase in cardiac device implantation.

The number of cases and deaths of IE has more than doubled from 30 years ago. This increase is largely due to the increase in population and life expectancy, but even taking into account population changes, the incidence and mortality rates increased from 1990 to 2019, which may be due to changes in the type and virulence of the organism and the changes in the high-risk population. In recent decades, the incidence of IE has gradually changed from young people to old people, reflecting the medical and care progress in IE control and prevention. The main risk factors associated with IE (elevated systolic blood pressure, high sodium diet, lead exposure) are potentially modifiable. The rapid and accurate diagnosis of suspected cases of IE is the core challenge of the disease. Our research results can be used by policymakers to effectively allocate resources to develop early diagnosis methods for IE, reduce its modifiable risk factors, and evaluate new treatment strategies to reduce mortality through appropriate treatment strategies.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Conflict of interest: none declared.

Ethics approval and consent to participate

The GBD 2019 study is a publicly available database and all data were anonymous. Our study protocol was approved by the Institutional Review Boards of Qilu Hospital of Shandong University with approval number KYLL-202011(KS)-239.

Data availability

All data could be extracted from the online database (http://ghdx.healthdata.org/gbd-results-tool).

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