

Global and Regional Trends and Projections of Infective Endocarditis-Associated Disease Burden and Attributable Risk Factors from 1990 to 2030

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ABSTRACT

Objective To forecast the future burden and its attributable risk factors of infective endocarditis (IE).

Methods We analyzed the disease burden of IE and its risk factors from 1990 to 2019 using the Global Burden of Disease 2019 database and projected the disease burden from 2020 to 2030 using a Bayesian age-period-cohort model.

Results By 2030, the incidence of IE will increase uncontrollably on a global scale, with developed countries having the largest number of cases and developing countries experiencing the fastest growth. The affected population will be predominantly males, but the gender gap will narrow. The elderly in high-income countries will bear the greatest burden, with a gradual shift to middle-income countries. The incidence of IE in countries with middle/high-middle social-demographic indicators (SDI) will surpass that of high SDI countries. In China, the incidence rate and the number of IE will reach 18.07 per 100,000 and 451,596 in 2030, respectively. IE-associated deaths and heart failure will continue to impose a significant burden on society, the burden on women will increase and surpass that on men, and the elderly in high-SDI countries will bear the heaviest burden. High systolic blood pressure has become the primary risk factor for IE-related death.

Conclusions This study provides comprehensive analyses of the disease burden and risk factors of IE worldwide over the next decade. The IE-associated incidence will increase in the future and the death and heart failure burden will not be appropriately controlled. Gender, age, regional, and country heterogeneity should be taken seriously to facilitate in making effective strategies for lowering the IE disease burden.

Key words: infective endocarditis; disease burden; risk factors; Bayesian age-period-cohort model; projection

INTRODUCTION

Infective endocarditis (IE) is an inflammatory process caused by bacterial or fungal infection of the heart valves or endocardium^[1, 2]. IE remains a significant challenge to global cardiovascular health, with high morbidity and mortality despite advances in disease diagnosis and applications of antibiotics^[2-4]. A recent study discovered that the patient population

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was gradually shifting from the young to the elderly^[5]. Notably, the high Socio-demographic Index (SDI) region has the highest burden compared to other SDI regions^[5], which may be explained by the increased use of invasive procedures in the aging population and the changes in microbiological profiles in high-income regions^[2, 6]. Therefore, it is essential to project the future trends in the disease burden of IE based on the current situations in specific subgroups.

Here we used the Global Burden of Disease (GBD) 2019 database to analyze the IE-associated incidence, mortality, and heart failure (HF) impairment and its attributable risk factors from 1990 to 2019. Using the Bayesian age-period-cohort model (BAPC), we further predicted the disease burdens of IE from 2020 to 2030 at the global, SDI, and national levels. Our findings will contribute to the development of targeted prevention strategies to combat the rising prevalence of IE in specific populations.

MATERIALS AND METHODS

Study data

The methodology of the GBD Study has been reported previously^[7-9]. Data on IE burden were obtained from the Global Health Data Exchange (GHDx) query tool (<http://ghdx.healthdata.org/gbd-results-tool>)^[10,11]. The database contains information on the numbers of incident cases and age-standardized rate of incidence (ASIR), number of deaths and age-standardized rate of mortality (ASMR), and number of HF prevalent cases and age-standardized prevalence rate (ASPR) of HF impairment globally, SDI regions, GBD regions, countries (China), sex (male, female, and both), and 20 age groups (0–95 plus years, with 5 years an interval). This database also provides three attributable risk factors for IE-related death, including metabolic (high systolic blood pressure [high SBP]), behavioral (diet high in sodium), and environmental/occupational (lead exposure) risk factors. Our research methodology adheres to the Accurate and Transparent Health Estimates Reporting Guidelines (**Table S1**).

Definition

The diagnostic criteria of IE were based on the standardized Duke-Li classification^[12]. The GBD online databases also reported the long-term sequelae of HF caused by IE, as defined by the 2013 ACCF/AHA guideline^[13]. In the 2019 GBD, the International Clas-

sification of Diseases 10 (ICD-10) codes corresponding to IE are B33.21, I33-I33.9, I38-I38.0, and I39-I39.9. Detailed methods and procedures for confirming the diagnosis are available on the website (http://www.healthdata.org/results/gbd_summaries/2019). GBD 2019 defined high SBP as having a theoretical minimum risk exposure level (TMREL) between 110 mmHg and 115 mmHg, which is the population-level exposure level that minimizes risk. Diet high in sodium is characterized by an average 24-hour urinary sodium excretion (in grams per day) greater than 3 g. Two types of lead exposure are distinguished: acute (measured in micrograms of lead per deciliter of blood) and chronic (measured in micrograms of lead per gram of bone). The TMREL is 2 micrograms per deciliter of blood. Besides, SDI is a comprehensive indicator of development status calculated using income per capita, educational attainment, and fertility rates on a scale of 0–1^[14]. The SDI categorizes countries into five quintiles: low, low-middle, middle, high-middle, and high SDI regions. Additionally, GBD 2019 divided countries and territories into 21 GBD regions according to their geographical locations.

Model development and validation

We chose to use the data from 1990 to 2019 to predict the data for 2020 to 2030^[15-18]. We collected the number and age-standardized rate of three indicators of IE for all age groups globally and regionally from 1990 to 2019 and restored the corresponding annual total populations through the following formula: the number of incidence (or death or impairment) caused by IE for all ages in a given year divided by the corresponding rate.

The BAPC model has been extensively used to predict epidemiological trends, and its superior predictive performance has been validated previously^[15, 19]. To project the disease burden of IE through 2030, the BAPC model was utilized. As the age-period-cohort (APC) assumes there is a multiplicative effect of age, period, and cohort, the trend in the age-standardized rate of three indicators of IE was modeled using the BAPC method as follows:

$$Y_{at} \sim B(n_{at}, p_{at}) \quad (1)$$

$$Y_{at} = u' \theta' a \phi' t \varphi' k \quad (2)$$

$$\log(Y_{at}) = u + \theta_a + \phi_t + \varphi_k \quad (3)$$

where Y_{at} denotes the IE burden indicator case counts in age group a during period t , which are assumed to

follow a binomial distribution with parameters p_{at} and n_{at} . The parameter n_{at} is the known population size of age group a at period t , and p_{at} is the unknown IE burden indicator rate probability. Y_{at} denotes the IE burden indicator, $a=1\dots, A$ represents age groups, $t=1\dots, T$ represents the observation period, and $k=1\dots, K$ represents the index of the birth cohort. As the IE burden indicator rate is given per year while age groups are depicted in 5-year intervals, $k=k(a, t) = 5 \times (A-a) + t$. In our current study, $A = 20$ (0–95+ years, with an interval of 5 years), and $T = 30$ (1990–2019). By taking the logarithm of Y_{at} , the model can be transformed into an additive model in which the IE burden probability is decomposed into an intercept μ , age effect θ_a , period effect Φ_t , and cohort effect φ_k . We conducted BAPC analysis with integrated nested laplace approximation.

To determine the accuracy of the BAPC model, we conducted four tests with varying input and output points, used the data between input points to predict the data in output points, and compared the predicted value to the actual value. The input/output rate was greater than 2, and the mean absolute percentage error (MAPE) was acceptable (**Table S2**). In our projection, there were 30 data points as input (data from 1990 to 2019) and 11 data points as output (data from 2020 to 2030). The input/output rate was 2.73. We split the dataset from the past three decades into a training set (data between 1990 and 2011) and a validation set (data between 2012 and 2019), with a comparable input/output rate of 2.75. The prediction error rate was calculated using the MAPE to evaluate the performance of the model, during which the following formula was used.

$$MAPE = \frac{\sum \left(\left(\frac{|\text{Predictive value} - \text{obsational value}|}{\text{obsational value}} \right) \times 100\% \right)}{\text{Projection year}} \quad (4)$$

Furthermore, to validate the robustness of the model, we used an additional autoregressive integrated moving average (ARIMA) time series model to conduct the projection, all MAPEs in the model were satisfactory (**Table S3**).

Quantifying the trends of the burden of IE

The age-standardized rate (ASR) was calculated to quantify the trends of indicators caused by IE. ASR was computed using the following formula for eliminating the impact of the age distribution:

$$ASR = \frac{\sum_{i=1}^A a_i w_i}{\sum_{i=1}^A w_i} \times 100,000 \quad (5)$$

a_i , where i represents the i^{th} age class, and the number of persons (or weight) (w_i) in the same age subgroup i based on the world 2000 standard population.

The estimated average percentage change (EAPC) is utilized to determine the ASR trend. Because it was assumed that the natural logarithm of ASR is linear over time, the following formula was used:

$$Y = \alpha + \beta X + \varepsilon \quad (6)$$

where Y represents $\ln(\text{ASR})$, X represents the calendar year, and ε represents the error term. EAPC was calculated with the formula:

$$\text{EAPC} = 100 \times (\exp(\beta) - 1) \quad (7)$$

and the 95% confidence intervals (CIs) were derived from the model. ASR increases when EAPC and the lower limit of 95% CI are both positive. When both EAPC and the upper limit of the 95% CI are negative, the ASR trends downward. ASR is considered stable otherwise.

All statistical analyses were conducted with the R-3.6.3 program (R Foundation for Statistical Computing, Vienna, Austria). All images were created using GraphPad Prism (version 9.0.0) and R, and edited using Adobe Illustrator software (version CS6). The "BAPC" and "INLA" packages were used to predict the disease burden, and the "tseries" packages was utilized for model sensitivity analysis. Two-tailed P values less than 0.05 were considered statistically significant.

RESULTS

The characteristics and trends of IE incidence over the next decade

Globally, the ASIR of IE has increased significantly over the past three decades. The number of IE cases is projected to increase to 1.67 million (95% CI: 1.56–1.78 million) by 2030 (**Table S4**), with the ASIR rising from 14.07 per 100,000 (95% CI: 13.65–14.48 per 100,000) in 2020 to 16.33 per 100,000 (95% CI: 12.56–20.10 per 100,000) in 2030 (**Table 1** and **Fig. 1D**). From 2020 to 2030, the ASIRs in both sexes will exhibit increasing trends (with the EAPC being 1.60 for males and 1.47 for females) (**Table 1**).

In SDI regions, ASIRs are expected to rise in all SDI regions over the next decade, with relatively high SDI regions remaining higher than relatively low SDI regions (**Fig. 1A-B**). The ASIRs in middle and high-middle SDI regions will eventually approach or surpass those of the high SDI region, with the fastest growth occurring in the low-middle SDI region. The ASIR in the low SDI region will increase more rapidly than in the high SDI region (**Table 1** and **Fig. 1A**). ASIRs will increase dramatically across nearly 21 GBD regions. In regions with relatively high SDI, including Australasia and Western Europe, the ASIRs will continue to rise. Nevertheless, its upward trend will be less pronounced than that of middle/high-middle SDI regions (East Asia and Central Latin America). ASIRs are expanding most rapidly in Tropical Latin America and Central Latin America, with a significant impact on middle-income countries. In addition, ASIRs in regions with a relatively low SDI (Central Sub-Saharan Africa and Southern Latin America) will increase (**Table 1** and **Fig. 1C-D**).

Over the entire study period, males will have a consistently higher global ASIR than females, and this is consistent in all SDI regions and almost all GBD regions (**Fig. 2A-D**). However, in low SDI regions, the male-to-female ratio of ASIR will decrease, indicating that females will experience a higher incidence of ASIR (**Fig. 2B-C**). The global ASIR in the 0 - 24 age group will remain extremely low and trend downward, whereas it will increase rapidly in those over 60 years. As the rate accelerates with age, older adults will bear the greatest burden incidence (**Fig. 3A**). This aging trend is prevalent in relatively high SDI regions (from middle to high SDI regions) (**Fig. 3D-F**); in contrast, in the relatively low SDI regions (low and low-middle SDI regions), there will be a greater incidence burden among the younger population (**Fig. 3B-C**). This pattern will be confirmed across 21 GBD regions (**Fig. 3G**).

In China, the ASIR for IE is projected to reach 18.07 per 100,000 (95% *CI*: 12.36–23.78) by 2030, with the number of IE patients reaching 452 thousands (95% *CI*: 363 - 540 thousands) (**Table S5** and **S6**). The ASIR in China is comparable to that in high-middle SDI regions and greater than that globally and in high SDI regions, despite its middle SDI level (**Table 1**). In the subgroup analysis, the incidence in China will show male predominance and aging trends (**Fig. S7A-B** and **Fig. S8A**).

Trends and characteristics of IE-related death and heart failure in the next decade

Globally, death cases and HF cases are projected to reach 88.49 thousands (95% *CI*: 81.03-95.95 thousands) and 467.25 thousands (95% *CI*: 439.66-494.84 thousands), respectively, by 2030, despite a slight decrease in IE's ASMR and HF ASPR (**Table 1** and **Table S4**).

In comparison to other SDI regions, the high SDI region will continue to have the highest ASMR and HF ASPR caused by IE, resulting in a large number of IE patients with a poor prognosis in highly developing counties. While IE-related ASMRs and ASPRs will show rising trends in the low and low-middle SDI regions (**Fig. S1A-B** and **Fig. S4A-B**) Regionally, the death and HF burden of IE will not be controlled in high SDI regions such as High-income North America and Western Europe. However, given the rapid rise in IE-related burden, the burden in some regions with high-middle (Southern Latin America) and low SDIs (Oceania) requires special attention in the coming decade (**Fig. S1C-D** and **Fig. S4C-D**).

ASMR remains higher in males than in females worldwide between 2020 and 2030, whereas HF ASPR will be the opposite, indicating that women will bear a greater burden of heart failure caused by IE. Males will continue to exceed females in various SDI regions when it comes to ASMR. While the male-to-female ASMR ratio in all SDI regions is expected to fall over the next decade. In contrast, males will have a higher ASPR of IE-associated HF than females in low and low-middle SDI regions, whereas females will preponderance in middle to high SDI regions (**Fig. S2A-C** and **Fig. S5A-C**). A comparable phenomenon can be observed in low-income GBD regions (**Fig. S2D** and **Fig. S5D**). The elderly population will be particularly vulnerable to IE-associated death and heart failure worldwide, particularly in middle/high-middle/high SDI regions (**Fig. S3** and **Fig. S6**).

In China, IE-related ASMR is decreasing gradually and will remain stable over the next decade. The number of deaths attributable to IE will continue to rise to 7,034, with males and elderly individuals carrying the heaviest death burden (**Table S5** and **Table S6**). In the past, IE-related heart failure ASPR was at a lower static level, but in the coming years, it will rise rapidly. IE-related heart failure injuries were discovered to be more common in older adults, with older women bearing a slightly higher burden (**Fig. S7C-F** and **Fig. S8B-C**).

Table 1. Age-standardized rates (ASR), estimated average percentage changes (EAPC) of ASR, death, and heart failure prevalence due to IE in 2020 and 2030.

Characteristics	Incidence			Death			Heart failure		
	ASR per 10 ⁵ in 2020 <i>n</i> (95% <i>UI</i>)	ASR per 10 ⁵ in 2030 <i>n</i> (95% <i>UI</i>)	EAPC of ASR 2020 to 2030 <i>n</i> (95% <i>CI</i>)	ASR per 10 ⁵ in 2020 <i>n</i> (95% <i>UI</i>)	ASR per 10 ⁵ in 2030 <i>n</i> (95% <i>UI</i>)	EAPC of ASR 2020 to 2030 <i>n</i> (95% <i>CI</i>)	ASR per 10 ⁵ in 2020 <i>n</i> (95% <i>UI</i>)	ASR per 10 ⁵ in 2030 <i>n</i> (95% <i>UI</i>)	EAPC of ASR 2020 to 2030 <i>n</i> (95% <i>CI</i>)
Overall									
Global	14.07 (13.65, 14.48)	16.33 (12.56, 20.10)	1.50 (1.46, 1.54)	0.88 (0.86, 0.91)	0.83 (0.61, 1.06)	-0.58 (-0.59, -0.57)	4.53 (4.45, 4.60)	4.34 (3.59, 5.09)	-0.42 (-0.46, -0.37)
Sex									
Male	16.61 (16.15, 17.07)	19.46 (15.09, 23.83)	1.60 (1.56, 1.63)	0.94 (0.92, 0.96)	0.86 (0.65, 1.07)	-0.90 (-0.91, -0.88)	4.21 (4.14, 4.29)	4.07 (3.31, 4.83)	-0.34 (-0.38, -0.30)
Female	11.82 (11.48, 12.17)	13.68 (10.49, 16.88)	1.47 (1.43, 1.51)	0.79 (0.77, 0.82)	0.74 (0.50, 0.99)	-0.62 (-0.63, -0.61)	4.75 (4.67, 4.83)	4.62 (3.77, 5.46)	-0.28 (-0.32, -0.24)
SDI									
Low SDI	7.51 (7.29, 7.74)	8.56 (3.97, 13.14)	1.31 (1.30, 1.32)	0.79 (0.76, 0.82)	0.80 (0.60, 1.00)	0.10 (0.09, 0.11)	2.01 (1.96, 2.07)	2.07 (1.61, 2.52)	0.27 (0.26, 0.28)
Low-middle SDI	9.60 (9.45, 9.76)	12.32 (9.61, 15.03)	2.52 (2.50, 2.55)	0.67 (0.65, 0.69)	0.70 (0.52, 0.89)	0.48 (0.47, 0.49)	1.56 (1.52, 1.60)	1.65 (1.32, 1.99)	0.59 (0.57, 0.60)
Middle SDI	13.59 (13.16, 14.03)	16.72 (10.76, 22.68)	2.10 (2.05, 2.14)	0.61 (0.60, 0.63)	0.58 (0.42, 0.74)	-0.49 (-0.51, -0.47)	3.30 (3.24, 3.35)	3.40 (2.82, 3.99)	0.32 (0.30, 0.34)
High-middle SDI	16.12 (15.63, 16.60)	18.60 (14.06, 23.14)	1.45 (1.40, 1.49)	0.69 (0.67, 0.71)	0.58 (0.43, 0.72)	-1.81 (-1.84, -1.78)	3.10 (3.03, 3.16)	3.15 (2.35, 3.95)	0.16 (0.11, 0.21)
High SDI	16.15 (15.56, 16.74)	17.84 (13.30, 22.38)	1.00 (0.96, 1.04)	1.14 (1.10, 1.18)	1.03 (0.43, 1.63)	-0.99 (-0.99, -0.99)	8.52 (8.28, 8.76)	7.97 (5.97, 9.96)	-0.67 (-0.69, -0.65)
Regions									
Western Sub-Saharan Africa	9.41 (9.19, 9.63)	10.44 (7.74, 13.14)	1.04 (1.04, 1.05)	0.78 (0.74, 0.83)	0.70 (0.38, 1.03)	-1.06 (-1.06, -1.06)	2.51 (2.42, 2.60)	2.57 (1.92, 3.21)	0.22 (0.21, 0.22)
Oceania	12.03 (11.35, 12.70)	13.18 (9.07, 17.29)	0.92 (0.91, 0.93)	1.66 (1.44, 1.89)	1.76 (0.89, 2.64)	0.60 (0.60, 0.60)	4.35 (3.86, 4.85)	4.23 (2.40, 6.07)	-0.28 (-0.30, -0.25)
Eastern Sub-Saharan Africa	6.96 (6.79, 7.14)	8.29 (5.95, 10.63)	1.76 (1.75, 1.77)	0.90 (0.86, 0.95)	0.87 (0.60, 1.14)	-0.33 (-0.35, -0.31)	3.76 (3.64, 3.89)	3.87 (2.92, 4.82)	0.27 (0.27, 0.28)
South Asia	7.28 (7.16, 7.41)	8.78 (6.55, 11.01)	1.89 (1.88, 1.90)	0.64 (0.62, 0.66)	0.68 (0.49, 0.87)	0.57 (0.57, 0.57)	1.31 (1.27, 1.34)	1.34 (1.05, 1.62)	0.23 (0.22, 0.23)
Central Sub-Saharan Africa	7.06 (6.83, 7.29)	8.33 (6.06, 10.60)	1.67 (1.66, 1.67)	1.00 (0.93, 1.07)	0.99 (0.64, 1.33)	-0.08 (-0.09, -0.07)	2.63 (2.48, 2.77)	2.75 (1.92, 3.57)	0.46 (0.46, 0.46)
Tropical Latin America	22.45 (20.73, 24.18)	32.97 (9.10, 56.84)	3.92 (3.87, 3.97)	1.05 (1.00, 1.09)	0.93 (0.63, 1.23)	-1.15 (-1.19, -1.11)	2.39 (2.31, 2.48)	2.47 (1.87, 3.08)	0.33 (0.30, 0.35)

Continued Table 1. Age-standardized rates (ASR), estimated average percentage changes (EAPC) of ASR, death, and heart failure prevalence due to IE in 2020 and 2030.

Characteristics	Incidence			Death			Heart failure		
	ASR per 10 ⁵ in 2020 <i>n</i> (95% <i>UI</i>)	ASR per 10 ⁵ in 2030 <i>n</i> (95% <i>UI</i>)	EAPC of ASR 2020 to 2030 <i>n</i> (95% <i>CI</i>)	ASR per 10 ⁵ in 2020 <i>n</i> (95% <i>UI</i>)	ASR per 10 ⁵ in 2030 <i>n</i> (95% <i>UI</i>)	EAPC of ASR 2020 to 2030 <i>n</i> (95% <i>CI</i>)	ASR per 10 ⁵ in 2020 <i>n</i> (95% <i>UI</i>)	ASR per 10 ⁵ in 2030 <i>n</i> (95% <i>UI</i>)	EAPC of ASR 2020 to 2030 <i>n</i> (95% <i>CI</i>)
Southern Sub-Saharan Africa	8.21 (7.93, 8.49)	9.58 (6.85, 12.30)	1.55 (1.54, 1.55)	0.78 (0.70, 0.86)	0.73 (0.16, 1.30)	-0.72 (-0.74, -0.69)	4.23 (4.04, 4.42)	4.18 (3.03, 5.33)	-0.13 (-0.13, -0.12)
Southeast Asia	13.04 (12.82, 13.25)	14.60 (12.02, 17.18)	1.14 (1.12, 1.16)	1.28 (1.24, 1.32)	1.26 (0.90, 1.63)	-0.16 (-0.18, -0.13)	8.95 (8.78, 9.12)	9.35 (7.65, 11.04)	0.43 (0.40, 0.47)
North Africa and Middle East	15.61 (15.37, 15.86)	18.31 (14.76, 21.85)	1.60 (1.60, 1.61)	0.65 (0.62, 0.67)	0.58 (0.42, 0.74)	-1.10 (-1.11, -1.09)	2.29 (2.22, 2.36)	2.25 (1.60, 2.91)	-0.17 (-0.19, -0.15)
Central Latin America	17.60 (17.00, 18.19)	25.29 (16.48, 34.10)	3.69 (3.66, 3.72)	0.54 (0.51, 0.57)	0.53 (0.34, 0.72)	-0.21 (-0.22, -0.19)	1.80 (1.73, 1.86)	1.84 (1.38, 2.30)	0.21 (0.20, 0.23)
Central Asia	6.45 (6.24, 6.66)	7.24 (5.41, 9.08)	1.16 (1.15, 1.18)	0.33 (0.30, 0.37)	0.32 (0.17, 0.47)	-0.37 (-0.40, -0.34)	0.31 (0.28, 0.35)	0.30 (0.17, 0.42)	-0.57 (-0.57, -0.57)
Caribbean	18.91 (18.39, 19.44)	20.78 (15.88, 25.67)	0.95 (0.93, 0.96)	0.89 (0.82, 0.96)	0.93 (0.59, 1.26)	0.39 (0.39, 0.40)	1.78 (1.67, 1.88)	1.75 (1.20, 2.31)	-0.12 (-0.12, -0.12)
Andean Latin America	13.84 (13.44, 14.25)	15.99 (12.14, 19.84)	1.45 (1.45, 1.46)	0.57 (0.53, 0.62)	0.51 (0.32, 0.71)	-1.09 (-1.10, -1.08)	2.68 (2.54, 2.82)	3.01 (2.09, 3.92)	1.14 (1.10, 1.19)
Southern Latin America	20.77 (20.25, 21.28)	24.31 (18.65, 29.97)	1.59 (1.57, 1.60)	1.83 (1.73, 1.93)	1.79 (1.08, 2.50)	-0.22 (-0.23, -0.21)	6.50 (6.28, 6.72)	6.72 (5.08, 8.36)	0.34 (0.26, 0.42)
Eastern Europe	15.55 (15.13, 15.98)	16.66 (9.97, 23.34)	0.69 (0.67, 0.71)	0.78 (0.71, 0.84)	0.70 (-0.06, 1.46)	-1.00 (-1.02, -0.97)	0.77 (0.74, 0.81)	0.75 (0.52, 0.97)	-0.38 (-0.39, -0.37)
East Asia	15.65 (14.83, 16.47)	18.82 (12.07, 25.57)	1.87 (1.81, 1.92)	0.28 (0.26, 0.29)	0.24 (0.05, 0.42)	-1.56 (-1.58, -1.55)	2.15 (2.10, 2.20)	2.23 (1.78, 2.69)	0.38 (0.35, 0.41)
Central Europe	12.23 (11.92, 12.53)	12.99 (9.63, 16.35)	0.61 (0.57, 0.64)	0.48 (0.45, 0.51)	0.44 (0.27, 0.62)	-0.74 (-0.76, -0.71)	1.16 (1.10, 1.22)	1.11 (0.66, 1.56)	-0.42 (-0.43, -0.41)
Australasia	16.31 (15.81, 16.81)	16.09 (12.18, 20.00)	-0.14 (-0.15, -0.12)	0.82 (0.75, 0.89)	0.77 (0.44, 1.09)	-0.69 (-0.69, -0.68)	7.97 (7.55, 8.39)	8.00 (3.17, 12.83)	0.03 (0.03, 0.04)
Western Europe	18.15 (17.61, 18.68)	19.55 (15.12, 23.98)	0.75 (0.70, 0.79)	1.25 (1.19, 1.30)	1.04 (0.42, 1.65)	-1.83 (-1.85, -1.80)	7.26 (7.12, 7.40)	7.38 (5.84, 8.93)	0.16 (0.16, 0.16)
High-income North America	14.83 (13.95, 15.72)	16.87 (10.86, 22.89)	1.30 (1.26, 1.34)	1.35 (1.26, 1.44)	1.35 (-0.21, 2.92)	-0.01 (-0.02, -0.01)	11.55 (10.95, 12.16)	9.92 (5.73, 14.12)	-1.52 (-1.54, -1.50)
High-income Asia Pacific	12.44 (11.95, 12.94)	13.06 (9.42, 16.69)	0.48 (0.44, 0.52)	0.73 (0.69, 0.76)	0.67 (0.29, 1.05)	-0.76 (-0.78, -0.74)	6.93 (6.71, 7.16)	6.56 (4.55, 8.58)	-0.54 (-0.55, -0.53)

ASR: age-standardized rate; EAPC: estimated average percentage change; IE: infectious endocarditis; *UI*: uncertainty interval; *CI*: confidence interval; SDI: socio-demographic index.

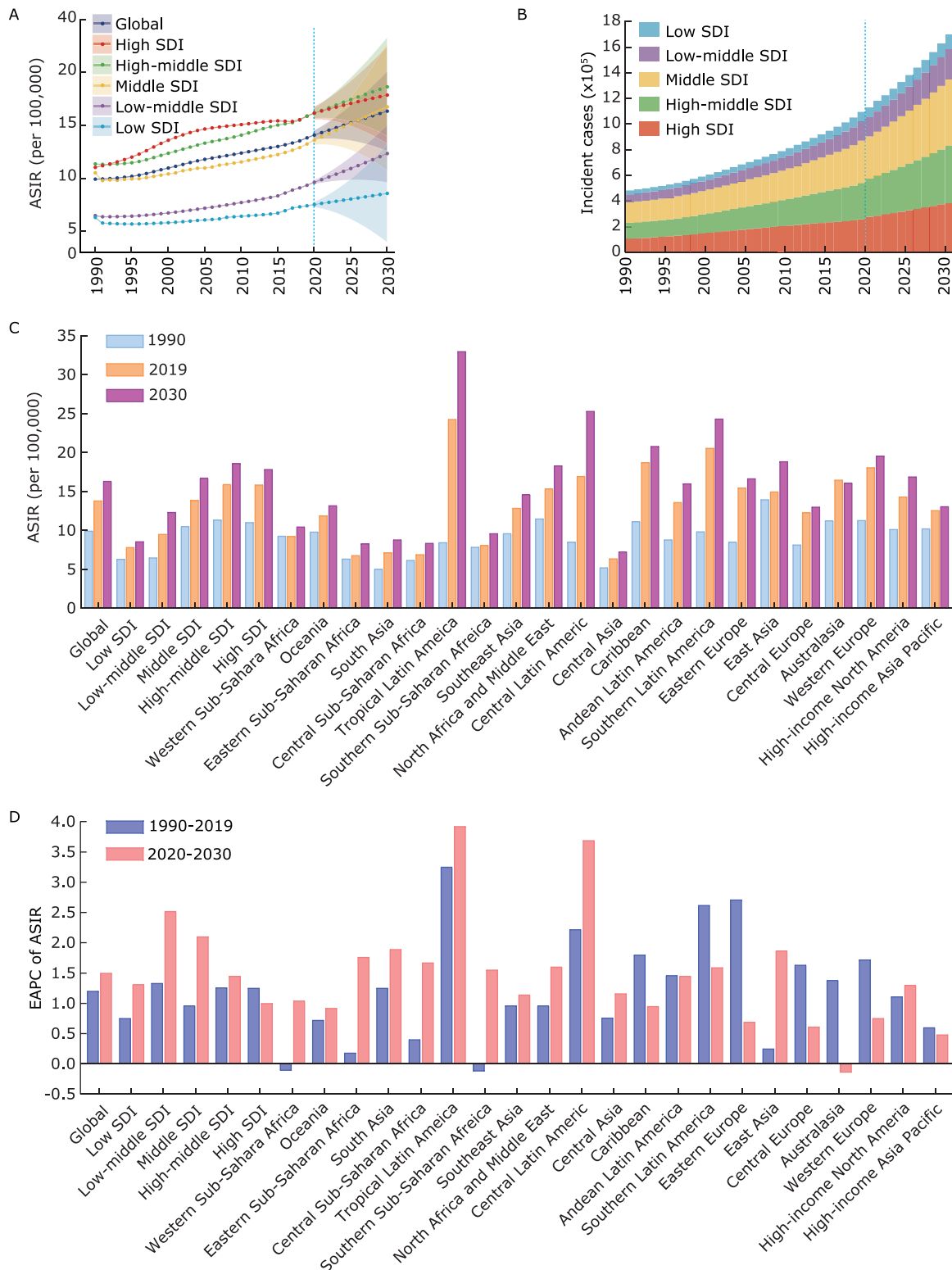


Figure 1. IE-related ASIRs and their EAPCs in global, SDI regions, and 21 GBD regions from 1990 to 2030.

(A) ASIRs in different SDI regions from 1990 to 2030; (B) death cases in SDI regions from 1990 to 2030; (C) ASIRs in global, SDI regions, and 21 GBD regions in 1990, 2019, and 2030; (D) the EAPCs of IE-related ASIRs in global, SDI regions, and 21 GBD regions between 1990-2019 and 2020-2030.

IE: infective endocarditis; ASIR: age-standardized incidence rates; SDI: socio-demographic index; EAPC: estimated annual percentage change; GBD: global burden of disease.

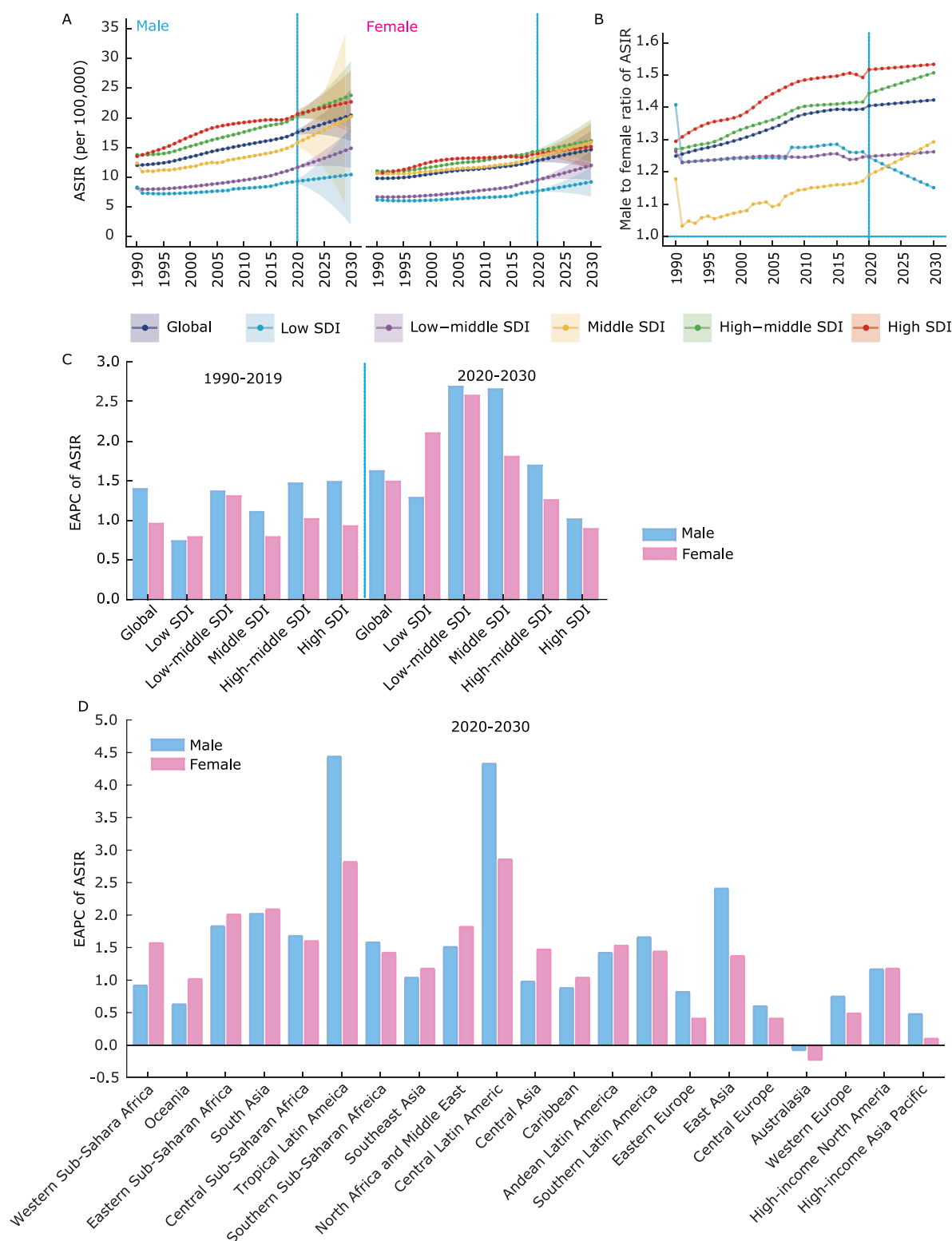


Figure 2. IE-related ASIRs and their EAPCs by sex in global, SDI regions, and 21 GBD regions from 1990 to 2030.

(A) IE-related ASIRs in different SDI regions by males (the left) and females (the right) from 1990 to 2030; (B) male to female ratio of IE-related ASIRs in SDI regions from 1990 to 2030; (C) EAPCs of IE-related ASIRs in SDI regions between 1990-2019 (the left) and 2020-2030 (the right); (D) EAPCs of IE-related ASIRs in GBD regions in 2020-2030.

IE: infective endocarditis; ASIR: age-standardized incidence rate; SDI: socio-demographic index; EAPC: estimated annual percentage change; GBD: global burden of disease.

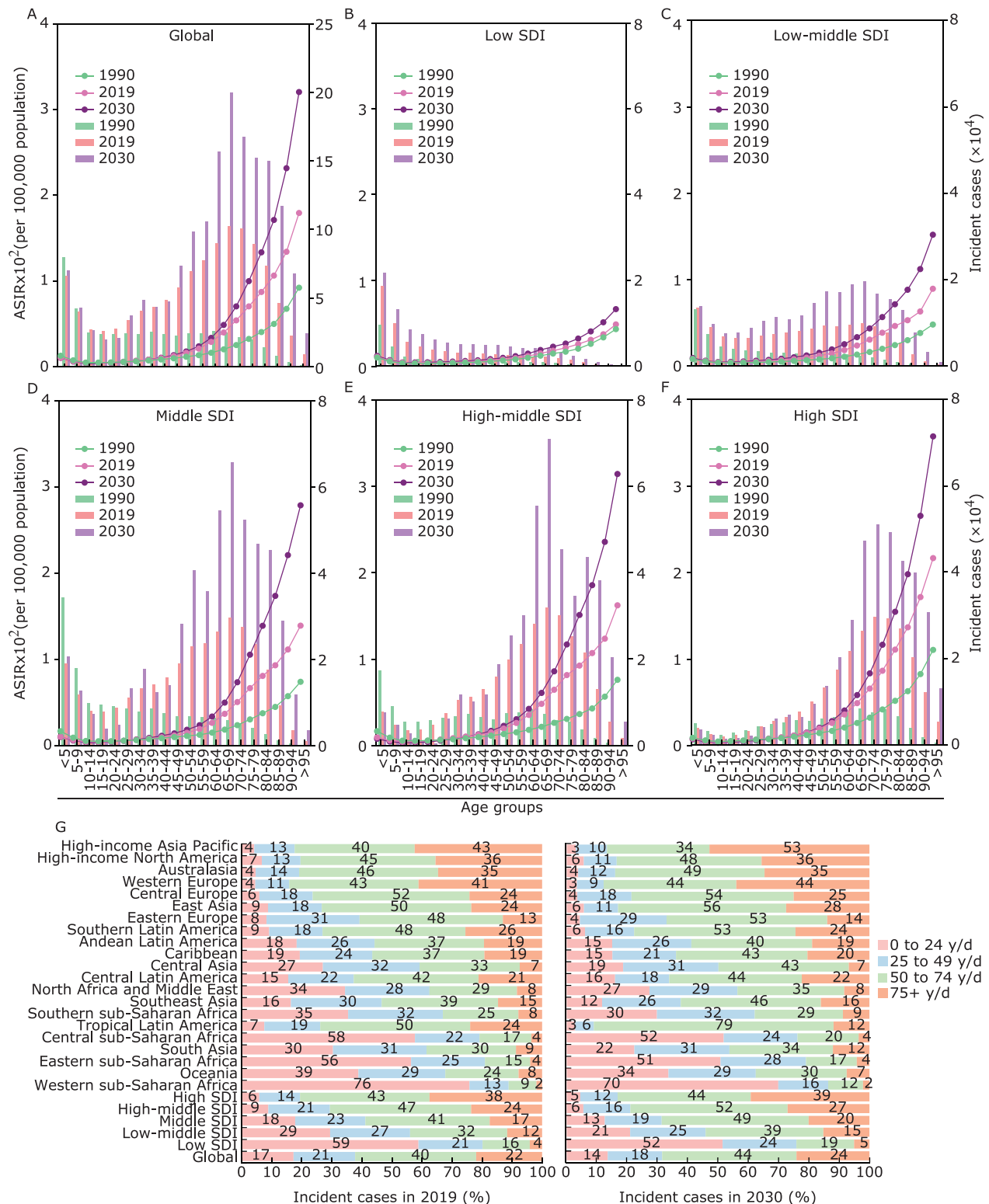


Figure 3. IE-related ASIRs, death cases, and their compositions in all age groups in 1990, 2019, and 2030.

(A)-(F) IE-related incident cases and ASIRs in 0-95+ years groups (5 years an interval) in 1990, 2019, and 2030 in global and SDI regions; (G) the age composition of (0-24, 25-49, 50-74, and 75+ years old) in incident cases of IE in global, SDI regions, and 21 GBD regions in 2019 (the left) and 2030 (the right).

IE: infective endocarditis; ASIR: age-standardized incidence rates; SDI: socio-demographic index; GBD: global burden of disease.

Trends and characteristics of IE death burden attributable to risk factors in the next decade

Over the last 30 years, the number of IE-related deaths associated with three risk factors (high SBP, high-sodium diet, and lead exposure) has increased globally and has been increasing with the SDI level. This trend will continue unabated in the next decade (**Fig. S10A**). ASMR associated with these three risk factors has decreased or remained stable, but the decline in risk factors has slowed or even increased in different regions over the last decade. If this trend continues, the burden of deaths attributable to three risk factors will rise (**Fig. S9A**). High SBP will be the most important risk factor for IE-related mortality (**Fig. S9A**) and the IE-related ASMR of high SBP will be slightly higher in men than in women (**Fig. S9B-C**), which may explain the high burden in men (**Fig. S10B-C**). In China, high SBP is still the leading cause of IE-related deaths. The number of IE-related deaths attributable to high SBP has risen in the last decade and is expected to accelerate in the future (**Fig. S11B**). While ASMR associated with high SBP has previously shown a downward trend, such a slow decline is expected to continue over the next decade (**Fig. S11A**).

To ensure the robustness of our findings, we further performed a sensitivity analysis using the ARIMA model and discovered that projection trends in the IE-related ASIRs, ASMRs, and heart failure ASPRs were consistent with the BAPC model results globally and in five SDI regions (**Fig. S12A-C**).

DISCUSSION

This study provides a global assessment and projection of the IE-associated incidence, mortality, and heart failure impairment and its attributable risk factors. By 2030, it is anticipated that the incidence of IE will increase, and the mortality and heart failure burden of IE will not be adequately managed, with developing countries experiencing the fastest growth rates and developed countries having the highest number of cases. The ASIR and ASMR will indicate male preponderance, whereas the ASPR will indicate female superiority; the elderly in high SDI countries will bear a higher burden of IE. High SBP is the primary risk factor for IE-related mortality. In China, it is anticipated that the burden of IE will increase over the coming years, and age and gender disparities are evident.

Fewer studies have been conducted on IE compared to those focusing on other cardiovascular diseases^[4, 20, 21]. Our findings suggested that the incidence of IE will not be effectively controlled shortly and the regional heterogeneity will persist. Factors contributing to the high incidence of IE included traditional risk factors such as rheumatic heart disease, native valves, and congenital heart disease in low-income countries and emerging risk factors such as degenerative valve disease and medical intervention in high-income countries^[5, 22-24]. In recent years, the rapid expansion of the global economy may bring new opportunities for healthcare-associated infections in developing nations^[22, 25]. In addition to the traditional risk factors previously mentioned, middle-income regions, just like high-income regions, will face new risk factors associated with IE. This may explain why IE is more common in middle-income countries than in high-income countries. These regional variability risk factors may contribute to the varying incidence and prevalence of IE.

Additionally, insufficient control of the prevalence of IE may also be attributable to factors including male sex^[26, 27], population aging^[28, 29], valve-containing prosthetics^[30], cardiac implantable electronic devices^[31], hemodialyses^[32], and interventional therapies^[33]. In patients undergoing mitral and aortic valve replacement, male gender was identified as a risk factor for IE^[26, 27]. The elderly have a higher incidence of IE due to the rising incidence of degenerative heart valve disease, the increased number of invasive interventions, and the longer lifespan of patients with multiple comorbidities^[28, 34, 35]. According to the recommendations of the European Society of Cardiology, a growing number of bacteria, such as hypervirulent staphylococci, are developing resistance to numerous antibiotics. With the advancements in ultrasound technology and other new diagnostic tools, IE will be diagnosed more precisely.

IE accounts for only 0.4% of cardiovascular disease deaths and may be overlooked as a burden^[4]. The mortality and complication rates of IE remained unproportionately high despite the significant survival benefits of surgical intervention and antibiotic therapy. HF is one of the most severe complications of IE, and it may necessitate immediate surgery^[34]. Our findings demonstrated that the death and HF burden of IE has been insufficiently managed globally. According to our additional analysis, the deteriorating prognosis of IE has been significantly affected by aging and the associated rise in comorbidities^[36]. This also explains the potential

causes of the high mortality rate in regions with a high SDI. Life expectancy is relatively long in high-income nations with richer medical resources and higher birth rates. In addition, staphylococcal infections, which are more prevalent in countries with high incomes, are associated with worse outcomes^[29, 37]. These factors will inevitably contribute to the poor prognosis of IE.

Although the incidence of IE is relatively low in low-income regions, ASMRs and ASPRs are expected to increase in the coming decades mainly due to delayed diagnosis and inaccessibility of health services^[38]. It is known that the most urgent indication for surgery is IE-associated HF, which may be overlooked or undertreated in low-income countries^[34]. While the HF burden caused by IE will increase in females and surpass that in males, which may result in a poor prognosis^[39, 40]. Consequently, reducing IE mortality in low-SDI regions requires a focus on priority populations, an improvement in the ability to perform complex surgery, and an increase in health care resources. Using the GBD database, we also found that metabolic factor (high SBP) was a key risk factor attributable to IE-related mortality worldwide. Recent cohort research identified elevated blood pressure as a risk factor for the development of IE^[41]. As more cardiovascular metabolic risk factors have been discovered, public health policymakers should further evaluate the effect of high SBP on IE-related mortality.

Our current study revealed that the burden of IE persisted over the past three decades and will increase in the coming years, and the burden was higher than those in high-income countries^[29, 42] and in previous single-center studies conducted in China^[43, 44]. Thus, we need to identify the most emerging risk factors in China to control the prevalence of IE. Recent studies have confirmed that congenital heart disease and chronic rheumatic heart disease were the most common risk factors for IE in China^[43-45]. In addition, there was an alarming increase in prosthetic-valve endocarditis, which is expected to further expand indications for valvular replacement and transcatheter valvular interventions^[46]. While *Staphylococcus aureus* and streptococci are the most prevalent pathogens, other risk factors including hemodialysis and drug abuse should not be neglected^[43, 47]. To prevent the increase in the burden of endocarditis in China over the next decade, both traditional and emerging risk factors should be identified and managed.

The mortality and heart failure burden caused by

IE must also be carefully managed in China. Population aging portends an increase in IE-related fatalities in the future. Intravenous drug abuse, prosthetic valve endocarditis, hemorrhagic stroke, acute congestive heart failure, renal insufficiency, left-sided endocarditis, and early surgical intervention were the most significant factors contributing to the increased mortality^[43, 48, 49]. Surgical intervention may have neutralized the adverse effects of advanced age and comorbidities, thereby contributing to the stagnant mortality trend^[44, 50]. Nevertheless, additional epidemiological studies on the risk factors are required.

Our current study had several limitations. First, the data retrieved from the GBD database was variable resources, which may be inevitably biased from the actual data, particularly in some countries with scarce information. Second, no external database was available to validate the results from BAPC modeling. Nevertheless, we conducted internal validation using the data from the different time frames and supported the stability of the model. Third, potential IE-related incidence attributable to risk factors such as valvular degeneration, intravenous drug addiction, surgical interventions, hemodialysis or central venous catheter placement, and congenital heart disease were not available in the database. Thus, we could not exclude the impacts of those factors. Fourth, potential IE-related death-attributable risk factors such as pathogens, underlying disease, cardiac involvement, embolic complications, infectious shock, and surgical intervention were not available in the database. Thus, we could not analyze the impact of those factors.

CONCLUSIONS

The burden of IE has been neglected and inadequately controlled worldwide over the past three decades. Projections indicate that the disease burden will not be alleviated if the current situation continues. The incidence of IE will increase uncontrollably in the future and the death and HF burden will not be sufficiently managed. Gender, age, and regional/national heterogeneities should be taken into account, and attributable risk factors should be identified and managed to facilitate making targeted preventative strategies for reducing the surge of IE disease burden.

Supplementary materials

Available at <http://cmsj.cams.cn/EN/10.24920/004118>.

Table S1. Checklist of accurate and transparent global health estimates reporting (ie. GATHER checklist).

Table S2. The evaluation of the Bayesian age-period-cohort model's predictive accuracy in the primary analysis.

Table S3. The evaluation of the Bayesian age-period-cohort model's predictive accuracy in the sensitivity analysis.

Table S4. Cases of incidence, death, and heart failure prevalence caused by IE in 2020 and 2030.

Table S5. ASIRs, ASMRs, heart failure ASPRs, and their related EAPCs of IE in China 1990, 2019, 2020, and 2030.

Table S6. Cases of incidence, death, and heart failure prevalence caused by IE in China in 1990, 2019, 2020, and 2030.

Figure S1. IE-related ASMRs and their EAPCs at the global, SDI regions, and 21 GBD regions from 1990 to 2030.

Figure S2. IE-related ASMRs and its EAPCs by sex, in global, SDI regions, and 21 GBD regions from 1990 to 2030.

Figure S3. The IE-related ASMRs, death cases, and their compositions in all age groups in 1990, 2019, and 2030.

Figure S4. IE-related ASPRs and their EAPCs by sex, in global, SDI regions, and 21 GBD regions from 1990 to 2030.

Figure S5. IE-related ASPRs and their EAPCs by sex, in global, SDI regions, and 21 GBD regions from 1990 to 2030.

Figure S6. IE-related ASPRs, heart failure cases, and their compositions in all age groups in 1990, 2019, and 2030.

Figure S7. IE-related age-standardized rates and cases of incidence, death, and heart failure prevalence by sex in China from 1990 to 2030.

Figure S8. IE-related ASRs and cases of incidence, death, and heart failure prevalence in all age groups by sex in China in 1990, 2019, and 2030.

Figure S9. Trends in ASMRs associated with IE risk factors in global and SDI regions by sex from 1990 to 2030.

Figure S10. Trends in death cases associated with IE risk factors in global and SDI regions by sex from 1990 to 2030.

Figure S11. Trends in ASMRs and death cases associated with IE risk factors in China by sex from 1990 to 2030.

Figure S12. Sensitivity analyses of ASIRs, ASMRs,

and heart failure ASPRs of IE in global and SDI regions from 1990 to 2030.

Data availability

All data in this analysis are publicly available from the Global Health Data Exchange query tool (<http://ghdx.healthdata.org/gbd-results-tool>). Source: Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.

Ethical approval statement

The Ethics Committee of Renmin Hospital of Wuhan University determined that this study did not require ethical approval because it used publicly available data.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

The study was designed by Lin LJ and Liu YM, who also collected and analyzed data and wrote the manuscript. The statistical analysis and interpreted data were carried out by Qin JJ, Lei F, Wang WX, Huang XW, and Liu WF. The data were collected, reviewed, interpreted, and checked by Zhang XY, She ZG, and Zhang P. The manuscript was written and revised by Zhang XJ. Jin ZX and Li HL contributed equally to designing the project, editing the manuscript, and supervising the study. The final manuscript was read, critically reviewed, and approved by all authors.

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1990–2030 年全球和区域感染性心内膜炎的疾病负担及其归因 危险因素的趋势和预测

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摘要

目的 预测感染性心内膜炎 (Infective endocarditis, IE) 未来的疾病负担及其归因危险因素。

方法 我们利用 2019 年全球疾病负担数据库分析了 1990 年至 2019 年 IE 的疾病负担及其危险因素, 并利用贝叶斯年龄 - 时期 - 队列模型预测了 2020 年至 2030 年 IE 的全球疾病负担。

结果 到 2030 年, 全球 IE 发病率将会不可控制地增加。其中, 发展中国家的发病率增长速度最快, 发达国家的新发病例数量最高, 男性发病率较高, 但性别差距将会缩小。高收入国家的老年人的发病负担最重, 逐渐向中等收入国家转移。在中 / 高 - 中社会人口指数 (social-demographic indicators, SDI) 国家的发病率将超过高 SDI 国家。在中国, 预计到 2030 年, IE 的年龄标化发病率将达 18.07/10 万人, 而 IE 患者的数量将达 45 万人。IE 导致的死亡和心力衰竭负担仍然较重, 女性的负担将增加并超过男性, 而高 SDI 国家的老年人将承担最严重的疾病负担。高收缩压成为 IE 相关死亡的主要危险因素。

结论 未来十年全球范围内 IE 的疾病负担和危险因素分析表明, IE 的发病率将会增加, IE 相关的死亡和心衰负担的控制将成为严峻问题。应关注 IE 疾病负担的性别、年龄以及区域和国家的异质性, 以便制定降低 IE 疾病负担的有效策略。

关键词: 感染性心内膜炎; 发病率; 死亡率; 心力衰竭; 贝叶斯年龄 - 时期 - 队列模型; 预测

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