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Temporal trends in incidence and mortality rates of laryngeal cancer at the global, regional, and national levels, 1990-2017

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Title:

Temporal trends in incidence and mortality rates of laryngeal cancer at the global, regional, and national levels, 1990-2017

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Running title: Epidemiology of laryngeal cancer

Article summary

Strengths and limitations of this study

- We provided the most comprehensive description of laryngeal cancer incidence and mortality.
- The incidence and mortality rates of laryngeal cancer were significantly decreased at the global level and in most countries.
- The temporal trends of incidence and mortality are critical to update the laryngeal cancer prevention strategies.
- The data used in this study were lack of individual data.
- We cannot specify the laryngeal cancer into several subgroups according to the anatomical position.

ABSTRACT

Objective

Laryngeal cancer is the most prevalent entity of the head and neck cancer. Knowing the trends of incidence and mortality of laryngeal cancer are of importance for the reduction in related disease burden.

Design

Population-based observational study

Methods

The incidence and mortality data of laryngeal cancer were retrieved from the Global Burden of Disease study 2017 online database. Estimated average percentage change was used to quantify the trends of the laryngeal cancer incidence and mortality at the global, regional, and national levels.

Results

Globally, the number of incident cases and deaths of laryngeal cancer has increased 58.7% and 33.9%, respectively, from 1990 to 2017. The overall age-standardized incidence rate (ASIR) and age-standardized mortality rate (ASMR) decreased by 0.99% (95% CI 0.83%, 1.14%) and by 1.62% (95% CI 1.50%, 1.74%) per year, respectively. These decreases were ubiquitous across the world. However, an unfavorable trend in the ASIR of laryngeal cancer was also observed in a total of 51 developing countries.

Conclusions

The incidence and mortality rates of laryngeal cancer were significantly decreased at the global level and in most countries over the past three decades. The regions where showed an increasing incidence trend deserve more attentions.

Keywords Laryngeal cancer; incidence; mortality; global

INTRODUCTION

Constituting 25-30 % of all head and neck cancer cases, laryngeal carcinoma is the most common cancer site of the aero-digestive tract [1]. In 2018, it is estimated that a total of 177 thousand and 95 thousand new cases of laryngeal cancer and its related deaths were occurred worldwide, respectively [2]. Laryngeal cancer diagnoses more commonly in men than in women [2]. The most well-determined risk factors for laryngeal caner include smoking and alcohol consumption [3, 4]. Owning to the disparities in risk factor distribution from country to country, the incidence and mortality patterns of laryngeal cancer are geographically heterogeneous [5]. In this context, a comprehensive description of the epidemiological characteristics of laryngeal cancer at the national level is needed. In addition, the incidence and mortality trends of laryngeal cancer were commonly reported together with that of other head and neck cancers (HNC) [6]. There were few studies have individually described and analyzed the epidemiological features of laryngeal cancer. However, since the differences of histology, pathology, clinical manifestation, and prognosis of HNC, separately knowing their evolving incidence and mortality rates is important for the HNC prevention.

In the current study, leveraging the data from Global Burden of Disease (GBD) study 2017, we comprehensively described the epidemiology and analyzed the temporal trends of incidence and mortality rates of laryngeal cancer at the global, regional, and national levels. Our findings were of importance to assess the current prevention strategies of laryngeal cancer and allowed the future establishment of health care planning.

METHODS

Study data

The GBD study provides a tool to quantify health loss from hundreds of diseases, injuries, and risk factors, so that health systems can be improved and disparities can be eliminated. The GBD data have been widely used to assess the disease burden of cancers. Herein, we retrieved the incidence and mortality data of laryngeal cancer by sex, country or territory, region, and single calendar year, from 1990 to 2017 using the online Global Health Data Exchange query tool. The electronic searches were complemented with additional epidemiologic measures such as "metric" (i.e., "rate" and "number"), "measure" (i.e., "incidence" and "deaths"), "year" (i.e., from 1990 to 2017), "sex" (i.e., "male" and "female"), "age" (i.e., "All Ages" and "Age-standardized") and "location". The data were available at 5 regions in terms of socio-demographical index (SDI; i.e., high SDI, high-middle SDI, middle SDI, low-middle SDI, and low SDI), 21 GBD regions in terms of the geography (e.g., Western Europe), and 195 countries or territories (e.g., China). The collection and processing procedures of cancer data in GBD study have been extensively described elsewhere [7, 8]. In brief, the crude incidence and mortality data of laryngeal cancer were collected from cancer registries identifying by the ICD-10 codes of C32-C32.9 and ICD-9 codes of 161-161.9. For regions that lack of incidence data, cancer incidence was estimated from cancer mortality using mortality to incidence ratios. These data were then modeled by Cause of Death Ensemble modelling (CODEm), which is the framework used to model most cause-specific death rates in the GBD study [8]. The national SDIs were also retrieved from GBD online database. SDI is a composite average of the rankings of the incomes per capita, average educational attainment, and fertility rates of all areas in the GBD study.

Statistical analysis

We used the estimated average percentage change (EAPC) to quantify the trends of the laryngeal cancer incidence and mortality from 1990 to 2017. The EAPC can be calculated from the regression model, which was fitted the calendar years with the natural logarithm of the rates (i.e., $y = \alpha + \beta x + \varepsilon$, where $y = \ln(\text{rate})$, and x = calendar year) [9]. The Pearson correlation tests were applied to assess the correlations between SDIs and other indexes (e.g., the incidence and the EAPC of incidence). All statistical analyses were performed using the R program (Version 3.6.3, R core team, Vienna, Austria). A P-value less than 0.05 was considered statistically significant.

Results

Incidence and its trend of laryngeal cancer at the global, regional, and national levels

Globally, the incident case number of laryngeal cancer increased from 132.7 thousand in 1990 to 210.6 thousand in 2017 (Figure 1; Table 1). Approximately 85% of total cases were occurred in men (Table 1). The case number was highest in regions with high SDIs and decreased with the SDI levels. During the study period, the overall age-standardized incidence rate (ASIR) of laryngeal cancer experienced a significant decrease (EAPC = -0.99, 95% CI, -1.14, -0.83). The ASIR in different regions was decreased with different magnitudes. The greatest reduction was observed in high-SDI region (Table 1). As for GBD regions, the highest ASIR and case number of laryngeal cancer was found in Caribbean and East Asia, respectively, in 2017 (Table 1). Between 1990 and 2017, we only found three of 21 GBD regions, including East Asia, Caribbean, and Oceania, have experienced a significant increase in the ASIR (Table 1; Figure 2). In the remaining GBD regions, the ASIR was significantly decreased, with the most pronounced reduction was found in Andean Latin America (EAPC = -2.21, 95% CI, -2.41, -2.00) (Table 1; Figure 2). In 2017, the ASIR of laryngeal cancer was varied 12-fold across the world. The highest ASIR was observed in Cuba (8.58/100,000), followed by Seychelles and Montenegro (Figure 3A). A total of 51 countries, most are located in developing regions, experienced a significant increase in the ASIR of laryngeal cancer from 1990 to 2017 (Figure 3B). The greatest increase was found in Sri Lanka (EAPC = 2.31, 95% CI, 2.04, 2.58). In contrast, a total of 122 countries experienced a significant decrease in the ASIR of laryngeal cancer (Figure 3B). The most remarkable reduction was seen in Bahrain (EAPC = -4.79, 95% CI, -5.37, -4.21).

Mortality and its trend of laryngeal cancer at the global, regional, and national levels

While the number of deaths from laryngeal cancer has increased 33.9% between 1990 and 2017, the corresponding age-standardized mortality rate (ASMR) was decreased by 1.62% per year during the same period (Table 1; Figure 1). Most of deaths were occurred in men and in regions with low to middle SDIs (Table 1). The most significant reduction in the ASMR was found in high-SDI regions. Only one GBD region (i.e., Oceania) has seen a significant increase in the ASMR of laryngeal cancer between 1990 and 2017. The ASMR in the remaining GBD regions were remarkably decreased (Table 1; Figure 2). The greatest decrease was observed in high-income Asia Pacific (EAPC = -3.85, 95% CI, -4.14, -3.56). At the national level, the highest ASMR was found in Pakistan (5.17/100,000) in 2017, followed by Cuba and Seychelles (Figure 3C). Between 1990 and 2017, 30 countries experienced a significant increase in the ASMR. The greatest increase was found in Guinea (EAPC = 1.77, 95% CI, 1.56, 1.98), followed by Chad and Mongolia (Figure 3D). On the contrary, a total of 150 countries experienced a significant decrease in the ASMR of laryngeal cancer. The most remarkable reduction was found in South Korea (EAPC = -7.10, 95% CI, -7.81, -6.40) (Figure 3D).

The associations of SDI with laryngeal cancer related indexes

We also assessed the associations of the SDI with laryngeal cancer related indexes at the national level (Figure 4). As shown in Figure 4A & B, the ASIR and ASMR and their corresponding trends, quantified by the EAPC, of laryngeal cancer were both highly correlated ($\rho = 0.795$, $P < 0.001$; $\rho = 0.907$, $P < 0.001$). The countries with higher SDI seemed to have higher ASIR of laryngeal cancer (Figure 4C; $\rho = 0.369$, $P < 0.001$). However, this relationship was reversed for ASMR, although the correlation index was not statistically significant (Figure 4D; $\rho = -0.127$, $P = 0.079$). While no association was found between the SDI and the EAPC of ASIR (Figure 4E; $\rho = -0.120$, $P = 0.097$), a significantly negative association was found between the SDI and the EAPC of ASMR (Figure 4F; $\rho = -0.403$, $P < 0.001$). This finding suggest that countries with higher SDI have made greater improvement in the treatment of laryngeal cancer than those with lower SDI.

DISCUSSION

In this study, we reported the incidence and mortality trends of laryngeal cancer at the global, regional, and national levels. In brief, our findings showed highly geographical heterogeneities in both the incidence and mortality rates of laryngeal cancer worldwide. We observed significant decreasing trends in the incidence and mortality rates of laryngeal cancer at the global level and in most countries between 1990 and 2017. These reductions suggested the efficacy of current prevention strategies and highlighted the importance of continuous application and even strengthening these strategies. However, we also observed an unfavorable trend in the incidence of laryngeal cancer in a few countries. Most of these countries were located in East Asia and North Africa and were not advanced in economy. Owing to the large population size in these countries, the increase of laryngeal cancer incidence might suggest a considerable disease burden of this malignant carcinoma.

Several risk factors have been implicated in the pathogenesis of laryngeal cancer. The most significant of these are tobacco and alcohol consumption. In addition, the risk of laryngeal cancer increases with the amount of alcohol consumed [10]. In previous studies conducted in North America, Europe, Japan, and Korea, the multivariate relative risks for the highest levels of consumption ranged between 2 and 10, and were 1.94 for 50 g/day and 3.95 for 100 g/day in a meta-analysis of 20 studies [11]. In our study, we found that the incidence of laryngeal cancer was higher in Europe, where the alcohol consumption is higher than the global average [12]. The decreasing trend of laryngeal cancer incidence might be partly attributed to the reduction of alcohol use in these countries. In a recent study conducted in British, the authors found that for those born post-1985, alcohol abstention rates are increasing and male consumption is falling relative to preceding cohorts [13]. However, in a large-scale modeling study [14], the authors reported that between 1990 and 2017, global adult per-capita consumption increased from 5.9 L to 6.5 L, and is forecasted to reach 7.6 L by 2030. In parallel, globally, the prevalence of lifetime abstinence decreased from 46% in 1990 to 43% in 2017, and is predicted to further decrease to 40% in 2030. These results alarmed us that the global goals for reducing the harmful use of alcohol are unlikely to be achieved and the alcohol use related diseases including laryngeal cancer remain the major challenges for human health. In this unfavorable context, although we have seen a significant reduction in the incidence of laryngeal cancer in most countries over the past three decades, the primary prevention for alcohol use is well worth strengthening. For example, increasing the tax of alcohol beverage and strictly forbidding the sale to children and adolescents.

Tobacco use has also been shown to have a linear association with the development of laryngeal cancer, with a risk for smokers that is 10 to 15 times higher than the risk for nonsmokers, and the heaviest smokers have as much as a 30 times greater risk [15]. Fortunately, owing to the persistent efforts to combating tobacco, such as the Framework Convention on Tobacco Control, the prevalence of daily smoking has declined for both men and women in many countries [16]. However, given the continuing increase in the number of smokers worldwide and the rapid emergence of new tobacco products, additional efforts are needed to achieve a smoke-free world, help smokers to quit, and protect youth from initiating tobacco use [16].

Although the global decrease in the incidence of laryngeal cancer, of note is the unexpected increase of this rate in a few developing countries, such as China and Vietnam. We suspected that this increase might be partly explained by the following reasons: 1) since the improvement of health care service and the cancer surveillance system, more laryngeal cancer cases have been diagnosed and recorded; and 2) the high prevalence of risk factors, especially smoking, in these countries [17, 18]. For example, the implementation of tobacco control policies in China since the signing of the WHO Framework Convention on Tobacco Control in 2003 has not been effective in reducing smoking prevalence. Smoking prevalence among adolescents of both genders has increased substantially and there has been a steady increase among young women [17]. The similar phenomenon was observed in Vietnam, in which the reduction in the prevalence of tobacco smoking during the last 5 years has not been as high as expected, especially in rural areas [18]. These findings highlight more practical and effective policies targeting smoking are urgently needed.

In our study, we also observed a ubiquitous decrease in the mortality rate of laryngeal cancer. Unsurprisingly, the greatest reduction was mostly seen in developed countries. The development of the mortality rate of laryngeal cancer was largely based on the evolution of incidence and was likely also due to the change in the medical practices, including screening, diagnosis and treatment [1]. Scheduled and opportunistic screening, coupled with efforts to enhance education and health behavior modification, are highly recommended for pre-defined, high-risk, targeted populations [19]. This can enable early detection and therefore improve mortality. Previous studies have demonstrated the feasibility of developing and implementing large-scale community-based head and neck cancer screenings [20].

The limitations of this study should be noted here. First, all data used in our study were retrieved from GBD study, which were obtained from mathematical models based on surveillance data rather than the surveillance data itself. Therefore, for those countries that are lack of useable cancer surveillance data, the incidence and mortality of laryngeal cancer were estimates from mathematical models and should be interpreted with cautions. Second, we cannot specify the laryngeal cancer into several subgroups (e.g., glottic carcinoma and supraglottic carcinoma) according to the anatomical position because of the data unavailability.

In conclusion, we reported a global decrease in both the incidence and mortality of laryngeal cancer over the past three decades. These decreases suggest the effectiveness of control for tobacco and alcohol use. However, an unfavorable increase in the incidence of laryngeal cancer was observed in a few developing countries. More targeted and potent prevention strategies for laryngeal cancer are therefore warranted.

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Disclosure statement

No potential conflict of interest was reported by the authors.

Authors' contributions:

Conceptualization: J.Y.W. and Q.W.Z.; Data curation: J.Y.W., Q.W.Z., and K.X.W.; Formal analysis: J.Y.W. and Q.W.Z.; Methodology: C.W. and J.Y.W.; Software X.L.J, and X.Z.; Supervision: J.Y.W. and X.Z.; Roles/Writing - original draft: all authors; Writing - review & editing: all authors.

Data sharing:

The data used in our study were available at online Global Health Data Exchange query tool (http://ghdx.healthdata.org/gbd-2017).

Patient and Public involvement:

No patient involved

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Figure legend

Figure 1. The temporal trends of incident case number (A), death number (B), age-standardized incidence rate (ASIR) (C), and age-standardized mortality rate (ASMR) (D) of laryngeal cancer from 1990 to 2017.

Figure 2. The estimated average percentage change (EAPC) and its 95% confidence interval (CI) of age-standardized incidence rate (A) and age-standardized mortality rate (B) of laryngeal cancer at the global and regional levels.

Figure 3. The age-standardized incidence rate (A), the estimated average percentage change of incidence rate between 1990 and 2017 (B), the age-standardized mortality rate (C), and the estimated average percentage change of mortality rate between 1990 and 2017 (D) of laryngeal cancer at the national level.

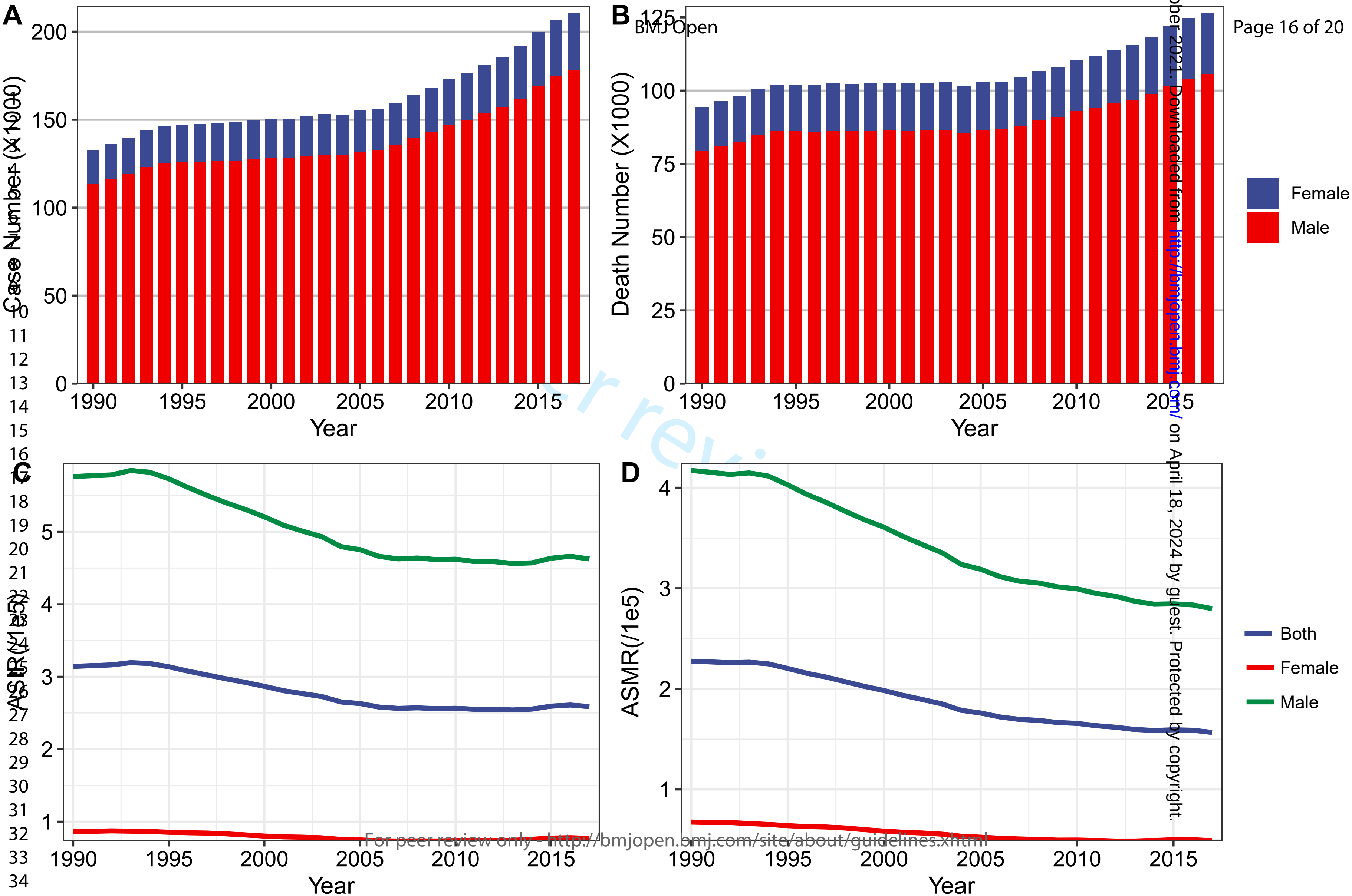
Figure 4. The associations between national socio-demographical index (SDI) and laryngeal cancer related indexes. (A, the association between age-standardized incidence rate [ASIR] and age-standardized mortality rate [ASMR] of laryngeal cancer in 2017; B, the association between changing trends of ASIR and ASMR; C, the correlations of SDI with ASIR of laryngeal cancer; D, the correlations of SDI with ASMR of laryngeal cancer; E, the correlations of SDI with the changing trends of ASIR of laryngeal cancer; F, the correlations of SDI with the changing trends of ASMR of laryngeal cancer.

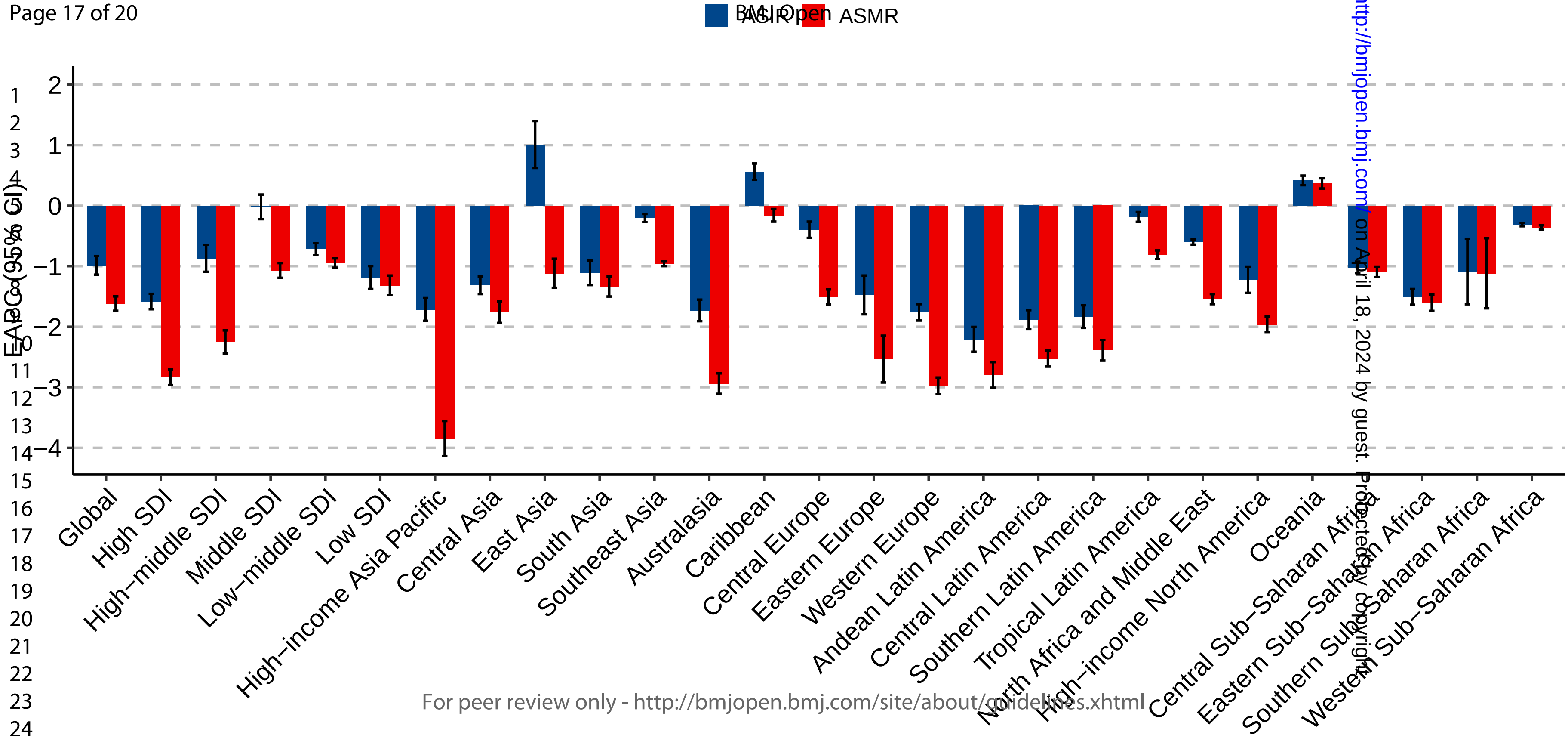
Table 1. The incidence and mortality of larynx cancer in 1990 and 2017 and the temporal trends between 1990 and 2017, by sex, SDI region, and GBD region.

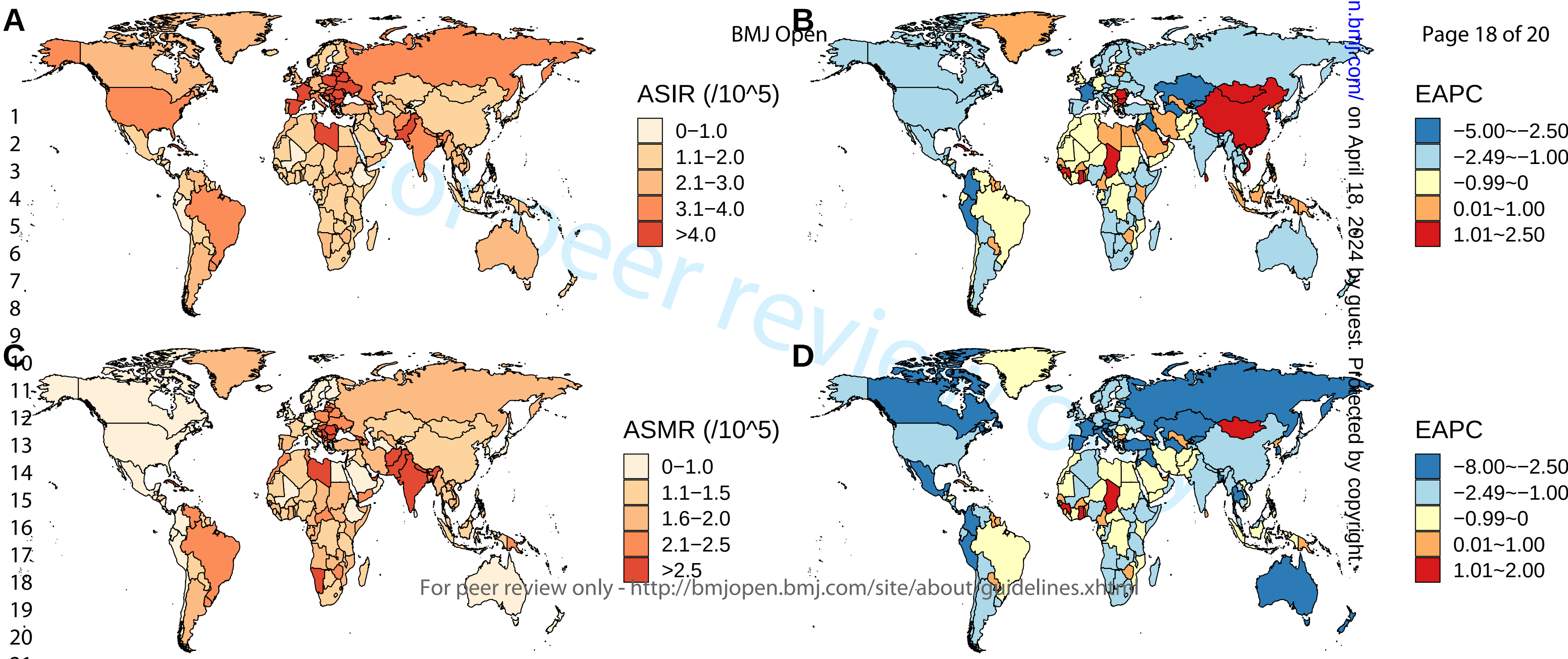
	Age-standardized incidence rate					Age-standardized mortality rate				
	1990		2017		1990-2017	1990		2017		1990-2017
	Case number (×1000)	ASIR (/10^5)	Case number (×1000)	ASIR (/10^5)	EAPC (95% CI)	Death number (×1000)	ASMR (/10^5)	Death number (×1000)	ASMR (/10^5)	EAPC (95% CI)
Global	132.7	3.14	210.6	2.59	-0.99 (-1.14, -0.83)	94.5	2.27	126.5	1.57	-1.62 (-1.74, -1.50)
Sex										
Male	113.3	5.76	178.0	4.63	-1.08 (-1.23, -0.93)	79.5	4.17	105.6	2.80	-1.71 (-1.82, -1.59)
Female	19.4	0.87	32.6	0.77	-0.66 (-0.83, -0.50)	15.0	0.68	20.9	0.49	-1.40 (-1.56, -1.25)
SDI regions										
High	48.9	3.91	57.8	2.82	-1.58 (-1.71, -1.46)	22.9	1.81	19.7	0.92	-2.83 (-2.96, -2.70)
High-middle	30.2	3.04	49.5	2.68	-0.87 (-1.09, -0.65)	23.0	2.37	26.6	1.46	-2.25 (-2.44, -2.06)
Middle	20.8	2.10	49.1	2.17	-0.02 (-0.22, 0.18)	18.0	1.90	32.5	1.48	-1.07 (-1.19, -0.95)
Low-middle	18.8	3.11	32.6	2.64	-0.72 (-0.82, -0.62)	17.3	2.97	28.2	2.36	-0.95 (-1.02, -0.87)
Low	13.8	3.88	20.8	2.84	-1.19 (-1.38, -1.00)	13.0	3.80	19.0	2.68	-1.32 (-1.48, -1.15)
GBD region										
Andean Latin America	0.3	1.48	0.5	0.90	-2.21 (-2.41, -2.00)	0.3	1.44	0.4	0.75	-2.80 (-3.01, -2.59)
Australasia	0.7	3.01	1.0	2.08	-1.73 (-1.91, -1.55)	0.3	1.20	0.3	0.60	-2.94 (-3.11, -2.77)
Caribbean	1.1	3.97	2.4	4.64	0.56 (0.43, 0.70)	0.8	3.12	1.5	3.02	-0.16 (-0.26, -0.05)
Central Asia	1.5	2.95	1.7	2.20	-1.32 (-1.46, -1.17)	1.2	2.47	1.2	1.64	-1.76 (-1.94, -1.58)
Central Europe	7.2	4.68	8.7	4.39	-0.40 (-0.53, -0.26)	5.3	3.48	5.0	2.44	-1.51 (-1.63, -1.38)
Central Latin America	1.8	2.15	3.4	1.48	-1.88 (-2.04, -1.73)	1.6	1.96	2.5	1.11	-2.52 (-2.66, -2.39)
Central Sub-Saharan Africa	0.5	1.98	0.8	1.55	-1.02 (-1.11, -0.92)	0.5	2.00	0.8	1.53	-1.09 (-1.18, -1.01)

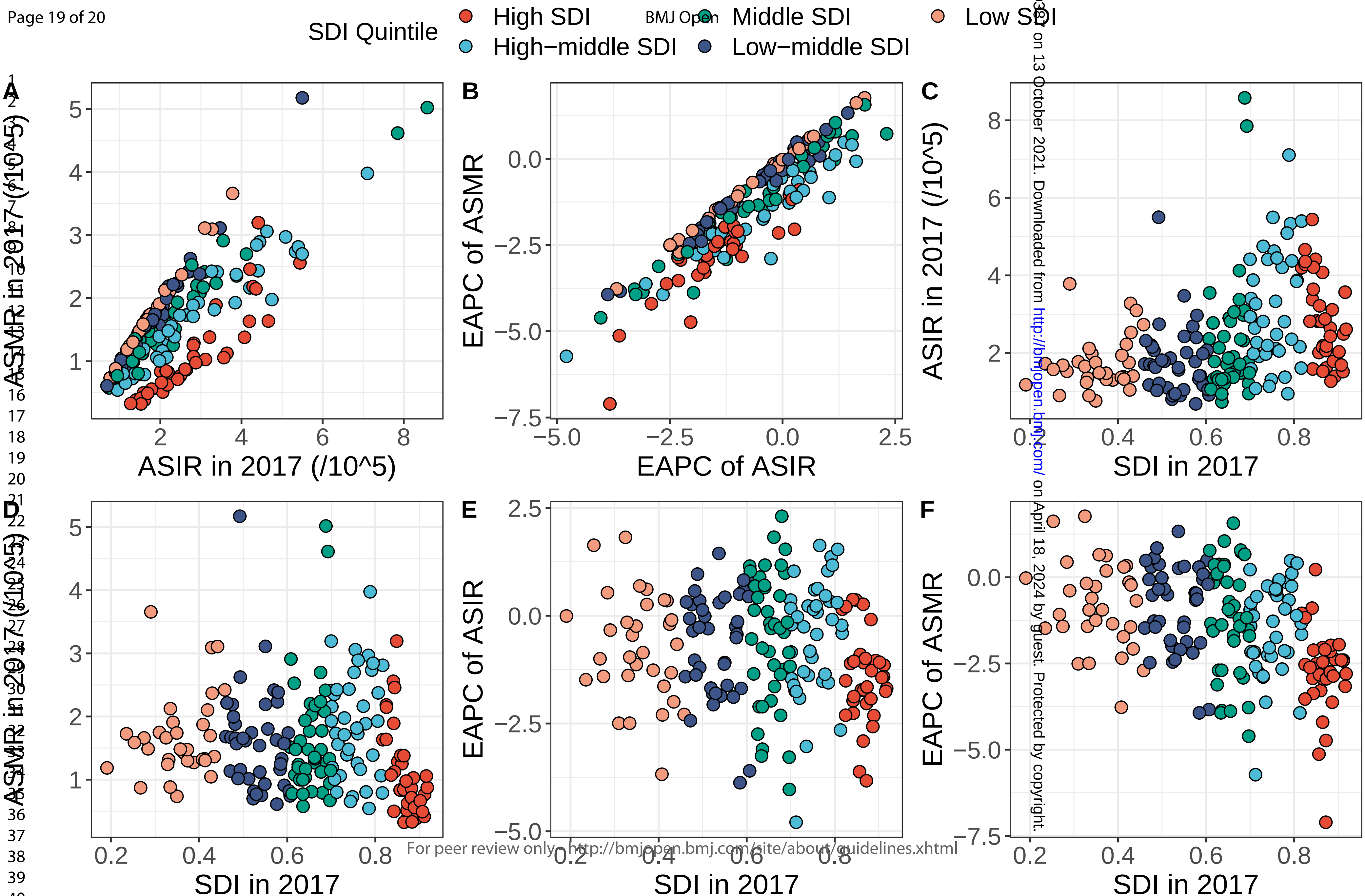
East Asia	14.4	1.53	41.9	1.98	1.01 (0.62, 1.40)	12.0	1.33	20.4	1.00	-1.12 (-1.36, -0.88)
Eastern Europe	13.2	4.52	12.3	3.67	-1.48 (-1.79, -1.15)	9.4	3.20	6.9	2.02	-2.54 (-2.92, -2.15)
Eastern Sub-Saharan Africa	1.6	1.92	2.3	1.38	-1.51 (-1.64, -1.38)	1.5	1.89	2.2	1.33	-1.60 (-1.74, -1.47)
High-income Asia Pacific	4.8	2.28	6.9	1.64	-1.71 (-1.90, -1.53)	1.7	0.84	1.7	0.36	-3.85 (-4.14, -3.56)
High-income North America	12.7	3.71	18.6	3.11	-1.22 (-1.44, -1.01)	5.0	1.41	5.7	0.92	-1.96 (-2.09, -1.83)
North Africa and Middle East	4.9	2.71	10.1	2.33	-0.60 (-0.64, -0.56)	4.3	2.46	6.8	1.66	-1.54 (-1.63, -1.46)
Oceania	0.1	1.91	0.1	2.05	0.42 (0.34, 0.50)	0.1	1.79	0.1	1.88	0.37 (0.28, 0.45)
South Asia	29.7	4.62	50.6	3.57	-1.11 (-1.31, -0.90)	27.6	4.45	44.3	3.22	-1.33 (-1.50, -1.17)
Southeast Asia	5.3	1.95	11.5	1.89	-0.20 (-0.27, -0.14)	4.6	1.76	8.0	1.38	-0.96 (-1.00, -0.92)
Southern Latin America	1.6	3.42	1.9	2.32	-1.83 (-2.02, -1.65)	1.2	2.62	1.2	1.48	-2.39 (-2.56, -2.22)
Southern Sub-Saharan Africa	0.7	2.30	1.1	1.84	-1.09 (-1.63, -0.55)	0.6	2.08	0.9	1.63	-1.12 (-1.70, -0.54)
Tropical Latin America	3.0	3.08	7.2	3.03	-0.18 (-0.27, -0.10)	2.5	2.62	5.1	2.16	-0.81 (-0.88, -0.74)
Western Europe	26.3	4.78	25.3	3.19	-1.76 (-1.90, -1.63)	12.9	2.27	9.3	1.08	-2.98 (-3.12, -2.84)
Western Sub-Saharan Africa	1.4	1.47	2.4	1.33	-0.31 (-0.34, -0.28)	1.3	1.44	2.3	1.29	-0.36 (-0.40, -0.32)

SDI, socio-demographical index; ASIR, age-standardized incidence rate; ASMR, age-standardized mortality rate; EAPC, estimated average percentage change.


A
Case Number (X1000)
Year
B
Death Number (X1000)
Year
Female
Male
C
ASIR(/1e5)
Year
D
ASMR(/1e5)
Year
Both
Female
Male


ASIR
ASMR
EAPC (95% CI)
2
1
0
−1
−2
−3
−4
Global
High SDI
High−middle SDI
Middle SDI
Low−middle SDI
Low SDI
High−income Asia Pacific
Central Asia
East Asia
South Asia
Southeast Asia
Australasia
Caribbean
Central Europe
Eastern Europe
Western Europe
Andean Latin America
Central Latin America
Southern Latin America
Tropical Latin America
North Africa and Middle East
High−income North America
Oceania
Central Sub−Saharan Africa
Eastern Sub−Saharan Africa
Southern Sub−Saharan Africa
Western Sub−Saharan Africa


A
ASIR (/10^5)
0−1.0
1.1−2.0
2.1−3.0
3.1−4.0
>4.0
B
EAPC
−5.00~−2.50
−2.49~−1.00
−0.99~0
0.01~1.00
1.01~2.50
C
ASMR (/10^5)
0−1.0
1.1−1.5
1.6−2.0
2.1−2.5
>2.5
D
EAPC
−8.00~−2.50
−2.49~−1.00
−0.99~0
0.01~1.00
1.01~2.00


SDI Quintile
High SDI
High−middle SDI
Middle SDI
Low−middle SDI
Low SDI
A
ASMR in 2017 (/10^5)
ASIR in 2017 (/10^5)
B
EAPC of ASMR
EAPC of ASIR
C
ASIR in 2017 (/10^5)
SDI in 2017
D
ASMR in 2017 (/10^5)
SDI in 2017
E
EAPC of ASIR
SDI in 2017
F
EAPC of ASMR
SDI in 2017

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1, 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	4
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	Report numbers of outcome events or summary measures over time	6

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5-6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7-8
Generalisability	21	Discuss the generalisability (external validity) of the study results	7
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Temporal trends in incidence and mortality rates of laryngeal cancer at the global, regional, and national levels, 1990-2017

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Title:

Temporal trends in incidence and mortality rates of laryngeal cancer at the global, regional, and national levels, 1990-2017

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Running title: Epidemiology of laryngeal cancer

ABSTRACT

Objectives

Laryngeal cancer is the most prevalent entity of head and neck cancer. Knowing the trends of incidence and mortality of laryngeal cancer is important for the reduction in related disease burden.

Design

Population-based observational study

Main outcomes and measures

The incidence and mortality data of laryngeal cancer were retrieved from the Global Burden of Disease study 2017 online database. The estimated average percentage change was used to quantify the trends of laryngeal cancer incidence and mortality at the global, regional, and national levels.

Results

Globally, the numbers of incident cases and deaths due to laryngeal cancer increased 58.7% and 33.9%, respectively, from 1990 to 2017. However, the overall age-standardized incidence rate (ASIR) and age-standardized mortality rate (ASMR) decreased by 0.99% (95% CI 0.83%, 1.14%) and 1.62% (95% CI 1.50%, 1.74%) per year, respectively. These decreases were ubiquitous worldwide. However, unfavourable trends in the ASIR of laryngeal cancer were also observed in a total of 51 developing countries.

Conclusions

The incidence and mortality rates of laryngeal cancer have significantly decreased at the global level and in most countries over the past three decades. The regions that showed an increasing incidence trend deserve more attention.

Keywords Laryngeal cancer; incidence; mortality; global

Article summary

Strengths and limitations of this study

- We provided the most comprehensive description of laryngeal cancer incidence and mortality.

- The temporal trends of incidence and mortality are critical to update laryngeal cancer prevention strategies.
- The data used in this study lacked individual data.
- Laryngeal cancer cannot be further classified according to the anatomical position.

INTRODUCTION

Laryngeal carcinoma is the most common cancer site of the aerodigestive tract and accounts for 25-30% of all head and neck cancer cases [1]. In 2018, it was estimated that a total of 177,000 cases of laryngeal cancer and 95,000 related deaths occurred worldwide [2]. Laryngeal cancer is diagnosed more commonly in men than in women [2]. The most well-determined risk factors for laryngeal cancer include smoking and alcohol consumption [3, 4]. Owing to the disparities in risk factor distribution from country to country, the incidence and mortality patterns of laryngeal cancer are geographically heterogeneous [5]. In this context, a comprehensive description of the epidemiological characteristics of laryngeal cancer at the national level is needed. In addition, the incidence and mortality trends of laryngeal cancer were commonly reported together with those of other head and neck cancers (HNCs) [6]. Few studies have individually described and analysed the epidemiological features of laryngeal cancer in the international/global setting. However, due to the differences in the histology, pathology, clinical manifestation, and prognosis of HNC, separately knowing their evolving incidence and mortality rates is important for HNC prevention.

In the current study, leveraging the data from the 2017 Global Burden of Disease (GBD) study [7], we comprehensively described the epidemiology and analysed the temporal trends of incidence and mortality rates of laryngeal cancer at the global, regional, and national levels.

METHODS

Study data

The GBD study provides a tool to quantify health loss from hundreds of diseases, injuries, and risk factors so that health systems can be improved and disparities can be eliminated [7, 8]. GBD data have been widely used to assess the disease burden of cancers [5, 9]. Herein, we retrieved the incidence and mortality data of laryngeal cancer by sex, country or territory, region, and single calendar year from 1990 to 2017 using the online Global Health Data Exchange query tool. The electronic searches were complemented with additional epidemiologic measures such as "metric" (i.e., "rate" and "number"), "measure" (i.e., "incidence" and "deaths"), "year" (i.e., from 1990 to 2017), "sex" (i.e., "male" and "female"), "age" (i.e., "all ages" and "age-standardized") and "location". The data were available at four geographical levels: global (level 1); 5 regions in terms of sociodemographic index (SDI; i.e., high SDI, high-middle SDI, middle SDI, low-middle SDI, and low SDI; level 2); 21 GBD regions in terms of geography (e.g., Western Europe; level 3); and 195 countries or territories (e.g., China; level 4). The SDI is a composite indicator of development status that is strongly correlated with health outcomes. It is the geometric mean of 0 to 1 indexes of total fertility rate under the age of 25, mean education for those ages 15 and older, and lag-distributed income per capita. As a composite, a location with an SDI of 0 would have a theoretical minimum level of development relevant to health, while a location with an SDI of 1 would have a theoretical maximum level [10].

The collection and processing procedures of cancer data in GBD studies have been extensively described elsewhere [11, 12]. In brief, the crude incidence and mortality data were collected from cancer registries or aggregated databases of the cancer registry, such as "Cancer Incidence In Five Continents (CI5)". Data were excluded if they were not representative of the general population (e.g., hospital-based registries). Laryngeal cancer was identified by the ICD-10 codes C32-C32.9 and the ICD-9 codes 161-161.9 from the cancer databases. Most cancer registries only report cancer incidence. However, if a cancer registry also reported cancer mortality, mortality data were also extracted from the source to be used in the mortality to incidence estimation. For regions that lack incidence data, cancer incidence was estimated from cancer mortality using mortality to incidence ratios. These data were then modelled by cause of death ensemble modelling (CODEm), which is the framework used to model most cause-specific death rates in the GBD study [12, 13]. In brief, the CODEm approach is based on the principles that all types of available data should be used even if data quality varies; that individual models but also ensemble models should be tested for their predictive validity; and that the best model or sets of models should be chosen based on the out-of-sample predictive validity. Despite the advanced modelling strategies used in GBD studies, we should bear in mind that the estimates provided were based on modelling data rather than raw data. The national SDIs were also retrieved from the GBD online database.

Statistical analysis

We used the estimated average percentage change (EAPC) to quantify the trends of laryngeal cancer incidence and mortality from 1990 to 2017 [14]. The EAPC can be calculated from the regression model, which was fitted to the calendar years with the natural logarithm of the rates (i.e., $y = \alpha + \beta x + \varepsilon$, where $y = \ln(\text{rate})$, and x = calendar year) [15]. Pearson correlation tests were applied to assess the correlations between SDIs and other indexes (e.g., the incidence and the EAPC of incidence). All statistical analyses were performed using the R program (Version 3.6.3, R core team, Vienna, Austria). A P-value less than 0.05 was considered statistically significant.

Patient and public involvement

No patients were involved.

Results

Incidence and its trend for laryngeal cancer at the global, regional, and national levels

Globally, the number of incident cases of laryngeal cancer increased from 132.7 thousand in 1990 to 210.6 thousand in 2017 (Figure 1A; Table 1). Approximately 85% of total cases occurred in men (Table 1). The case numbers were highest in regions with high SDIs and decreased with the SDI levels. During the study period, the overall age-standardized incidence rate (ASIR) of laryngeal cancer experienced a significant decrease (EAPC = -0.99, 95% CI, -1.14, -0.83) (Figure 1B). The ASIR decreased with different magnitudes in different regions. The greatest reductions were observed in high-SDI regions (Table 1). For GBD regions, the highest ASIR and case number of laryngeal cancer were found in the Caribbean and East Asia, respectively, in 2017 (Table 1). Between 1990 and 2017, we found that only three of 21 GBD regions, namely, East Asia, the Caribbean, and Oceania, experienced significant increases in the ASIR (Table 1; Figure 1C). In the remaining GBD regions, the ASIR was significantly decreased, with the most pronounced reduction found in Andean Latin America (EAPC = -2.21, 95% CI, -2.41, -2.00) (Table 1; Figure 1C). In 2017, the ASIR of laryngeal cancer varied 12-fold worldwide. The highest ASIR was observed in Cuba (8.58/100,000), followed by Seychelles and Montenegro (Figure 1D). A total of 51 countries, most of which are located in developing regions, experienced significant increases in the ASIR of laryngeal cancer from 1990 to 2017 (Figure 1E). The greatest increase was found in Sri Lanka (EAPC = 2.31, 95% CI, 2.04, 2.58). In contrast, a total of 122 countries experienced significant decreases in the ASIR of laryngeal cancer (Figure 1E). The most marked reduction was seen in Bahrain (EAPC = -4.79, 95% CI, -5.37, -4.21).

Mortality and its trend for laryngeal cancer at the global, regional, and national levels

While the number of deaths from laryngeal cancer increased 33.9% between 1990 and 2017, the corresponding age-standardized mortality rate (ASMR) decreased by 1.62% per year during the same period (Table 1; Figure 2A& B). Most deaths occurred in men and in regions with low to medium SDIs (Table 1). The most significant reductions in the ASMR were found in high-SDI regions. Only one GBD region (i.e., Oceania) showed a significant increase in the ASMR of laryngeal cancer between 1990 and 2017. The ASMRs in the remaining GBD regions were significantly decreased (Table 1; Figure 2C). The greatest decrease was observed in high-income Asia Pacific (EAPC = -3.85, 95% CI, -4.14, -3.56). At the national level, the highest ASMR was found in

Pakistan (5.17/100,000) in 2017, followed by Cuba and Seychelles (Figure 2D). Between 1990 and 2017, 30 countries experienced significant increases in the ASMR. The greatest increase was found in Guinea (EAPC = 1.77, 95% CI, 1.56, 1.98), followed by Chad and Mongolia (Figure 2E). In contrast, a total of 150 countries experienced significant decreases in the ASMR of laryngeal cancer. The most marked reduction was found in South Korea (EAPC = -7.10, 95% CI, -7.81, -6.40) (Figure 2E).

The associations of SDI with laryngeal cancer-related indexes

We also assessed the associations of the SDI with laryngeal cancer-related indexes at the national level (Figure 3). As shown in Figure 3A & B, the ASIR and ASMR and their corresponding trends, quantified by the EAPC, of laryngeal cancer were both highly correlated ($\rho = 0.795$, $P < 0.001$; $\rho = 0.907$, $P < 0.001$). Countries with a higher SDI had a higher ASIR of laryngeal cancer (Figure 3C; $\rho = 0.369$, $P < 0.001$). However, this relationship was reversed for ASMR, although the correlation index was not statistically significant (Figure 3D; $\rho = -0.127$, $P = 0.079$). While no significant association was found between the SDI and the EAPC of ASIR (Figure 3E; $\rho = -0.120$, $P = 0.097$), a significantly negative association was found between the SDI and the EAPC of ASMR (Figure 3F; $\rho = -0.403$, $P < 0.001$). These findings suggest that countries with higher SDIs have made greater improvements in the treatment of laryngeal cancer than those with lower SDIs.

DISCUSSION

In this study, we reported the incidence and mortality trends of laryngeal cancer at the global, regional, and national levels. In brief, our findings showed high geographical heterogeneity in both the incidence and mortality rates of laryngeal cancer worldwide. We observed significant decreasing trends in the incidence and mortality rates of laryngeal cancer at the global level and in most countries between 1990 and 2017. These reductions suggested the efficacy of current prevention strategies and highlighted the importance of continuous application and even strengthening of these strategies. However, we also observed unfavourable trends in the incidence of laryngeal cancer in a few countries. Most of these countries were located in East Asia and North Africa in areas that lacked advanced economies. Owing to the large population sizes in these countries, the increase in laryngeal cancer incidence might suggest a considerable disease burden of this malignant carcinoma.

Several risk factors have been implicated in the pathogenesis of laryngeal cancer. The most significant of these are tobacco use and alcohol consumption. In addition, the risk of laryngeal cancer increases with the amount of alcohol consumed [16]. In previous studies conducted in North America, Europe, Japan, and Korea, the multivariate relative risks for the highest levels of consumption ranged between 2 and 10 and were 1.94 for 50 g/day and 3.95 for 100 g/day in a meta-analysis of 20 studies [17]. In our study, we found that the incidence of laryngeal cancer was higher in Europe, where alcohol consumption is higher than the global average [18]. The decreasing trend of laryngeal cancer incidence might be partly attributed to the reduction of alcohol use in these countries. In a recent study conducted in Great Britain, the authors found that for those born post-1985, alcohol abstention rates are increasing and male consumption is decreasing relative to preceding cohorts [19]. However, in a large-scale modelling study [20], the authors reported that between 1990 and 2017, global adult per capita consumption increased from 5.9 L to 6.5 L and is forecasted to reach 7.6 L by 2030. In parallel, globally, the prevalence of lifetime abstinence decreased from 46% in 1990 to 43% in 2017 and is predicted to further decrease to 40% in 2030. These results alarmed us that the global goals for reducing the harmful use of alcohol are unlikely to be achieved and that alcohol use-related diseases, including laryngeal cancer, remain the major challenges for human health. In this unfavourable context, although we have seen a significant reduction in the incidence of laryngeal cancer in most countries over the past three decades, the primary preventive strategy of decreasing alcohol use is worth strengthening, such as by increasing the tax of alcohol beverages and strictly forbidding sales to children and adolescents.

Tobacco use has also been shown to have a linear association with the development of laryngeal cancer, with a risk for smokers that is 10 to 15 times higher than the risk for nonsmokers, and the heaviest smokers have as much as a 30 times greater risk [21]. Fortunately, owing to persistent efforts to combat tobacco use, such as the Framework Convention on Tobacco Control, the prevalence of daily smoking has declined for both men and women in many countries [22]. However, given the continuing increase in the number of smokers worldwide and the rapid emergence of new tobacco products, additional efforts are needed to achieve a smoke-free world, help smokers quit, and protect youth from initiating tobacco use [22].

Despite the global decrease in the incidence of laryngeal cancer, of note are the unexpected increases in this rate in a few developing countries, such as China and Vietnam. We suspected that these increases might be partly explained by the following reasons: 1) since the improvement of health care services and the cancer surveillance system, more laryngeal cancer cases have been diagnosed and recorded; and 2) the prevalence rates of risk factors, especially smoking, are high in these countries [23, 24]. For example, the implementation of tobacco control policies in China since the signing of the WHO Framework Convention on Tobacco Control in 2003 has not been effective in reducing smoking prevalence. Smoking prevalence among adolescents of both sexes has increased substantially, and there has been a steady increase in smoking among young women [23]. A similar phenomenon was observed in Vietnam, in which the reduction in the prevalence of tobacco smoking during the last 5 years was not as high as expected, especially in rural areas [24]. These findings highlight that more practical and effective policies targeting smoking are urgently needed.

In our study, we also observed a ubiquitous decrease in the mortality rate of laryngeal cancer. Unsurprisingly, the greatest reductions were mostly seen in developed countries. The development of the mortality rate of laryngeal cancer was largely based on the evolution of incidence and was likely also due to changes in medical practices, including screening, diagnosis and treatment [1]. Taking radiotherapy as an example, Atun et al. reported that the coverage of radiotherapy was positively associated with gross national income [25]. Moreover, countries with a relatively higher income will benefit more from investment in radiotherapy than countries with lower or lower-middle income [25]. Scheduled and opportunistic screening, coupled with efforts to enhance education and health behaviour modification, are highly recommended for predefined, high-risk, targeted populations [26]. These measures can enable early detection and therefore improve mortality. Previous studies have demonstrated the feasibility of developing and implementing large-scale community-based head and neck cancer screenings [27].

The limitations of this study should be noted here. First, all data used in our study were retrieved from GBD studies, which were obtained from mathematical models based on surveillance data rather than the surveillance data itself. Therefore, for countries that lack useable cancer surveillance data, the incidence and mortality of laryngeal cancer are estimated from mathematical models and should be interpreted with caution. In other words, the data used in our study were largely dependent on the quality and quantity of data used in the modelling. For example, the cancer surveillance system was generally more complete in developed countries than in developing countries, which might lead to a larger number of reported cancer cases or a higher ASIR/ASMR of cancer in developed countries. However, GBD studies incorporate sparse data worldwide and provide the most comprehensive data source for the study of cancer disease burden. Second, because of a lag in data availability, estimates for the most recent years are based on past time trends and covariates rather than data, which is reflected in the larger uncertainty [5]. Finally, we cannot specify laryngeal cancer into several subgroups (e.g., glottic carcinoma and supraglottic carcinoma) according to the anatomical position because of data unavailability. A previous study reported that the temporal trends differed markedly between cancers of different anatomical subsites [28]. Moreover, different subtypes of laryngeal cancer might be considered different entities that are distinct in clinicopathological and immunohistochemical staining characteristics [29].

In conclusion, we reported global decreases in both the incidence and mortality of laryngeal cancer over the past three decades. These decreases suggest the effectiveness of the control of tobacco and alcohol use. However, unfavourable increases in the incidence of laryngeal cancer were observed in a few developing countries. More targeted and potent prevention strategies for laryngeal cancer are therefore warranted.

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Disclosure statement

No potential conflict of interest was reported by the authors.

Authors' contributions:

Conceptualization: J.Y.W. and Q.W.Z.; Data curation: J.Y.W., Q.W.Z., and K.X.W.; Formal analysis: J.Y.W. and Q.W.Z.; Methodology: C.W. and J.Y.W.; Software X.L.J, and L.X.Z.; Supervision: J.Y.W. and L.X.Z.; Roles/Writing - original draft: all authors; Writing - review & editing: all authors.

Data sharing:

The data used in our study were available at online Global Health Data Exchange query tool (http://ghdx.healthdata.org/gbd-2017).

Ethics approval statement:

Ethics approval is not applicable for this study due to only public data were used. No individual data or human participants were involved.

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Figure legends

Figure 1. Epidemiological features of laryngeal cancer incidence.
(A) the temporal trends of incident case number and (B) age-standardized incidence rate (ASIR) of laryngeal cancer at the global level between 1990 and 2017. (C) the temporal trend of ASIR of laryngeal cancer at the regional level between 1990 and 2017. (D) the ASIR of laryngeal cancer at the national level in 2017. (E) the temporal trend of ASIR of laryngeal cancer at the national level between 1990 and 2017.

Figure 2. Epidemiological features of laryngeal cancer mortality.
(A) the temporal trends of incident death number and (B) age-standardized mortality rate (ASMR) of laryngeal cancer at the global level between 1990 and 2017. (C) the temporal trend of ASMR of laryngeal cancer at the regional level between 1990 and 2017. (D) the ASMR of laryngeal cancer at the national level in 2017. (E) the temporal trend of ASMR of laryngeal cancer at the national level between 1990 and 2017.

Figure 3. The associations between the national sociodemographic index (SDI) and laryngeal cancer-related indexes. (A), the association between age-standardized incidence rate [ASIR] and age-standardized mortality rate [ASMR] of laryngeal cancer in 2017; (B), the association between changing trends of ASIR and ASMR; (C), the correlations of SDI with ASIR of laryngeal cancer; (D), the correlations of SDI with ASMR of laryngeal cancer; (E), the correlations of SDI with the changing trends of ASIR of laryngeal cancer; (F), the correlations of SDI with the changing trends of ASMR of laryngeal cancer.

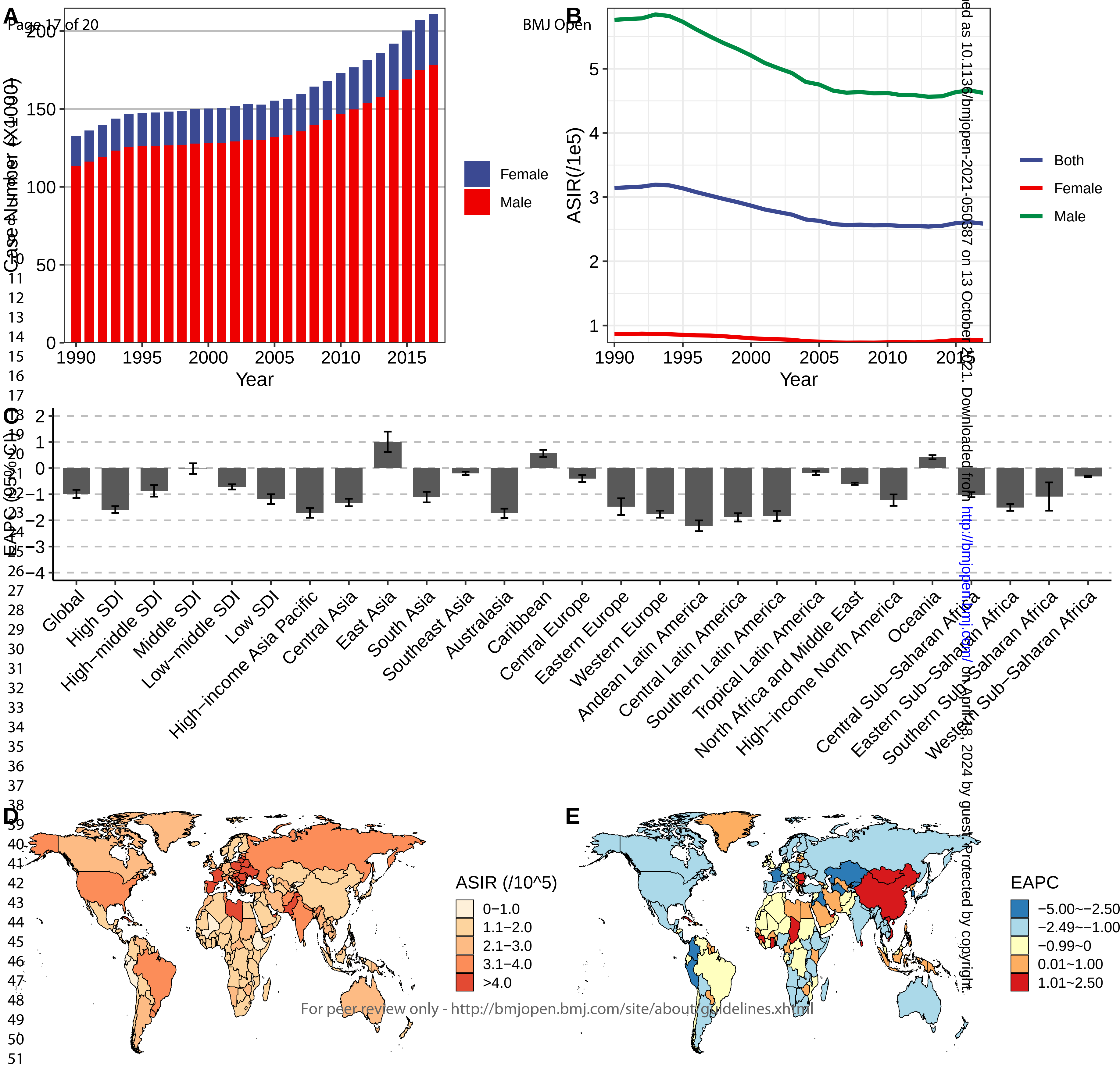
Table 1. The incidence and mortality of larynx cancer in 1990 and 2017 and the temporal trends between 1990 and 2017, by sex, SDI region, and GBD region.

	Age-standardized incidence rate					**Age-standardized mortality rate**				
	1990		2017		1990-2017	1990		2017		1990-2017
	Case number (×1000)	ASIR ($/10^5$)	Case number (×1000)	ASIR ($/10^5$)	EAPC (95% CI)	Death number (×1000)	ASMR ($/10^5$)	Death number (×1000)	ASMR ($/10^5$)	EAPC (95% CI)
Global	132.7	3.14	210.6	2.59	-0.99 (-1.14, -0.83)	94.5	2.27	126.5	1.57	-1.62 (-1.74, -1.50)
Sex										
Male	113.3	5.76	178.0	4.63	-1.08 (-1.23, -0.93)	79.5	4.17	105.6	2.80	-1.71 (-1.82, -1.59)
Female	19.4	0.87	32.6	0.77	-0.66 (-0.83, -0.50)	15.0	0.68	20.9	0.49	-1.40 (-1.56, -1.25)
SDI regions										
High	48.9	3.91	57.8	2.82	-1.58 (-1.71, -1.46)	22.9	1.81	19.7	0.92	-2.83 (-2.96, -2.70)
High-middle	30.2	3.04	49.5	2.68	-0.87 (-1.09, -0.65)	23.0	2.37	26.6	1.46	-2.25 (-2.44, -2.06)
Middle	20.8	2.10	49.1	2.17	-0.02 (-0.22, 0.18)	18.0	1.90	32.5	1.48	-1.07 (-1.19, -0.95)
Low-middle	18.8	3.11	32.6	2.64	-0.72 (-0.82, -0.62)	17.3	2.97	28.2	2.36	-0.95 (-1.02, -0.87)
Low	13.8	3.88	20.8	2.84	-1.19 (-1.38, -1.00)	13.0	3.80	19.0	2.68	-1.32 (-1.48, -1.15)
GBD region										
Andean Latin America	0.3	1.48	0.5	0.90	-2.21 (-2.41, -2.00)	0.3	1.44	0.4	0.75	-2.80 (-3.01, -2.59)
Australasia	0.7	3.01	1.0	2.08	-1.73 (-1.91, -1.55)	0.3	1.20	0.3	0.60	-2.94 (-3.11, -2.77)
Caribbean	1.1	3.97	2.4	4.64	0.56 (0.43, 0.70)	0.8	3.12	1.5	3.02	-0.16 (-0.26, -0.05)
Central Asia	1.5	2.95	1.7	2.20	-1.32 (-1.46, -1.17)	1.2	2.47	1.2	1.64	-1.76 (-1.94, -1.58)
Central Europe	7.2	4.68	8.7	4.39	-0.40 (-0.53, -0.26)	5.3	3.48	5.0	2.44	-1.51 (-1.63, -1.38)
Central Latin America	1.8	2.15	3.4	1.48	-1.88 (-2.04, -1.73)	1.6	1.96	2.5	1.11	-2.52 (-2.66, -2.39)
Central Sub-Saharan Africa	0.5	1.98	0.8	1.55	-1.02 (-1.11, -0.92)	0.5	2.00	0.8	1.53	-1.09 (-1.18, -1.01)

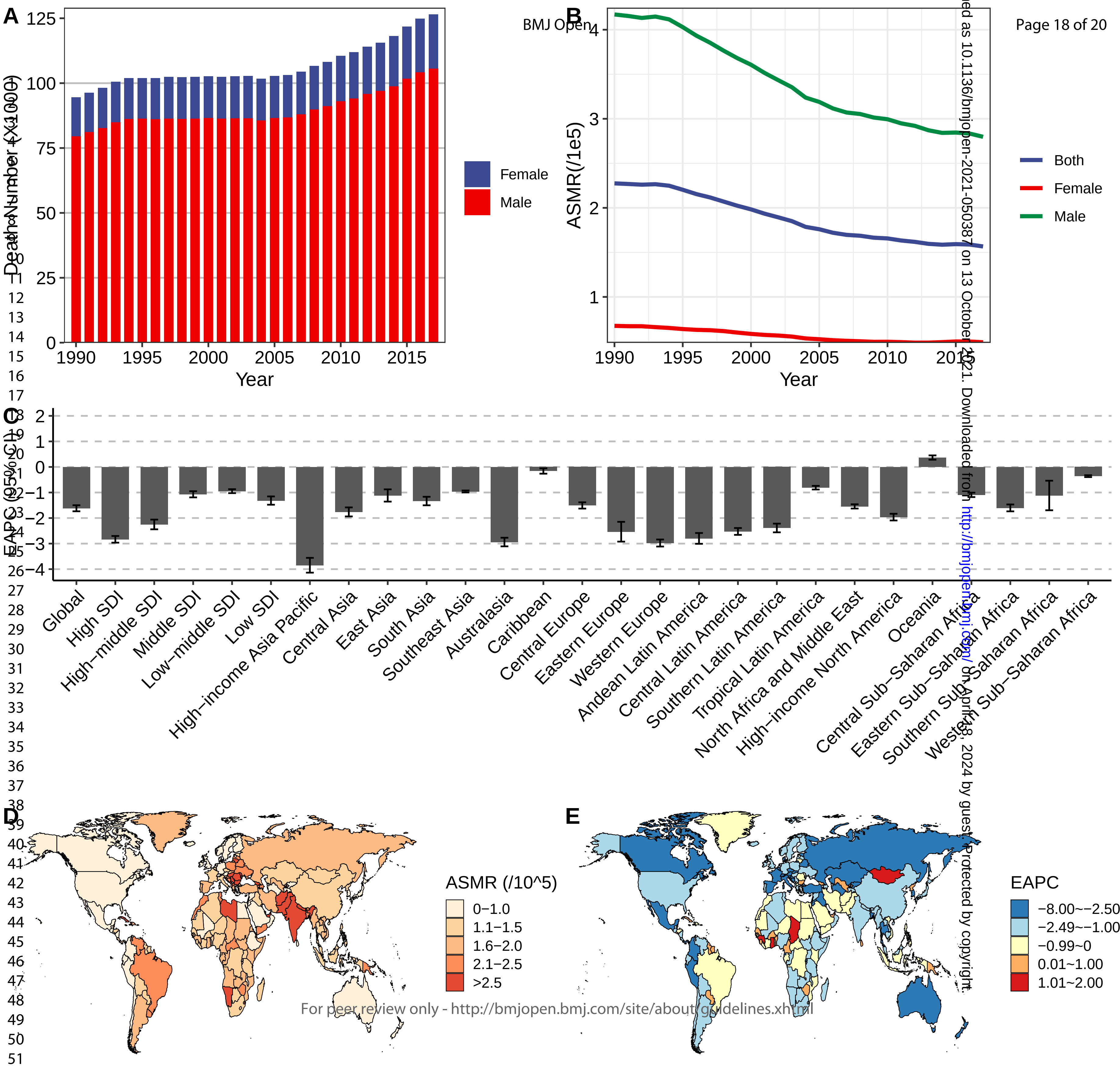
East Asia	14.4	1.53	41.9	1.98	1.01 (0.62, 1.40)	12.0	1.33	20.4	1.00	-1.12 (-1.36, -0.88)
Eastern Europe	13.2	4.52	12.3	3.67	-1.48 (-1.79, -1.15)	9.4	3.20	6.9	2.02	-2.54 (-2.92, -2.15)
Eastern Sub-Saharan Africa	1.6	1.92	2.3	1.38	-1.51 (-1.64, -1.38)	1.5	1.89	2.2	1.33	-1.60 (-1.74, -1.47)
High-income Asia Pacific	4.8	2.28	6.9	1.64	-1.71 (-1.90, -1.53)	1.7	0.84	1.7	0.36	-3.85 (-4.14, -3.56)
High-income North America	12.7	3.71	18.6	3.11	-1.22 (-1.44, -1.01)	5.0	1.41	5.7	0.92	-1.96 (-2.09, -1.83)
North Africa and Middle East	4.9	2.71	10.1	2.33	-0.60 (-0.64, -0.56)	4.3	2.46	6.8	1.66	-1.54 (-1.63, -1.46)
Oceania	0.1	1.91	0.1	2.05	0.42 (0.34, 0.50)	0.1	1.79	0.1	1.88	0.37 (0.28, 0.45)
South Asia	29.7	4.62	50.6	3.57	-1.11 (-1.31, -0.90)	27.6	4.45	44.3	3.22	-1.33 (-1.50, -1.17)
Southeast Asia	5.3	1.95	11.5	1.89	-0.20 (-0.27, -0.14)	4.6	1.76	8.0	1.38	-0.96 (-1.00, -0.92)
Southern Latin America	1.6	3.42	1.9	2.32	-1.83 (-2.02, -1.65)	1.2	2.62	1.2	1.48	-2.39 (-2.56, -2.22)
Southern Sub-Saharan Africa	0.7	2.30	1.1	1.84	-1.09 (-1.63, -0.55)	0.6	2.08	0.9	1.63	-1.12 (-1.70, -0.54)
Tropical Latin America	3.0	3.08	7.2	3.03	-0.18 (-0.27, -0.10)	2.5	2.62	5.1	2.16	-0.81 (-0.88, -0.74)
Western Europe	26.3	4.78	25.3	3.19	-1.76 (-1.90, -1.63)	12.9	2.27	9.3	1.08	-2.98 (-3.12, -2.84)
Western Sub-Saharan Africa	1.4	1.47	2.4	1.33	-0.31 (-0.34, -0.28)	1.3	1.44	2.3	1.29	-0.36 (-0.40, -0.32)

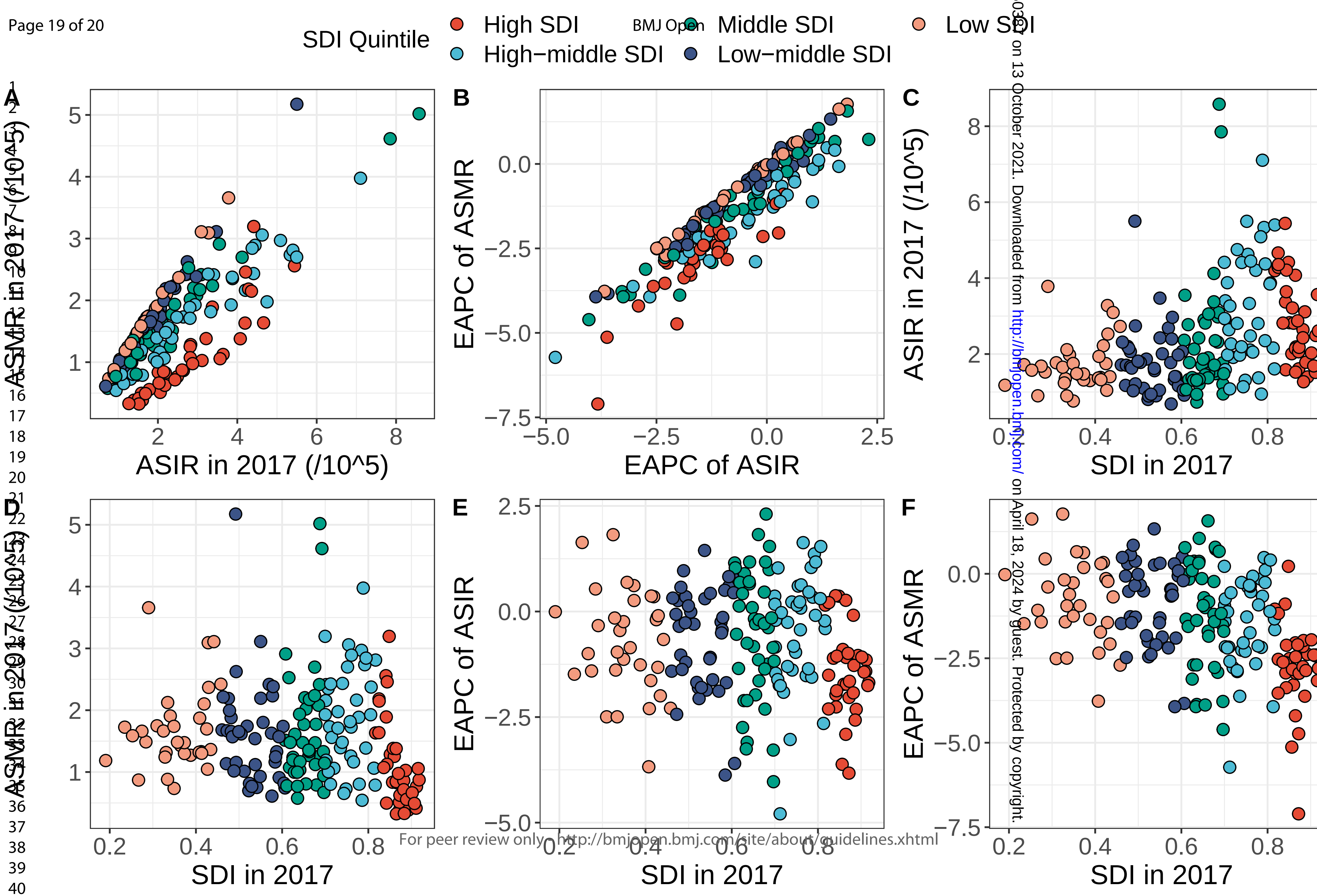
SDI, socio-demographical index; ASIR, age-standardized incidence rate; ASMR, age-standardized mortality rate; EAPC, estimated average percentage change.

BMJ Open



A
Case Number (X1000)
Year
Female
Male
B
ASIR(/1e5)
Year
Both
Female
Male
C
EAPC (95% CI)
Global
High SDI
High−middle SDI
Middle SDI
Low−middle SDI
Low SDI
High−income Asia Pacific
Central Asia
East Asia
South Asia
Southeast Asia
Australasia
Caribbean
Central Europe
Eastern Europe
Western Europe
Andean Latin America
Central Latin America
Southern Latin America
Tropical Latin America
North Africa and Middle East
High−income North America
Oceania
Central Sub−Saharan Africa
Eastern Sub−Saharan Africa
Southern Sub−Saharan Africa
Western Sub−Saharan Africa
D
ASIR (/10^5)
0−1.0
1.1−2.0
2.1−3.0
3.1−4.0
>4.0
E
EAPC
−5.00~−2.50
−2.49~−1.00
−0.99~0
0.01~1.00
1.01~2.50


A
Death Number (X1000)
125
100
75
50
25
0
1990
1995
2000
2005
2010
2015
Year
Female
Male
B
ASMR(/1e5)
4
3
2
1
Year
Both
Female
Male
C
EAPC (95% CI)
Global
High SDI
High−middle SDI
Middle SDI
Low−middle SDI
Low SDI
High−income Asia Pacific
Central Asia
East Asia
South Asia
Southeast Asia
Australasia
Caribbean
Central Europe
Eastern Europe
Western Europe
Andean Latin America
Central Latin America
Southern Latin America
Tropical Latin America
North Africa and Middle East
High−income North America
Oceania
Central Sub−Saharan Africa
Eastern Sub−Saharan Africa
Southern Sub−Saharan Africa
Western Sub−Saharan Africa
D
ASMR (/10^5)
0−1.0
1.1−1.5
1.6−2.0
2.1−2.5
>2.5
E
EAPC
−8.00~−2.50
−2.49~−1.00
−0.99~0
0.01~1.00
1.01~2.00


SDI Quintile
High SDI
Middle SDI
Low SDI
High−middle SDI
Low−middle SDI
A
ASMR in 2017 (/10^5)
ASIR in 2017 (/10^5)
B
EAPC of ASMR
EAPC of ASIR
C
ASIR in 2017 (/10^5)
SDI in 2017
D
ASMR in 2017 (/10^5)
SDI in 2017
E
EAPC of ASIR
SDI in 2017
F
EAPC of ASMR
SDI in 2017

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1, 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	4
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	Report numbers of outcome events or summary measures over time	6

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5-6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7-8
Generalisability	21	Discuss the generalisability (external validity) of the study results	7
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.