

# Global Magnitude and Temporal Trend of Mesothelioma Burden Along with the Contribution of Occupational Asbestos Exposure in 204 Countries and Territories From 1990 to 2019: Results from the Global Burden of Disease Study 2019

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## Research

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# Abstract

## Background

Understanding the annual incidence, mortality, and disability-adjusted life-years (DALYs) for mesothelioma globally provides essential foundations for cancer control, policy decisions and resource allocation.

## Materials and methods

Complying with the Global Burden of Disease Study 2019, we extracted the data of incidences, deaths and DALYs in 204 countries and territories from 1990 to 2019. Average annual percentage changes were used to quantify the temporal trends in mesothelioma burden. Besides, the population attributable fractions of the risk factor of mesothelioma were also estimated.

## Results

Globally, 34511 (95% uncertainty intervals[UI]: 31199, 37771) incident cases, 29251 (95%UI: 26668, 31006) deaths and 668104 (95%UI: 608269, 716475) DALYs of mesothelioma were estimated in 2019. The age-standardized rates of incidence, mortality and DALYs all showed a slightly declining trend over the past 30 years, but the latest absolute number of mesothelioma burden almost doubled since 1990. The age-standardized burden of mesothelioma among men was around 3 times more than women in 2019, which decreased among women while remained stable among men. The burden rate decreased among the population aged under 70 years, but increased among the population aged over 80 years, especially in the High socio-demographic index (SDI) region. The age-standardized DALYs rate (ASDR) of mesothelioma attributable to occupational asbestos exposure in 2019 was positively associated with SDI at the national levels ( $\rho = 0.3105$ ,  $P = 6.2e-06$ ).

## Conclusion

This study depicted a continuous increase in incidences, deaths and DALYs of mesothelioma globally over the past 30 years. Controlling occupational asbestos exposure will reduce the mesothelioma burden, especially for higher SDI regions.

## Introduction

Malignant mesothelioma is an aggressive, treatment-resistant cancer and its median survival time ranges from 4 to 12 months from diagnosis<sup>1-3</sup>. It is largely caused by asbestos exposure with an estimated proportion at 80% or more, other possible causes or contributing factors include family history, related germline gene mutations (such BAP1 and BML), ionizing radiation and exposure to other mineral fibers

such as erionite fibers in Turkey<sup>4-7</sup>. It has been estimated worldwide that 30870 new cases and 26278 new deaths of mesothelioma occurred in 2020, with huge regional disparity<sup>8</sup>. Mesothelioma is commonly diagnosed at older ages as its latency period is typically longer than 30 years, and for which the incidence and mortality rates are much higher in male individuals than female individuals<sup>9-10</sup>. There is no curative treatment for mesothelioma, with systemic treatment options including chemotherapy, radiotherapy and targeted therapy. Current unimodal or multimodal treatment is usually of little benefit<sup>2 11</sup>. A large proportion of cases have a well-established causal relationship between exposure to asbestos and the development of malignant mesothelioma, while recent studies revealed that the cessation of exposure may not reduce risk in exposed individuals<sup>12</sup>. Therefore, reasonable and effective prevention programs can better reduce the mesothelioma burden and medical expenses. By 1990, the use of asbestos in most industrialized countries had been reduced by at least 75% from the peak asbestos consumption. Iran, Korea, Chile, and Egypt reached the same level of reduction of asbestos usage in 1999, as did Nigeria, Zimbabwe, the United Arab Emirates, Ukraine, and Kazakhstan between 2000 and 2005<sup>13</sup>. The huge geographic disparity and poorly characterized epidemiologic trends represent the complexity in the intervention of mesothelioma<sup>14</sup>. This highlights the need for the latest spatial distribution and temporal trends of mesothelioma across the world, which are the basic prerequisites for policy decisions and resource allocation. Researchers have presented the estimation of mesothelioma burden of 195 countries and territories based on the study of Global Burden of Disease, Injuries, and Risk Factors (GBD) 2017, which found that incident cases and deaths of mesothelioma continuously increased worldwide, especially in resource-limited regions with low sociodemographic index (SDI) levels<sup>15</sup>.

The GBD study 2019 is the most recent comprehensive and comparable data set evaluating epidemiologic levels and trends of 369 diseases along with 87 risk factors globally, which has incorporated new datasets, enhanced method performance and standardization, therefore superseding previously published GBD estimates<sup>16-17</sup>. For example, compared with GBD 2017, the mortality-to-incidence ratio estimates in GBD 2019 were updated using lower case inclusion criteria and different model hyperparameters, resulting in more training data and less smoothing across time and geography. Nevertheless, there has been no study analyzing the latest mesothelioma burden and trends based on the GBD study 2019 until now. Therefore, the aim of this study was to use data from the GBD 2019 study to determine the global, regional, and national burdens of mesothelioma across 204 countries and territories between 1990 and 2019 by age, sex, and SDI. The findings would help increase the world's attention to mesothelioma, as well as design specific strategies for the prevention and intervention of mesothelioma for different regions respectively.

## Methods

### Data source

The exhaustive study framework and analysis methodology of the GBD 2019 study have been depicted in previous articles by the GBD collaborators<sup>16 18</sup>. The estimation of cancer burden in the GBD study across

the world was calculated based on many original national cancer registry systems and the combined databases of cancer registries, including Cancer Incidence in Five Continents (CI5), Surveillance, Epidemiology, and End Results (SEER), and NORDCAN. Moreover, GBD 2019 utilized all data from GBD 2017 and further added cancer registry data from other 14 countries, including Argentina, China, Uruguay, etc. Detailed information on the original cancer burden used in the GBD 2019 study can be collected by the GBD 2019 Data Input Sources Tool (<http://ghdx.healthdata.org/gbd-2019/data-input-sources>). The analysis process focusing on the mesothelioma burden in the GBD 2019 study complies with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) statements (Supplementary report checklist). The mesothelioma cases were identified based on the ICD10 codes pertaining to mesothelioma (C45-C45.2, C45.7, and C45.9) in the cancer systems. The detailed analysis flowchart and statistical codes for cancer burden estimation in the GBD study could be retrieved from the online supporting website: <http://ghdx.healthdata.org/gbd-2019/code/cod-2>. In short, the burden of mesothelioma in the GBD 2019 Study was estimated by the following steps<sup>18-19</sup>: (1) Calculate the mortality-to-morbidity ratio (MIR) of mesothelioma based on all data sources including both morbidity and mortality, and further predict the MIR for all locations using the Healthcare Access and Quality Index; (2) Collect the incidence of mesothelioma from all cancer registries; (3) Estimate the mesothelioma mortality by multiplying the incidence data and the corresponding MIR; (4) Input all mesothelioma mortality information into the death database of mesothelioma, and calculate the cancer-specific mortality of mesothelioma using the Cause of Death Ensemble model (CODEm) process; (5) Further assess the incidence of mesothelioma by the estimated cancer-specific mortality of mesothelioma and MIR.

The 95% uncertainty intervals (UIs) of all estimates in the GBD 2019 Study were calculated as the 25th and 975th-ordered percentiles of 1000 random draws based on the uncertainty distribution<sup>16</sup>. We extracted data on incidence, mortality, disability-adjusted life-years (DALYs), and its age-standardized rate (ASR) per 100 000 person-year of mesothelioma in 204 countries and territories by gender and 5-year age group, covering the period of 1990–2019 via the Global Health Data Exchange query tool (<https://ghdx.healthdata.org/gbd-results-tool>). To describe the disease burden of mesothelioma in different geographic units, 204 countries and territories were classified into seven super GBD regions based on geographic location and socioeconomic development, namely, High-income, Central Europe and Eastern Europe and Central Asia, Southeast Asia and East Asia and Oceania, South Asia, Sub-Saharan Africa, North Africa and Middle East, Latin America and Caribbean, which were further divided into 21 GBD regions according to a geographic hierarchy by the GBD collaborators, such as Western Europe, East Asia, and Australasia (Table 1). Moreover, the world was also simplified into five regions based on the corresponding SDI, namely, low, low-middle, middle, high-middle, and high SDI regions. The SDI could reflect the national healthcare development based on a country's lag-distributed income per capita, average years of schooling, and the total fertility rate in females under the age of 25 years<sup>16</sup>. According to the well-established inclusion criterion in GBD 2019 Study for a risk–outcome pair, only occupational exposure to asbestos was judged to have sufficient evidence to prove a causal association with mesothelioma from potential behavioral, environmental and occupational, and metabolic risk factors.

The disease burden attributable to potential risk factors was assessed via the GBD comparative risk assessment framework, which includes the assessment of risk–outcome pairs, relative risks, theoretical minimum risk exposure level, and population attributable fraction<sup>17</sup>.

Table 1

Incidence and age-standardized incidence rate per 100 000 people of mesothelioma in 1990 and 2019, and its average annual percentage change from 1990 to 2019.

Characteristics	1990		2019		AAPC of ASIR (95%CI) from 1990 to 2019
	ASIR/100 000 (95%UI)	Incident cases (95%UI)	ASIR/100 000 (95%UI)	Incident cases (95%UI)	
<b>Global</b>	0.49 (0.44, 0.54)	19072 (17055, 21157)	0.43 (0.38, 0.47)	34511 (31199, 37771)	-0.36 (-0.41, -0.3)
Male	0.76 (0.71, 0.84)	12899 (12107, 14391)	0.69 (0.62, 0.75)	25170 (22936, 27562)	-0.15 (-0.24, -0.07)
Female	0.29 (0.21, 0.36)	6173 (4401, 7981)	0.22 (0.16, 0.25)	9341 (6843, 10655)	-1.02 (-1.06, -0.97)
<b>SDI region</b>					
High SDI	1.01 (0.94, 1.10)	10596 (9880, 11548)	0.91 (0.81, 1.02)	17548 (15610, 19554)	-0.22 (-0.28, -0.17)
High-middle SDI	0.41 (0.35, 0.49)	4426 (3817, 5338)	0.36 (0.32, 0.40)	7234 (6385, 8000)	-0.45 (-0.55, -0.34)
Middle SDI	0.19 (0.16, 0.23)	2139 (1761, 2625)	0.19 (0.17, 0.21)	4797 (4312, 5267)	0.08 (-0.01, 0.18)
Low-middle SDI	0.21 (0.14, 0.29)	1331 (901, 1936)	0.25 (0.20, 0.31)	3505 (2852, 4346)	0.84 (0.74, 0.93)
Low SDI	0.22 (0.11, 0.47)	570 (262, 1165)	0.21 (0.13, 0.38)	1151 (681, 2029)	-0.13 (-0.26, 0.00)
<b>GBD Region</b>					
High-income Asia Pacific	0.40 (0.36, 0.45)	796 (728, 905)	0.47 (0.39, 0.55)	2102 (1747, 2468)	1.18 (0.93, 1.44)
High-income North America	0.86 (0.81, 0.92)	3073 (2885, 3321)	0.70 (0.59, 0.81)	4487 (3822, 5210)	-0.93 (-1.05, -0.81)
Western Europe	1.34 (1.22, 1.47)	7732 (7069, 8474)	1.33 (1.16, 1.52)	12080 (10554, 13696)	0.16 (0.09, 0.24)

Characteristics	1990		2019		AAPC of ASIR (95%CI) from 1990 to 2019
	ASIR/100 000 (95%UI)	Incident cases (95%UI)	ASIR/100 000 (95%UI)	Incident cases (95%UI)	
Australasia	2.49 (2.16, 3.05)	593 (513, 728)	2.20 (1.75, 2.76)	1131 (897, 1414)	-0.36 (-0.46, -0.26)
Southern Latin America	0.37 (0.33, 0.44)	170 (154, 204)	0.46 (0.36, 0.59)	380 (296, 482)	1.43 (1.15, 1.71)
Andean Latin America	0.50 (0.30, 0.67)	107 (64, 146)	0.25 (0.19, 0.32)	144 (107, 185)	-3.47 (-4.02, -2.92)
Tropical Latin America	0.52 (0.42, 0.62)	511 (409, 650)	0.49 (0.42, 0.55)	1195 (1021, 1350)	-0.05 (-0.17, 0.07)
Central Latin America	0.24 (0.21, 0.27)	221 (191, 245)	0.27 (0.23, 0.31)	654 (551, 756)	0.63 (0.46, 0.81)
Caribbean	0.25 (0.21, 0.31)	68 (57, 85)	0.23 (0.18, 0.28)	117 (95, 147)	-0.51 (-0.65, -0.37)
Eastern Europe	0.34 (0.23, 0.64)	934 (637, 1733)	0.35 (0.27, 0.46)	1115 (884, 1396)	-0.61 (-1.00, -0.22)
Central Europe	0.22 (0.20, 0.27)	330 (300, 406)	0.33 (0.28, 0.37)	665 (574, 754)	1.78 (1.62, 1.95)
Central Asia	0.29 (0.16, 0.61)	150 (80, 340)	0.27 (0.19, 0.37)	211 (151, 297)	-1.04 (-1.38, -0.7)
North Africa and Middle East	0.33 (0.24, 0.47)	599 (442, 895)	0.26 (0.21, 0.34)	1184 (946, 1520)	-0.83 (-0.96, -0.69)
South Asia	0.20 (0.14, 0.31)	1211 (802, 1911)	0.24 (0.19, 0.31)	3468 (2745, 4515)	0.62 (0.51, 0.73)
Southeast Asia	0.19 (0.15, 0.24)	604 (468, 781)	0.19 (0.15, 0.22)	1238 (994, 1483)	-0.40 (-0.59, -0.22)
East Asia	0.14 (0.11, 0.19)	1272 (969, 1789)	0.14 (0.12, 0.17)	2968 (2433, 3508)	0.84 (0.52, 1.16)

Characteristics	1990		2019		AAPC of ASIR (95%CI) from 1990 to 2019
	ASIR/100 000 (95%UI)	Incident cases (95%UI)	ASIR/100 000 (95%UI)	Incident cases (95%UI)	
Oceania	0.24 (0.17, 0.33)	8 (6, 11)	0.30 (0.21, 0.43)	24 (16, 35)	1.19 (1.03, 1.34)
Western Sub-Saharan Africa	0.16 (0.09, 0.27)	158 (85, 261)	0.12 (0.08, 0.19)	272 (183, 419)	-1.32 (-1.58, -1.06)
Eastern Sub-Saharan Africa	0.30 (0.10, 0.88)	241 (80, 670)	0.28 (0.11, 0.80)	475 (193, 1322)	-0.41 (-0.54, -0.29)
Central Sub-Saharan Africa	0.31 (0.11, 0.85)	75 (26, 195)	0.28 (0.11, 0.73)	159 (65, 416)	-0.47 (-0.59, -0.35)
Southern Sub-Saharan Africa	0.78 (0.58, 1.00)	216 (163, 275)	0.80 (0.65, 0.90)	441 (362, 495)	-0.19 (-0.74, 0.36)

ASIR, age-standardized incidence rate; UI, uncertainty interval; AAPC, average annual percentage change; CI, confidential interval; SDI, socio-demographic index; GBD, Global Burden of Disease, Injuries, and Risk Factors Study.

## Statistical Analyses

To eliminate the difference of the age composition of the populations, the age-standardized incidence rate (ASIR), age-standardized mortality rate (ASMR) and age-standardized DALY rate (ASDR) were calculated to compare the difference among different geographical areas, historical periods, and sexes, according to the standard age composition of GBD world population<sup>20</sup>. The average annual percentage change (AAPC) was widely used to estimate the overall temporal trend in burden rate of disease, which was derived via the following regression model,  $\ln(\text{burden rate}) = \alpha + \beta * \text{calendar year} + \epsilon$ , and the AAPC with its 95% confidence interval (CI) were calculated based on the formula of  $100 \times (\exp(\beta) - 1)$ <sup>19 21–22</sup>. In our study, the lower boundary of the 95%CI more than 0 indicated an increasing trend, conversely, the upper boundary of its 95%CI less than 0 indicated a decreasing trend. Otherwise, the burden rate was deemed to be relatively stable over the study period.

In addition, to explore the changing pattern of AAPCs in the burden rates of mesothelioma in 204 countries and territories, we applied the Spearman rank correlation method to calculate the overall correlation coefficients between the AAPCs and ASRs in 1990 as well as SDI in 2019, because of the non-normal distribution of data. The ASRs of mesothelioma in 1990 could reflect the baseline burden of mesothelioma and the SDI in 2019 could denote the healthcare development status of each region. The

relationship between the AAPC and ASRs of mesothelioma in 1990 was to test whether the high-burden countries paid more attention to the prevention and control of mesothelioma burden, and further identify high-burden countries with an overall upward trend. Taking into account the possible non-linear relationship, the Locally Weighted Scatterplot Smoothing (LOWESS) regression was applied to present more detailed information between the AAPC and possible factors<sup>21 23</sup>, which was performed using the `geom_smooth` function with default parameters of the `ggplot2` package. The research analysis was implemented using the R program (version 4.0.3). A two-sided *P* value of less than 0.05 was considered statistically significant.

## Results

### Global burden and temporal trend in mesothelioma

Globally, the estimated newly-diagnosed mesothelioma patients increased from 19072 (95%UI: 17055, 21157) in 1990 to 34511 (95%UI: 31199, 37771) in 2019, with an age-standardized incidence rate (ASIR) slightly decreased from 0.49 (95%UI: 0.44, 0.54) to 0.43 (95%UI: 0.38, 0.47) cases per 100 000 person-year over the past 30 years [AAPC= -0.36 (95%CI: -0.41, -0.30)] (Table 1, Figure 1). Mesothelioma was responsible for 29251 (95%UI: 26668, 31006) deaths in 2019 globally with an age-standardized mortality rate (ASMR) of 0.36 (95%UI: 0.33, 0.39), compared with 15385 (95%UI: 13815, 17017) deaths and ASMR of 0.4 (95%UI: 0.36, 0.44) in 1990 [AAPC= -0.2 (95%CI: -0.27, -0.14)] (Table S1, Figure 1). Likely, DALYs worldwide associated with mesothelioma increased from an estimated 390646 (95%UI: 342695, 443115) to 668104 (95%UI: 608269, 716475) from 1990 to 2019, with the age-standardized DALYs rate (ASDR) reduced from 9.44 (95%UI: 8.35, 10.59) to 8.10 (95%UI: 7.38, 8.68) from 1990 to 2019 [AAPC= -0.47 (95%CI: -0.52, -0.42)] (Table S2, Figure 1).

### Variation in mesothelioma burden at regional and national level

The new mesothelioma cases in 2019 were greatest in high SDI regions [17548 (95%UI: 15610, 19554)], and lowest in low SDI regions [1151 (95%UI: 681, 2029)] (Table 1, Figure 1). The ASIR of mesothelioma significantly increased in low-middle SDI regions from 1990 to 2019 [AAPC= 0.84 (95%CI: 0.74, 0.93)], conversely the ASIR remained stable in middle and low SDI regions [AAPC= 0.08 (95%CI: -0.01, 0.18) and -0.13 (95%CI: -0.26, 0.00) respectively], and decreased in high-middle and high SDI regions [AAPC= -0.45 (95%CI: -0.55, -0.34) and -0.22 (95%CI: -0.28, -0.17) respectively] (Table 1). The similar trend in ASMR and ASDR of mesothelioma were found during the period (Table S1-S2).

For the GBD regions, the highest ASIR of mesothelioma in 2019 was found in Australasia [2.20 (95%UI: 1.75, 2.76)], Western Europe [1.33 (95%UI: 1.16, 1.52)], and Southern Sub-Saharan Africa [0.80 (95%UI: 0.65, 0.90)], while the lowest ASIR was observed in Western Sub-Saharan Africa [0.12 (95%UI: 0.08, 0.19)], East Asia [0.14 (95%UI: 0.12, 0.17)] and Southeast Asia [0.19 (95%UI: 0.15, 0.22)] (Table 1). The geographic distribution of ASMR and ASDR of mesothelioma in 2019 were highly consistent with the distribution of ASIR (Table S1-S2). The AAPC of ASIR for mesothelioma during 1990 to 2019 was

different across GBD regions, with Central Europe [1.78 (95%CI: 1.62, 1.95)], High-income Asia Pacific [1.18 (95%CI: 0.93, 1.44)], Southern Latin America [1.43 (95%CI: 1.15, 1.71)], Oceania [1.19 (95%CI: 1.03, 1.34)] having the most obvious increasing trends; while Andean Latin America [-3.47 (95%CI: -4.02, -2.92)], Central Asia [-1.04 (95%CI: -1.38, -0.7)], Western Sub-Saharan Africa [-1.32 (95%CI: -1.58, -1.06)] and High-income North America [-0.93 (95%CI: -1.05, -0.81)] having the largest decreasing trends (Table 1). The trends of the ASMR and ASDR were corresponding with the AAPC of ASIR (Table S1-S2).

In 2019, the difference in ASIR of mesothelioma was around 40 times across the world, with Netherlands being the highest [2.34 (95%UI: 1.81, 2.96)] and Tunisia the lowest [0.06 (95%UI: 0.03, 0.13)]. Other 6 countries with ASIR exceeding 1.5 were Australia, UK, Andorra, Lesotho, France and Belgium (Figure 2, Table S3). On the contrary, 7 countries including Tunisia, Lebanon, Algeria, Palestine, El Salvador, Iran, and Sudan have ASIR lower than 0.07/100 000 in 2019 (Figure 2, Table S4). The highest ASMR in 2019 was observed in UK [2.11 (95%UI: 1.96, 2.21)], followed by Australia, Netherlands, Andorra and Lesotho (Table S3). Tunisia had the lowest ASMR [0.05 (95%UI: 0.02, 0.11)] in 2019, followed by Lebanon, Algeria, Palestine and El Salvador (Figure 2, Table S4). The geographical distributions of ASDR in 2019 were highly consistent with the distribution of ASMR (Figure 2, Table S3-S4).

From 1990 to 2019, ASIR was rising in 97 out of 204 countries and territories. The largest annualized growth of ASIR was in Georgia [AAPC = 8.48 (95%CI: 6.71, 10.29)] and the AAPC of ASIR in other 11 countries and territories including Croatia, Bahrain, Kuwait, Poland, Qatar and Fiji exceeded 2.0 (Figure 2, Table S5). Conversely, the fastest decline in ASIR was in Peru [AAPC = -5.58 (95%CI: -6.37, -4.77)], while the AAPC of ASIR in other 13 countries and territories was less than -2.0, including Thailand, Bermuda, Ghana, Maldives, Kazakhstan and Singapore (Figure 2, Table S6). Consistently, the AAPCs in both ASMR and ASDR were highest in Georgia [AAPC = 8.63 and 8.62, respectively] and lowest in Peru [AAPC = -5.45 and -5.59, respectively] from 1990 to 2019. The AAPC of ASMR and ASDR followed a very similar pattern as ASIR (Figure S2, Table S5-S6).

### **Variation in mesothelioma burden in two sexes and 5-year age groups**

The ASIR of mesothelioma among men was more than 3 times than women [0.69 (95%UI: 0.62, 0.75) vs 0.22 (95%UI: 0.16, 0.25)] per 100,000 population in 2019, and both the ASMR and ASDR among men were significantly greater than women (Table 1, Table S1-S2 and Figure 1). Of note, the ASIR of mesothelioma decreased among women from 1990 to 2019 [AAPC= -1.02 (95%CI: -1.06, -0.97)], while the ASIR remained relatively stable among men [AAPC= -0.15 (95%CI: -0.24, -0.07)] (Table 1, Figure 1). Similarly, the ASMR and ASDR of mesothelioma decreased among women while remained relatively stable among men during the period [AAPC of ASMR=-0.9 (95%CI: -0.94, -0.86) vs 0.01 (95%CI: -0.08, 0.1); AAPC of ASDR=-1.1 (95%CI: -1.14, -1.06) vs -0.23 (95%CI: -0.31, -0.15)] (Table S1-S2, Figure 1).

The incident cases of mesothelioma rose from age 50 years and remained relatively high level until age 90 years, with a peak at age 70-74 years among both sexes in 2019 (Figure 3, Figure S2). The incidence rate per 100000 rose to a peak at age 85-89 years and dropped substantially afterward in 2019 (Figure 3, Figure S2). The mortality rate reached a peak and remained high over age 85 years (Figure S2-S3). The

DALY rate increased significantly over age 60 years and held up highest among age 75-90 years (Figure S2, Figure S4). The difference of the incidence rate, mortality rate and DALY rate in five SDI regions focused on the population aged over 60 years, and high SDI regions account for the highest proportion (Figure 3, Figure S2-S4).

Globally, the incidence rate, mortality rate and DALY rate all decreased among the population aged under 70 years from 1990 to 2019, especially among higher SDI regions, though increased among the population aged over 80 years (Figure 3, Figure S3-S4).

### **The correlation between SDI and mesothelioma burden**

We found that the AAPC of ASRs were all negatively correlated with the baseline ASR in 1990 at the national level [ $\rho$  of ASIR: -0.2513 ( $P = 0.0003$ ), of ASMR: -0.2537 ( $P = 0.0003$ ), of ASDR: -0.3252 ( $P = 2.1 \times 10^{-6}$ )] (Figure 4A, Figure S5A, Figure S6A). Moreover, data analysis showed no statistically correlation between SDI in 2019 and AAPC values in ASIR, ASMR, and ASDR in 204 countries or territories [ $\rho$  of ASIR: 0.0888 ( $P = 0.2068$ ), of ASMR: 0.0769 ( $P = 0.2743$ ), of ASDR: 0.0315 ( $P = 0.6545$ )] (Figure 4B, Figure S5B, Figure S6B). Further, we analyzed the relationship between ASRs and SDI over time in 21 GBD regions, expressed in the annual time series of 1990 and 2019. During these 30 years, the ASRs in most GBD regions remained relatively stable, except Southern Sub-Saharan Africa, Andean Latin America, Eastern Europe, Western Europe, High-income Asia Pacific presented a climbing trend beforehand and following decline afterward; Australasia rebounded after the first declining and has been through another declining in recent years; Southern Latin America, Central Europe presented a climbing trend and remained stable recently; while High-income North America presented a decreasing trend over time (Figure 4C, Figure S5C, Figure S6C).

### **Risk Factors**

The ASDR of mesothelioma attributable to occupational exposure to asbestos in 2019 was positively associated with SDI in 2019 at the national levels ( $\rho = 0.3105$ ,  $P = 6.2 \times 10^{-6}$ ) (Figure 5A). Most countries and territories have remained relatively constant or changed moderately between 1990 and 2019 for the proportion of DALYs due to occupational exposure to asbestos, except the Georgia increased markedly from 1990 to 2019 (Figure 5B). The high-income GBD regions always showed the largest proportion of DALYs due to occupational exposure to asbestos, with most territories of high-income GBD regions reaching up to more than 90% (Figure 5B).

## **Discussion**

This study provides the latest and comprehensive assessment of the global burden of mesothelioma. From 1990 to 2019, the number of mesothelioma incident cases and deaths globally increased by nearly two times, while the age-standardized rates of incident cases, deaths and DALYs showed a slightly declining trend. The incidence rate of mesothelioma increased significantly in the 1960s due to the massive use of asbestos during World War II and thereafter, especially in those high-resource countries

with advanced industries<sup>24</sup>. Governments came to recognize that asbestos is one of the most important occupational carcinogens and announced the necessity of decreasing industrial use of asbestos, so as to reduce the burden of asbestos-related disease<sup>13</sup>. Since the late 1970s and early 1980s, asbestos bans and regulations were implemented in most areas, bringing about a declining trend of the incidence rates afterwards<sup>25</sup>. There can be several reasons for the continuous increase in the absolute number of incident cases and deaths during the three decades. Firstly, due to the long latency period from asbestos exposure to the development of mesothelioma, the mesothelioma populations are usually diagnosed at elderly<sup>26-27</sup>; Secondly, other carcinogenic mineral fibers has been increasingly used freely and resulted in unexpected environmental exposure<sup>6 28</sup>; Moreover, germline mutations and ionizing radiation indicating other susceptible subgroups for mesothelioma<sup>25</sup>.

Consistent with other worldwide studies, the incidence and mortality of mesothelioma were more than three times in males than in females globally across all age groups from 1990 to 2019. The ASIR, ASMR and ASDR decreased among females in the 30 years while remained relatively stable among males. The lower incidence and declining trend of mesothelioma in females might be partly owing to rare industrial labor and consequent less exposure to asbestos<sup>24</sup>. As previously reported, there is a 35–40 years latency period from asbestos exposure to the development of mesothelioma, consequently, the incident cases and deaths would increase with the aging of the population. In this study, we observed that the number of incident cases and deaths gradually increased with age and reached a peak in the elderly aged 70–90 years. Furthermore, the global incidence rate, mortality rate and DALY rate all decreased among the population aged under 70 years from 1990 to 2019, however increased among the population aged over 80 years. The elderly patients with mesothelioma are generally refractory because of the extent of disease, advanced age, comorbidities or poor performance status, therefore are usually considered for palliative treatment instead. Thus, early detection of mesothelioma, multi-channel interventions and novel targeted treatments are urgently needed to be developed. Of note, recently available data support a possible role of miRNAs and DNA methylation in the etiology of mesothelioma and suggest their potential as biomarkers for the early diagnosis and even for the screening of an at a high-risk population of asbestos-exposed individuals<sup>29-32</sup>. Besides, several novel therapeutic agents are under investigation in recent years, such as targeted therapies and immunotherapies, which may provide further treatment options and improve clinical outcomes for mesothelioma in the future<sup>33-34</sup>.

During the past three decades, ASIR has been higher in high and high-middle SDI regions and lower in low SDI regions. The high incidence rate of mesothelioma in the higher SDI regions may be related to the previous industrial use of asbestos. Although the limitation and bans of asbestos have been implemented earlier in industrialized countries, it would take a long time to observe the decrease of incident rates due to the more than 30 years of the latency period. It is supposed that mesothelioma cases might begin to decrease after 2 decades of a complete ban on asbestos use. In this 30-year cross-sectional study, we observed a declining trend of ASIR in the high-middle and high SDI regions, as well as ASMR and ASDR. This illustrates that the asbestos regulation earlier in those industrialized regions is beginning to take effect. For the middle, low-middle and low SDI regions, the incident cases, deaths and

DALYs were much lower compared with high SDI regions. The possible reason is that the resource-limited regions with small industrial volumes are related to comparatively few asbestos occupational exposure. Besides, the diagnosis rate and data availability of mesothelioma have been a matter of concern in developing regions<sup>35</sup>. Recent articles reported a very high rate of incorrect diagnoses, ranging from approximately 14% in the western world to approximately 50% in some developing countries, which can influence all the incidence, mortality and DALYs statistics<sup>36</sup>. The ASRs in the middle and low-middle SDI regions showed a rising trend, especially the low-middle SDI regions showed the highest increasing trend of ASRs, which might be partly owing to the later asbestos regulation, and also the gradually improved diagnosis rate and data accessibility.

The AAPC of age-standardized burden rates were all negatively correlated with baseline ASIR, ASMR and ASDR in 1990 at the national level, partially because the statistics change were more apparent in the countries with low burden and small base in 1990. Moreover, data analysis showed no statistical correlation between SDI and AAPC values in ASIR, ASMR, and ASDR in 204 countries or territories. This is different from the estimation of mesothelioma burden of 195 countries and territories based on GBD 2017, which showed the AAPC of incidence rate, death rate and DALY rate were all positively correlated with the SDI level in 2017 ( $\rho = 0.21, P = .003; \rho = 0.20, P = .005; \rho = 0.19, P = .006$  respectively)<sup>15</sup>. According to the latest estimations, we speculate there should be no definite linear correlation between the SDI level and the AAPC of mesothelioma burden rates, as the epidemic trend can be influenced by various factors such as the aging degree, asbestos exposure and regulation, germline predisposition, medical level and data accessibility<sup>25 37</sup>. The current study analyzed the latest data from more areas of 204 countries or territories, standing for more reliable statistical results and less possibility to be affected by particular data.

Most GBD regions hold relatively stable ASRs, or showed a fluctuating tendency but eventually going down curves such as Andean Latin America, Central Asia, Western Sub-Saharan Africa and High-income North America having the largest decreasing trends. The exception is Central Europe, Southern Latin America, Oceania and High-income Asia Pacific having obvious increasing trends for age-standardized burden rates, of which governments should be alerted to attach great importance to this matter.

At the national level, Netherlands, Australia, UK have the highest ASIR in 2019, of which UK holds the highest ASMR and ASDR. According to the analysis of the proportion of DALYs due to occupational exposure to asbestos, there are more than 90% of DALYs attributable to occupational exposure in these high-income countries. Moreover, data showed that ASDR attributable to occupational exposure to asbestos in 2019 was positively associated with SDI level, suggesting that the mesothelioma burden increased as the economy developed along with increases in industrial manufacturing and consequent exposure to asbestos<sup>38</sup>. Georgia displayed the highest increasing trend in the ASIR, ASMR and ASDR of mesothelioma during the 30-year period. Croatia, Bahrain, Kuwait and Poland also showed remarkable increase of ASRs. Notably, these countries also showed increased proportion of DALYs due to occupational exposure to asbestos, with Georgia rose most significantly from lower than 50% in 1990 to

about 90% in 2019. Besides, the small population of these countries may be another reason for the large variation change. A few more people diagnosed would have a big impact on the overall burden rates data. Nevertheless, these countries should raise more concern of the prevention and management policies for mesothelioma. On the other side, there is a definite and sometimes substantial fraction of mesotheliomas with no history of asbestos exposure. This fraction has been estimated greater in women and young populations<sup>39</sup>. It is of great significance to explore and determine the various contributing factors other than just asbestos in the future.

To our knowledge, this study is the most comprehensive and recent data set available that evaluates the annual incidence, mortality and DALYs associated with mesothelioma and its attributable risk factors over time across a global scale. However, it still has some limitations due to the restrictions of the GBD 2019 database. First, the GBD estimation on mesothelioma is reconstructed by mathematical models based on plenty of data sources with different quality, which may to some extent deviate from the actual data, especially in some underdeveloped regions with extremely scarce prior information, such as Africa and South Asia<sup>16-17</sup>. Second, due to the higher probability of missed diagnosis rate of mesothelioma in developing countries, there is an unavoidable deviation in the estimation of mesothelioma burden. Third, due to the lack of relevant data, we did not estimate the burden of different subtypes of mesothelioma, such as epithelioid, sarcomatoid, and biphasic<sup>40</sup>. Moreover, we only analysed the mesothelioma burden attributed to occupational exposure to asbestos and did not involve an analysis of other potential risk factors, such as other mineral fibers and family inheritance<sup>39</sup>. Future research should focus on this aspect, which will help guide different countries and regions to formulate specific prevention and treatment policies for mesothelioma.

In conclusion, mesothelioma incidence and deaths more than doubled over the study period, with a huge heterogeneity in different locations, sexes and age groups. Mesothelioma is aggressive cancer, often presents in old age, at an advanced stage, and has a poor prognosis. A major risk factor associated with mesothelioma is asbestos exposure. Reducing asbestos exposure through industry regulation with standardized occupational exposure limits remains a key factor to prevent mesothelioma development. The results of our study can be used by policy makers to allocate resources efficiently for improving the early diagnosis of mesothelioma, reducing its modifiable risk factors, and developing novel intervention and treatment strategies to reduce its fatality rate.

## **Declarations**

### **Acknowledgments**

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### **CRedit authorship contribution statement**

**Yali Han:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Roles/Writing – original draft; **Tongchao Zhang:** Data curation, Formal analysis, Methodology, Visualization, Software, Writing – review & editing; **Hui Chen:** Data curation, Formal analysis, Methodology, Visualization, Software, Writing – review & editing; **Xiaorong Yang:** Conceptualization, Methodology, Funding acquisition, Project administration, Supervision, Validation, Writing – review & editing; All authors; All authors approved the final version of the manuscript.

### **Conflict of interest**

The authors declare that they have no conflict of interest.

### **Ethics statement**

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

### **Patient consent statement**

Not applicable due to no individual information.

### **Patient and public involvement statement**

None.

### **Availability of data and materials**

The GBD 2019 study is a publicly available database (<http://ghdx.healthdata.org/gbd-2019>), and we fully complied with the GBD data usage requirements.

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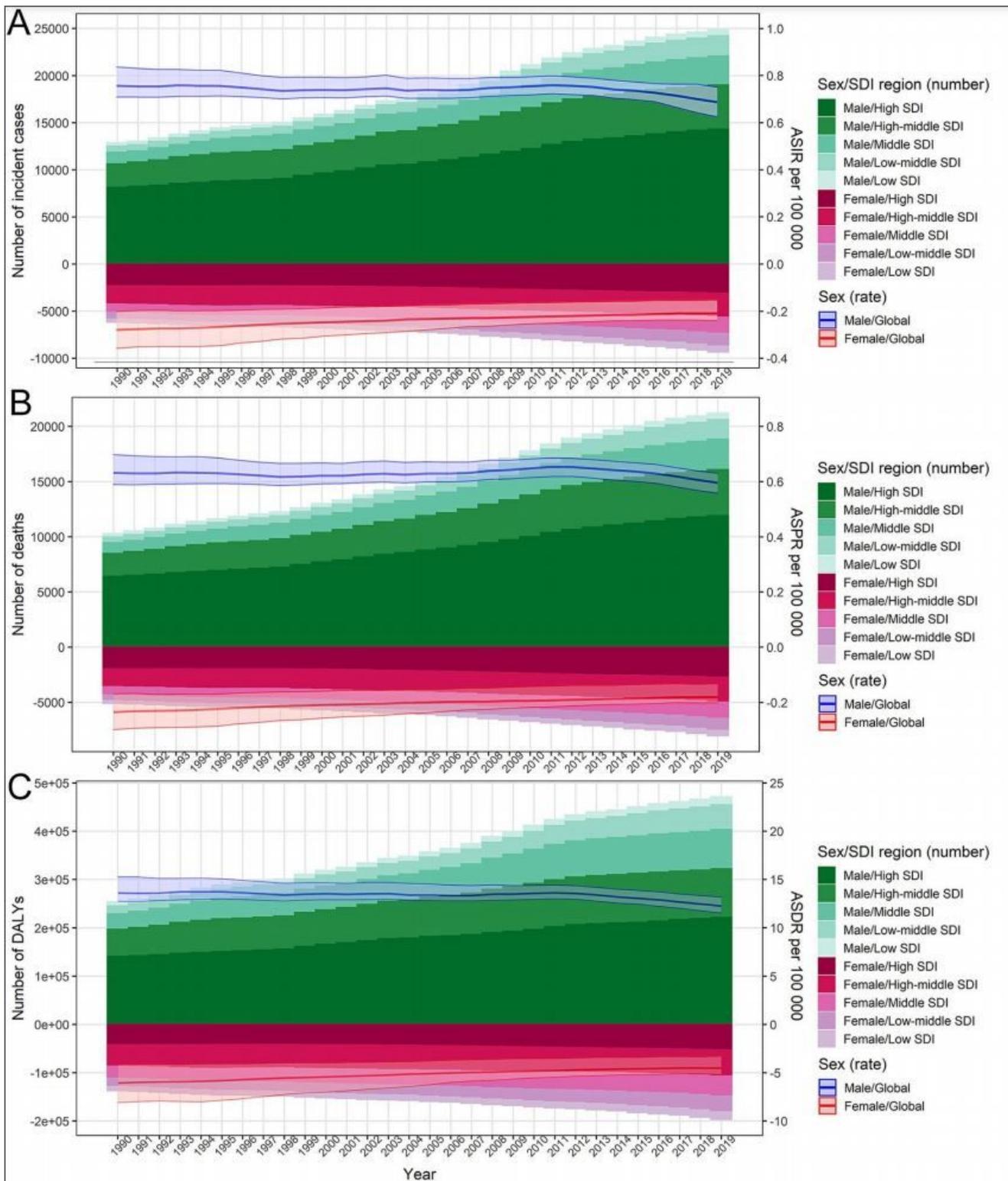
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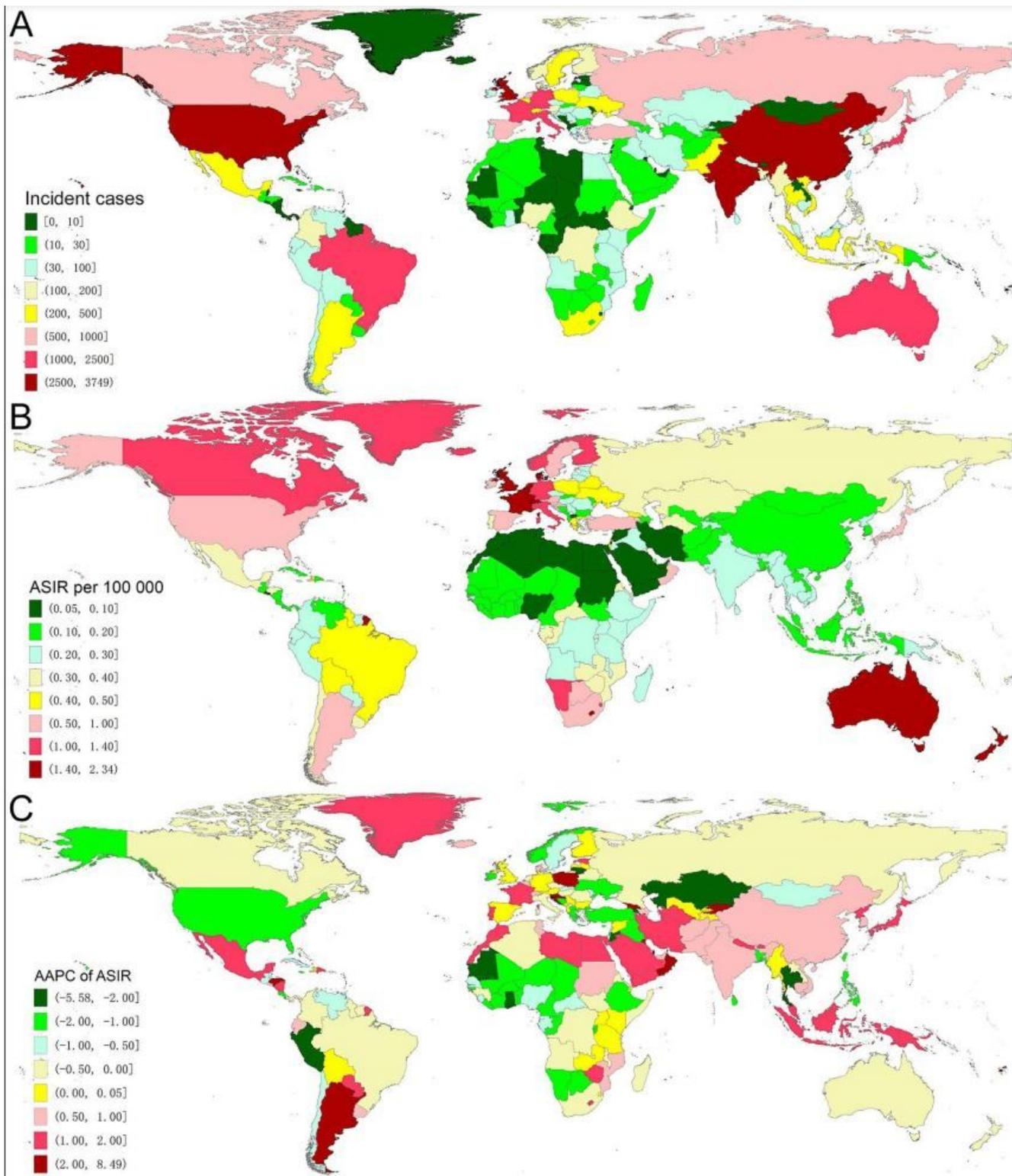
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## Figures



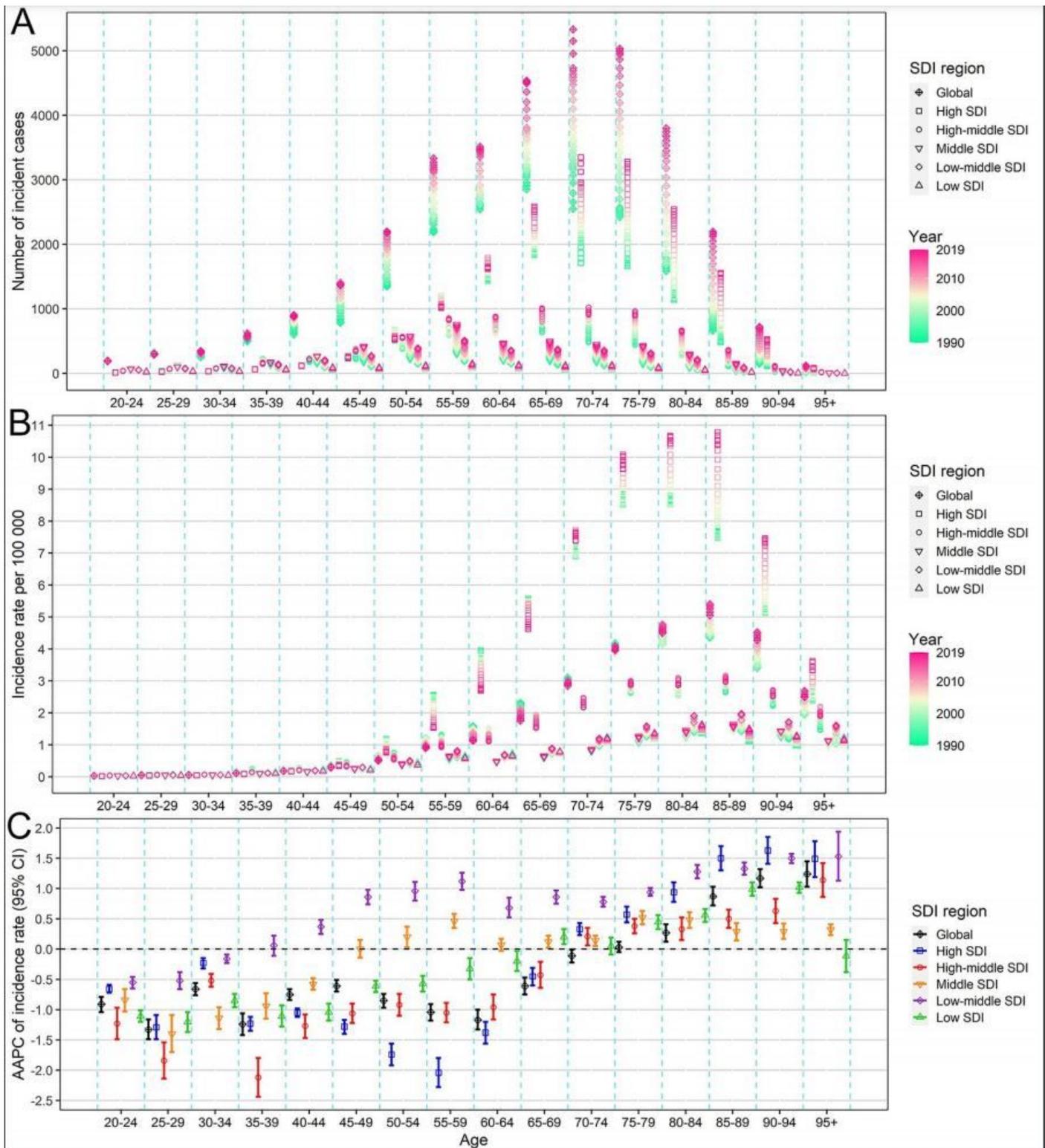
**Figure 1**

Mesothelioma burden by SDI regions and its ASRs by sex, 1990-2019. (A) incidence, (B) deaths, (C) DALYs. SDI, socio-demographic index; DALYs, disability-adjusted life years.



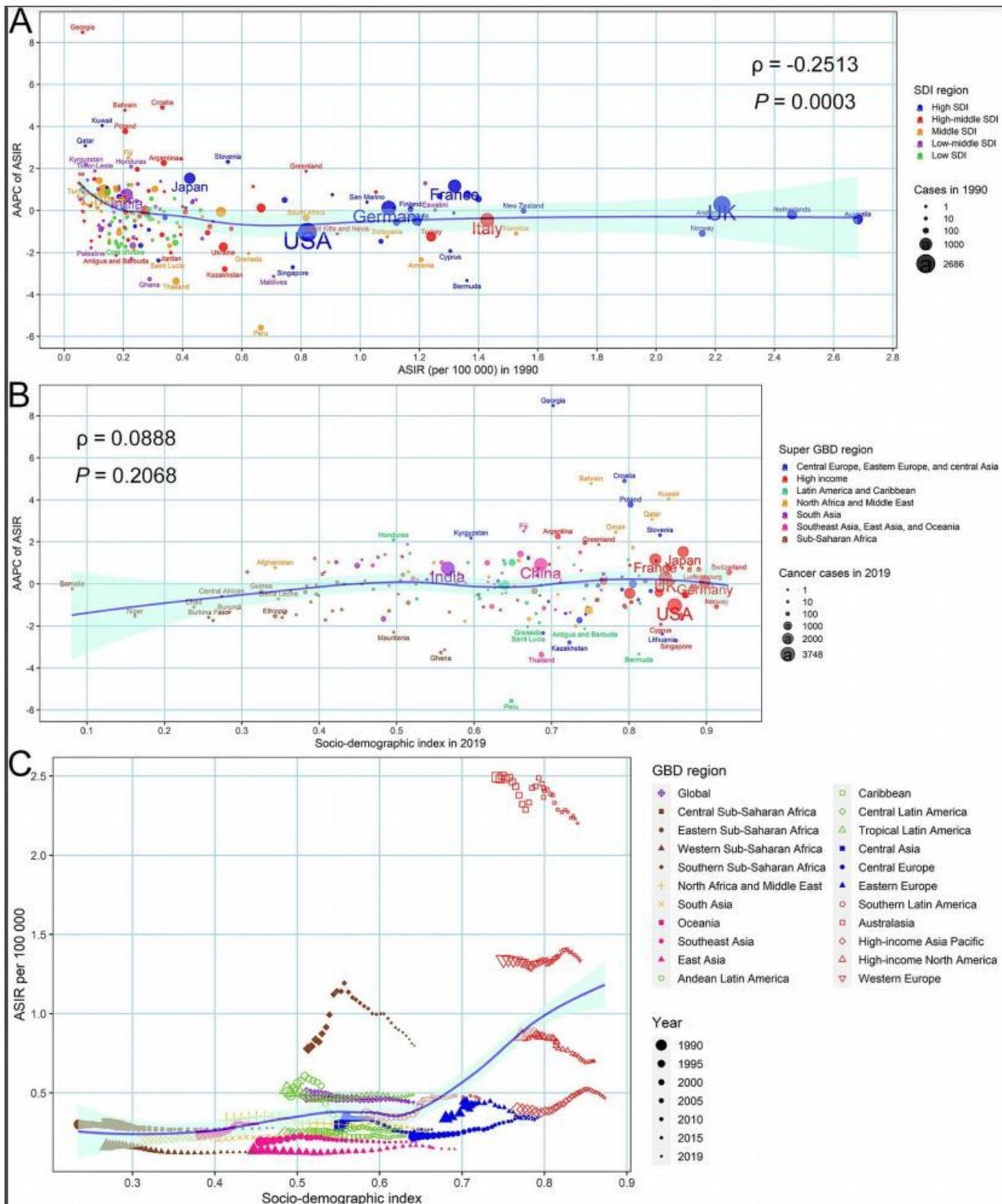
**Figure 2**

The global disease burden of mesothelioma in 204 countries and territories: (A) incident cases in 2019, (B) the ASIR per 100 000 in 2019, and (C) the AAPC of ASIR from 1990 to 2019. ASIR, age-standardized incidence rate; AAPC, average annual percentage change.



**Figure 3**

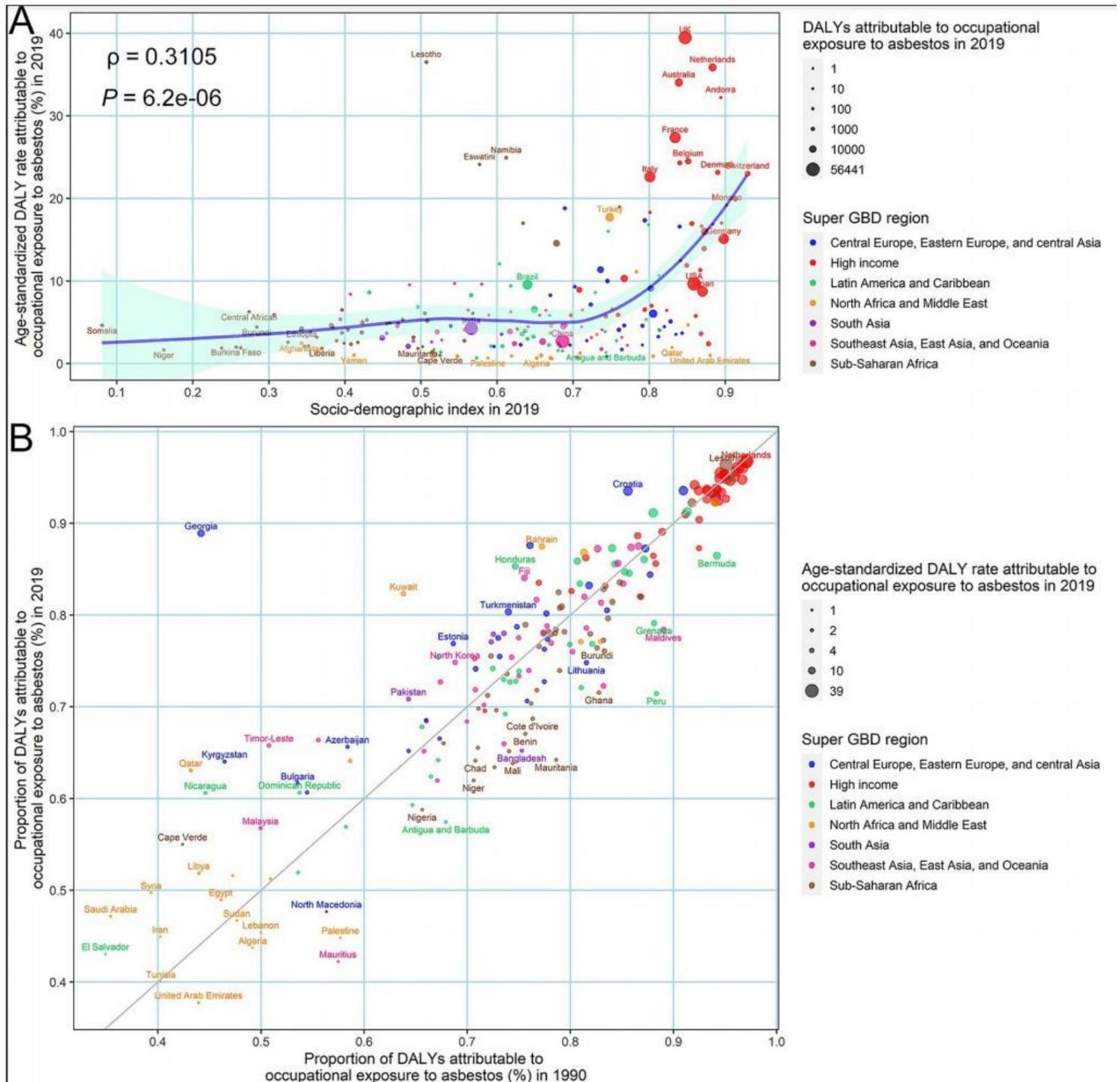
The annual burden of mesothelioma by different age groups, and SDI regions, from 1990 to 2019: (A) incidence cases, (B) incidence rate per 100 000 and (C) AAPC of incidence rate. SDI, socio-demographic index; AAPC, average annual percentage change.



**Figure 4**

The factors affected the AAPC of ASIR of mesothelioma from 1990 to 2019, both sexes, at the national level: (A) ASIR in 1990 and AAPC of ASIR, (B) SDI in 2019 and AAPC of ASIR, (C) The annual burden in ASIR across 21 GBD regions with SDI from 1990 to 2019. The circles in (A) and (B) represent countries and the size of the circle is increased with the number of burdens; The  $\rho$  indices and  $P$  values presented were derived from Spearman rank analysis; The icons in (C) represent GBD regions and the size of the

icons represent different years. AAPC, average annual percentage change; ASIR, age-standardized incidence rate; SDI, socio-demographic index; GBD, Global Burden of Disease, Injuries, and Risk Factors Study.



**Figure 5**

The DALYs of mesothelioma attributable to occupational exposure to asbestos: (A) the association between age-standardized DALY rates of mesothelioma attributable to occupational exposure to asbestos in 2019 and SDI in 2019, (B) the proportion of DALYs of mesothelioma attributable to

occupational exposure to asbestos between 1990 and 2019. DALYs, disability-adjusted life years; SDI, socio-demographic index.

## Supplementary Files

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