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Global burden and attributable risk factors of inflammatory cardiomyopathy and myocarditis from 1990 to 2019

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Abstract

Background Our understanding of the global burden distribution of inflammatory cardiomyopathy and myocarditis is very limited.

Objective To comprehensively assess the global burden distribution and attributable risk factors of inflammatory cardiomyopathy and myocarditis from 1990 to 2019.

Methods We extracted the data on death, disability-adjusted life years (DALY), and age-standardized rate (ASR) of inflammatory cardiomyopathy and myocarditis from the 2019 Global Burden of Disease (GBD) study, including the comprehensive data and the data classified by age/sex. Evaluate the epidemic trend by calculating the estimated annual percentage change (EAPC) of the above variables. This paper discusses the spatial differences from four aspects: global, five socio-demographic index regions, 21 GBD regions, and 204 countries and regions. We also estimated the risk factors attributable to inflammatory cardiomyopathy and myocarditis-related deaths.

Results In 2019, the global death toll from inflammatory cardiomyopathy and myocarditis was 340,349, and the age-standardized mortality rate (ASDR) was 4.40/100,000, of which the elderly and men were the majority. Although ASR has decreased in developed areas, inflammatory cardiomyopathy and myocarditis are still important health problems in those relatively underdeveloped areas. Similar DALYs burden pattern of inflammatory cardiomyopathy and myocarditis was also observed during the study period. Globally, among men over 60 and women over 65, the proportion of deaths caused by high systolic blood pressure in 2019 was higher than that in 1990.

Conclusions Inflammatory cardiomyopathy and myocarditis are still important global public health problems. The changing pattern of the burden of inflammatory cardiomyopathy and myocarditis varies with location, age, and sex, so it is essential to improve resource allocation to formulate more effective and targeted prevention strategies. In addition, the control of blood pressure should be emphasized.

Keywords Inflammatory cardiomyopathy, Myocarditis, Global burden of disease, Time trends, Risk factors

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Text box 1. Contributions to the literature

- Inflammatory cardiomyopathy and myocarditis remain an important global public health problem, especially in less developed regions.
- Attributable risk factors include blood pressure, among men over 60 and women over 65, the proportion of deaths caused by high systolic blood pressure in 2019 was higher than that in 1990.
- Public health policies targeting the global burden model and risk factors for inflammatory cardiomyopathy and myocarditis are urgently needed.

Introduction

Cardiovascular disease (CVD) is the main cause of death and disability in the world, which has caused a serious public health burden [1, 2]. In CVD, cardiomyopathy is a group of heterogeneous diseases characterized by changes in the structure and function of the heart [3], which often causes life-threatening. Nearly 50% of patients who died suddenly or received heart transplantation in childhood or adolescence are related to cardiomyopathy [4]. Inflammatory cardiomyopathy defined as myocardial associated with cardiac insufficiency and ventricular remodeling [3]. Myocarditis is defined as an inflammatory disease of myocardium, and it is also an important cause of many fatal diseases, such as acute heart failure, sudden death and dilated cardiomyopathy [5, 6]. About 2% of infants, 5% of children and 5-12% of young athletes' sudden death are caused by cardiomyopathy [7]. The incidence and causes of inflammatory cardiomyopathy and myocarditis are very different in different regions [8]. In developed countries, viral infection often causes myocarditis; However, in developing countries, rheumatic heart disease, trypanosoma cruzi and diphtheria are still the main causes of myocarditis [6].

A comprehensive understanding of the different epidemiological characteristics of inflammatory cardiomyopathy and myocarditis in different countries and populations may help policymakers fully understand this disease's global burden and rationally allocate limited health resources to narrow the global gap between inflammatory cardiomyopathy and myocarditis. However, up to now, most of our knowledge about the burden distribution of inflammatory cardiomyopathy and myocarditis is largely limited to epidemiological surveys conducted by individual developed countries [4]. The Global Burden of Disease (GBD) study is an ongoing global collaboration aimed at assessing the burden of disease in every country in the world [9, 10]. It provides an opportunity to comprehensively assess the distribution and development trend of the burden of inflammatory cardiomyopathy and myocarditis. Based on the latest data of the GBD study in 2019, we carried out this study, which aims to systematically reveal the levels and trends of global inflammatory cardiomyopathy and myocarditis mortality, disability-adjusted life years (DALY), and major risk factors according to location, age, and gender.

Methods

Study data

This study is based on the secondary analysis of GBD 2019. Through the Global Health Data Exchange (GHDx) query tool (http://ghdx.healthdata.org/gbd-results-tool), the information on annual inflammatory cardiomyopathy and myocarditis deaths, DALYs and age-standardized rate (ASR) from 1990 to 2019 were searched by location, age, and sex. The general methods of GBD study and burden estimation have been introduced in detail in previous studies [11].

Cardiomyopathy and myocarditis were identified using the codes of the 9th and 10th editions of the International Classification of Diseases (ICD-9, 10). Diseases coded as 422-422.9 in ICD-9 or B33.2, I40-I41.9, I42.3- I42.4 and I51.4 in ICD-10 are identified as inflammatory cardiomyopathy and myocarditis [12].

In order to further analyze the burden distribution of global inflammatory cardiomyopathy and myocarditis, we divide the location information into three levels. First of all, we use the Socio-Demographic Index (SDI) based on the country's per capita income, average years of education, and total fertility rate of people over 15 years old, and divide countries and regions into five SDI quintiles (high, high-middle, middle, low-middle and low). Secondly, as shown in Tables 1 and 2, the world is geographically divided into 21 GBD regions. Finally, by drawing a world map, we show the burden of inflammatory cardiomyopathy and myocarditis in 204 countries and regions. Human Development Index (HDI) is a general index to measure the average achievement of all key aspects of human development: A long and healthy life, being knowledgeable and having a declining standard of living. We also collected 2019 human development index data from World Bank.

Statistical analysis

We use ASR (age-standardized mortality rate [ASDR] and age-standardized DALY rate) and the corresponding estimated annual percentage change (EAPC) to quantify the time trend of the burden of inflammatory cardiomyopathy and myocarditis. DALY is calculated as the sum of years of disabled life due to inflammatory cardiomyopathy and myocarditis and years of life lost due to premature death [13]. Standardization is necessary when comparing the age structure of people with different age structures or the same population with time. The trend of ASR can be a good substitute for the change of disease patterns in the population, and EAPC is a common and important assessment of the trend of ASR in a specified time interval. Use the corresponding linear regression

Table 1 The death cases and age-standardized death rate of cardiomyopathy and myocarditis in 1990 and 2019, and its temporal trends from 1990 to 2019

Characteristics	1990		2019		1990–2019
	Death cases No. × 10^3 (95% UI)	ASR per 100,000 No. (95% UI)	Death cases No. × 10^3 (95% UI)	ASR per 100,000 No. (95% UI)	EAPC No. (95% UI)
Global	238.3 (212.4-256.7)	6.87 (5.67–7.37)	340.3 (284.9-371.3)	4.40 (3.66–4.79)	-1.63 (-1.82 to -1.44)
Sex					
Male	128.3 (113.0-150.6)	7.95 (6.38–8.60)	199.7 (159.4-224.2)	5.62 (4.47–6.27)	-1.28 (-1.51 to -1.05)
Female	110.0 (88.8-121.2)	5.79 (4.39–6.40)	140.7 (116.3-154.8)	3.27 (2.70–3.59)	-2.09 (-2.22 to -1.95)
Social-demographic index					
High SDI	73.5 (56.9–78.5)	7.34 (5.70–7.84)	84.3 (73.0-94.2)	4.32 (3.83–4.88)	-2.22 (-2.37 to -2.06)
High-middle SDI	103.4 (90.4-116.4)	11.86 (9.14–12.96)	150.0 (114.7-166.5)	7.92 (6.00-8.80)	-1.36 (-1.79 to -0.93)
Middle SDI	32.6 (28.0-44.2)	3.35 (2.86–4.27)	56.9 (46.5–65.8)	2.70 (2.13–3.06)	-0.74 (-0.91 to -0.57)
Low-middle SDI	15.8 (12.3–19.8)	2.78 (2.24–3.30)	28.7 (23.3–32.7)	2.29 (1.86–2.60)	-0.73 (-0.85 to -0.62)
Low SDI	12.9 (8.0-16.9)	4.68 (2.99–6.23)	20.3 (15.5–25.3)	3.51 (2.70–4.40)	-1.11 (-1.16 to -1.06)
Region					
Andean Latin America	0.52 (0.37–0.65)	2.16 (1.60–2.61)	0.87 (0.67–1.12)	1.55 (1.20-2.00)	-0.91 (-1.09 to -0.73)
Australasia	1.6 (1.2–1.7)	7.39 (5.25–8.06)	1.7 (1.5–2.1)	3.56 (3.15–4.41)	-2.56 (-2.87 to -2.25)
Caribbean	1.4 (1.1–1.9)	5.12 (4.23–6.60)	2.7 (2.2–3.3)	5.41 (4.41–6.62)	0.43 (0.26 to 0.60)
Central Asia	2.6 (2.2–3.7)	5.24 (4.47–7.18)	8.5 (5.1–10.1)	11.01 (6.55–12.97)	3.95 (2.85 to 5.06)
Central Europe	22.2 (16.9–24.3)	17.82 (13.41–19.63)	29.8 (22.1–34.2)	14.07 (10.40-16.17)	-0.97 (-1.15 to -0.79)
Central Latin America	2.1 (1.9–2.3)	2.37 (2.07–2.58)	4.5 (3.7–5.4)	1.97 (1.62–2.36)	-1.12 (-1.32 to -0.93)
Central Sub-Saharan Africa	2.5 (1.3–3.5)	10.14 (5.59–14.88)	4.8 (3.0-7.3)	8.86 (5.26–14.18)	-0.48 (-0.50 to -0.45)
East Asia	16.7 (13.2–27.7)	1.99 (1.55–3.34)	28.3 (19.0-33.8)	1.76 (1.19–2.08)	0.02 (-0.27 to 0.31)
Eastern Europe	35.8 (29.9–55.1)	14.13 (11.91–20.68)	71.3 (51.8–82.8)	24.06 (17.57–28.05)	1.96 (0.92 to 3.00)
Eastern Sub-Saharan Africa	5.6 (3.6–7.1)	4.77 (3.34–5.99)	8.5 (5.8–11.6)	3.93 (2.80–4.96)	-0.72 (-0.79 to -0.64)
High-income Asia Pacific	8.4 (5.2–9.2)	4.99 (2.90–5.54)	10.8 (6.8–12.5)	2.17 (1.58–2.44)	-2.74 (-3.09 to -2.39)
High-income North America	27.6 (22.0-29.3)	8.04 (6.38–8.52)	36.3 (32.0-40.4)	5.90 (5.26–6.60)	-1.71 (-1.92 to -1.49)
North Africa and Middle East	8.4 (5.9–13.6)	3.77 (2.85–5.49)	11.0 (8.9–15.4)	2.58 (2.12–3.62)	-1.33 (-1.38 to -1.29)
Oceania	0.17 (0.08–0.19)	3.56 (2.38–5.10)	0.30 (0.18–0.45)	3.66 (2.36–5.12)	0.23 (0.17 to 0.29)
Southeast Asia	9.6 (7.6–13.1)	4.17 (3.05–5.08)	20.0 (15.6–25.0)	3.86 (2.82–4.63)	-0.25 (-0.37 to -0.12)
Southern Latin America	5.5 (4.1–6.3)	12.84 (9.52–14.86)	7.4 (6.2–8.2)	8.80 (7.40–9.77)	-1.69 (-1.88 to -1.51)
Southern Sub-Saharan Africa	3.3 (2.6-4.0)	12.77 (9.94–15.26)	5.6 (4.6–7.1)	11.52 (9.5-14.47)	-0.46 (-0.74 to -0.17)
Tropical Latin America	13.5 (10.5–14.4)	15.62 (12.17–16.72)	21.6 (19.1–25.3)	9.29 (8.17–10.89)	-2.38 (-2.61 to -2.14)
Western Europe	59.3 (35.4–65.7)	10.63 (6.46–11.78)	47.0 (40.3–54.9)	4.50 (3.93–5.31)	-3.38 (-3.60 to -3.15)
Western Sub-Saharan Africa	7.6 (4.4–10.2)	8.97 (5.17–12.13)	11.2 (8.3–14.0)	5.98 (4.37–7.35)	-1.68 (-1.82 to -1.54)

mathematical model to control the natural logarithm of ASR with years: $y = \alpha + \beta x + \varepsilon$, where y represents ln ASR, x represents calendar year and ε represents error term. The regression model can also get EAPC = 100× (exp (β)−1) and its 95% uncertainty interval (UI). When the upper and lower boundaries of EAPC are positive, ASR is considered to be on the rise. On the contrary, when the upper and lower boundaries of EAPC are negative, ASR tends to decrease. Otherwise, ASR is considered a steady state [14].

In addition, to explore the influencing factors of EAPCs, we evaluated the association between EAPCs and ASRs (1990)/HDI (2019) at the national level. All statistical analysis was performed by the R program (Version 4.2.0). A p-value less than 0.05 is considered statistically significant.

Results

The deaths burden of inflammatory cardiomyopathy and myocarditis

In 2019, there were 340,349 deaths from inflammatory cardiomyopathy and myocarditis worldwide (95% UI = 284,904 – 371,305), and ASDR was 4.40/100,000 (95% UI = 3.66–4.79). Areas with higher SDI have more deaths; High-middle SDI has the largest number of quintiles (150,010,95% UI = 114,704 – 166,482), accounting for almost half of the world total. The highest number of ASDRs in high-middle SDI is 7.92/100,000 (95% UI = 6.00-8.80), which is much higher than the world average. Among the 21 GBD regions, Eastern Europe has the highest number of deaths (71,302,95% UI = 51,778 – 82,815), followed by Western Europe (47,047,95% UI = 40,299 – 54,877). The ASDR in Eastern Europe is also the highest, with 24.06/100,000 people (95% UI = 17.57–28.05), and the lowest in South Asia,

Table 2 The DALYs and age-standardized DALYs rate of cardiomyopathy and myocarditis in 1990 and 2019, and its temporal trends from 1990 to 2019

Characteristics	1990		2019		1990–2019
	DALYs No. × 10^3 (95% UI)	ASR per 100,000 No. (95% UI)	DALYs No. × 10^3 (95% UI)	ASR per 100,000 No. (95% UI)	EAPC No. (95% CI)
Global	7060.9 (6299.4-8631.2)	161.15 (146.73-185.58)	9135.8 (7865.0-10040.0)	114.76 (98.69-126.15)	-1.20 (-1.52 to -0.89)
Sex					
Male	4267.2 (3718.7-5481.4)	201.00 (178.19-242.23)	6029.0 (4906.0-6817.6)	155.36 (126.45-175.04)	-0.92 (-1.27 to -0.57)
Female	2793.7 (2378.4-3444.2)	122.31 (106.68-142.05)	3106.8 (2678.2-3460.4)	75.53 (65.00-84.20)	-1.70 (-1.95 to -1.46)
Social-demographic index					
High SDI	1740.3 (1419.3-1852.3)	184.06 (151.10-195.27)	1706.5 (1560.1-1934.5)	111.78 (102.54-125.49)	-2.04 (-2.16 to -1.93)
High-middle SDI	2713.1 (2497.4-3442.3)	260.68 (241.78-315.83)	4009.1 (3108.9-4493.5)	219.20 (170.06-245.23)	-0.54 (-1.19 to 0.12)
Middle SDI	1354.6 (1108.9-2058.4)	95.45 (80.78-133.62)	1611.8 (1395.1-1977.2)	69.20 (59.63–83.18)	-1.12 (-1.26 to -0.99)
Low-middle SDI	635.7 (464.9-898.2)	72.96 (57.65–93.27)	914.6 (753.8-1057.9)	60.87 (50.21–70.13)	-0.67 (-0.75 to -0.58)
Low SDI	613.3 (366.5-834.3)	144.76 (94.01-187.89)	888.0 (686.0-1105.2)	109.99 (86.2-134.94)	-1.02 (-1.07 to -0.97)
Region					
Andean Latin America	23.4 (15.1–31.0)	66.60 (45.91–84.18)	26.5 (20.4–34.0)	44.12 (34.05–56.28)	-1.33 (-1.54 to -1.12)
Australasia	42.5 (33.5–45.7)	195.83 (153.85-210.03)	40.6 (36.6–50.2)	99.52 (90.07-122.07)	-2.42 (-2.63 to -2.20)
Caribbean	52.7 (39.1–76.5)	165.85 (128.22-230.99)	83.8 (64.6-109.6)	171.85 (130.55-228.65)	0.35 (0.20 to 0.51)
Central Asia	93.7 (80.6-135.9)	166.23 (142.36-241.77)	294.1 (183.7-352.5)	330.33 (204.44-392.96)	3.59 (2.51 to 4.68)
Central Europe	455.0 (380.0-487.6)	341.38 (284.16-366.14)	529.6 (394.4-610.1)	276.59 (204.69-320.93)	-0.79 (-0.87 to -0.71)
Central Latin America	81.0 (71.4–91.3)	64.59 (57.32–70.22)	130.4 (105.2-157.1)	54.60 (43.98–65.70)	-0.82 (-0.94 to -0.70)
Central Sub-Saharan Africa	109.1 (52.3-165.1)	288.37 (157.99-397.68)	184.8 (116.8-260.6)	242.16 (152.52-358.43)	-0.61 (-0.63 to -0.59)
East Asia	808.2 (632.2-1388.4)	73.28 (57.71-125.19)	767.4 (550.2-911.8)	49.79 (35.95–58.09)	-1.13 (-1.36 to -0.89)
Eastern Europe	1219.4 (1005.7–1925.0)	473.89 (393.79-730.98)	2360.9 (1821.1-2735.5)	862.41 (661.96-998.74)	2.08 (0.93 to -3.24)
Eastern Sub-Saharan Africa	328.1 (204.4-431.4)	185.46 (127.41-232.77)	441.3 (309.5-634.8)	147.13 (105.13-190.22)	-0.79 (-0.85 to -0.73)
High-income Asia Pacific	209.0 (170.0-223.0)	118.50 (97.24-126.87)	189.3 (149.5-211.2)	58.32 (50.90-66.09)	-2.52 (-2.68 to -2.36)
High-income North America	754.8 (599.0-807.2)	237.47 (188.77-253.86)	839.4 (768.6–951.0)	166.21 (153.43-186.86)	-1.69 (-1.85 to -1.53)
North Africa and Middle East	447.0 (279.5-807.3)	129.89 (90.62-212.51)	418.0 (334.2-587.9)	79.53 (64.30-111.53)	-1.67 (-1.70 to -1.64)
Oceania	6.0 (3.3–10.2)	112.93 (71.23-171.09)	14.0 (7.6–23.1)	119.18 (71.69-181.83)	0.33 (0.25 to -0.40)
South Asia	145.3 (95.0-212.8)	18.82 (13.07–26.71)	253.4 (197.1-326.3)	16.22 (12.53–20.90)	-0.57 (-0.61 to -0.53)
Southeast Asia	330.8 (253.7-552.8)	100.63 (81.02–145.10)	549.7 (449.3-750.8)	89.81 (74.02-118.36)	-0.36 (-0.47 to -0.25)
Southern Latin America	134.6 (109.6-151.4)	290.76 (235.17-327.77)	146.1 (130.5-166.1)	184.48 (165.39-210.97)	-1.96 (-2.11 to -1.8)
Southern Sub-Saharan Africa	105.9 (83.9–120.0)	308.31 (248.30-358.90)	156.8 (130.6-194.8)	262.87 (219.61-322.97)	-0.66 (-0.85 to -0.46)
Tropical Latin America	434.2 (351.8-467.6)	391.42 (314.41-417.38)	550.1 (489.5-626.5)	234.21 (209.48-267.29)	-2.23 (-2.45 to -2.02)
Western Europe	1012.8 (717.5-1099.8)	193.80 (141.07-209.27)	739.5 (664.0-867.8)	90.99 (82.77-107.64)	-2.97 (-3.15 to -2.80)
Western Sub-Saharan Africa	267.3 (149.2–362.0)	231.46 (139.62-304.88)	420.3 (309.9-530.9)	161.21 (122.11-198.37)	-1.45 (-1.58 to -1.33)

with 0.61/100,000 people (95% UI = 0.47–0.80) (Table 1). Russia, the United States, China, and Brazil are the four countries that reported the most deaths from inflammatory cardiomyopathy and myocarditis. Montenegro, Kazakhstan, and Russia have the highest ASDRs, while India, Nepal, and Jordan have the lowest ASDRs (e-Table 1; Fig. 1A, B).

The death toll of inflammatory cardiomyopathy and myocarditis varies greatly among different ages and genders, and the highest death toll is observed among men aged 60 to 64 and women aged 85 to 89. People over 50

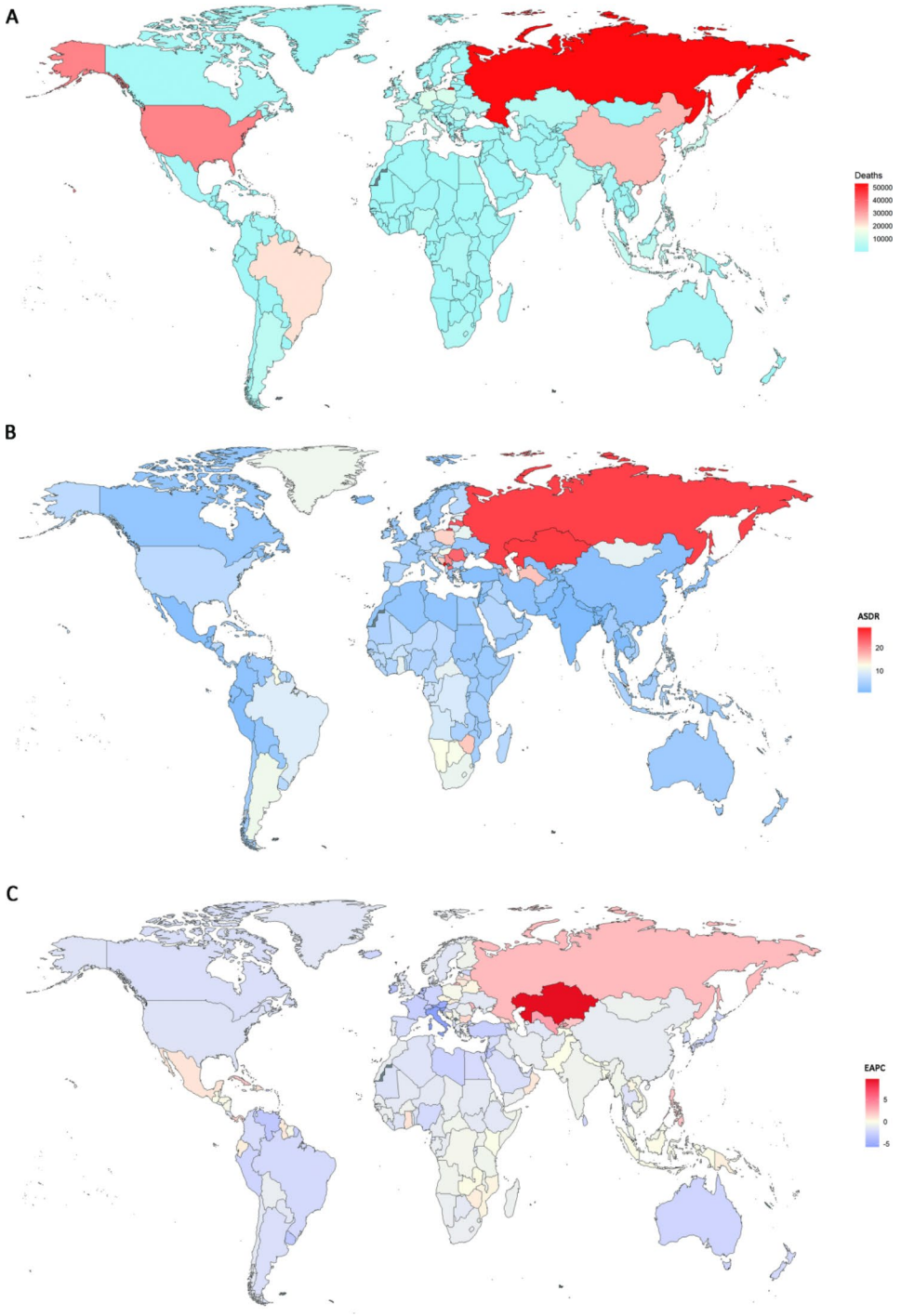

Fig. 1 The global deaths burden of cardiomyopathy and myocarditis in 204 countries and territories. **A**. The absolute number of death cases in 2019. **B**. The ASDR (per 100,000 persons) in 2019. **C**. The EAPC of ASDRs between 1990 and 2019. ASDR, age standardized death rate; EAPC, estimated annual percentage change

years old account for about 80% of the total deaths; People over 70 years old account for 74.26% of the deaths of women with inflammatory cardiomyopathy and myocarditis, while this proportion is only 39.4% of men. In all age groups under 80, more than two-thirds of the deaths were men, while the number of incidents among women over 80 was higher (Table 1, e- Fig. 1A).

At the global level, the number of deaths is increasing every year. This is reflected in both sexes, but the increase rate of males (97.14%) is much higher than that of females (27.90%) (Table 1). Contrary to the 42.80% increase

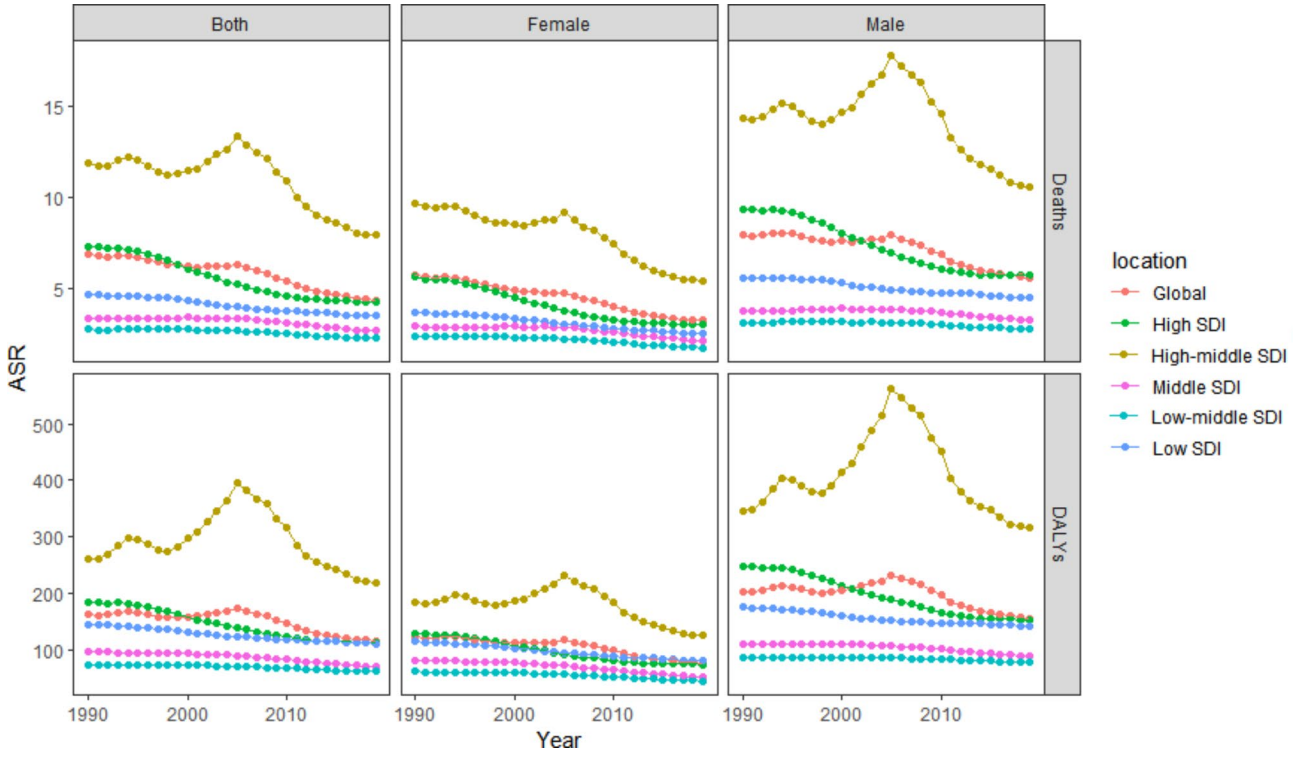

Fig. 2 The change trends of ASDR/age-standardized DALY rate (per 100,000 persons) globally and among different SDI quintiles between 1990 and 2019. **A**. ASDR. **B**. Age standardized DALY rate. ASDR, age-standardized death rate; DALY, disability-adjusted life year

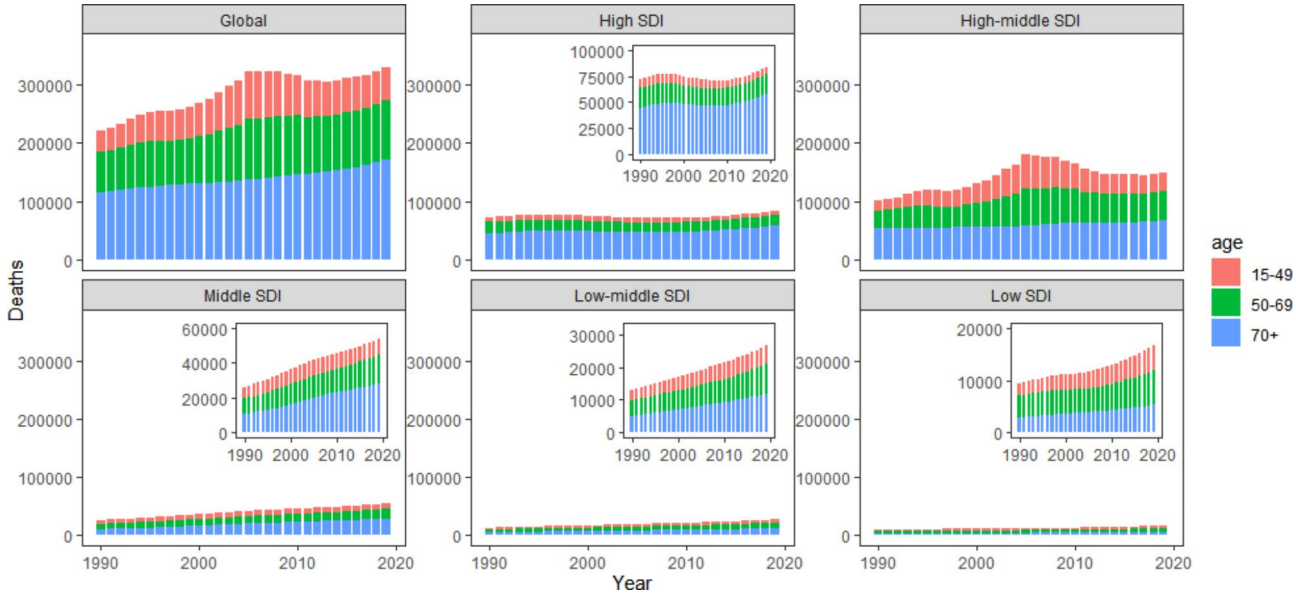

Fig. 3 The proportion of the three age groups (15–49 years, 50–69 years and 70 + years) for cardiomyopathy and myocarditis deaths globally and in five SDI quintiles between 1990 and 2019. SDI: social-demographic index

in total deaths in the past 30 years, the global ASDR decreased from 6.87/100,000 in 1990 to 4.40/100,000 in 2019, and the total EAPC was – 1.62 (95% UI = -1.82 to -1.44). The ASDR of male subjects was significantly higher than that of female subjects (Fig. 2). During the study period, the deaths related to inflammatory cardiomyopathy and myocarditis in the age group over 70 were still the highest among the three age groups (Fig. 3).

In terms of SDI level analysis, from 1990 to 2019, the number of deaths from inflammatory cardiomyopathy and myocarditis increased in all SDI quintiles, with a sharp increase in the middle, middle and low SDI

quintiles (74.54%, and 81.65%, respectively), but no significant increase in the high SDI quintile (14.69%). However, the ASDR showed the biggest downward trend in the high SDI group, and the EAPC was – 2.22 (95% UI = -2.37 to-2.06). The ASDRs in the other SDI quintiles were stable (Table 1; Fig. 2).

Regarding regions, the absolute number of deaths from inflammatory cardiomyopathy and myocarditis increased in almost all GBD regions except Western Europe from 1990 to 2019. The growth in Eastern Europe is the most significant (Table 1). Compared with the data of 1990, the death rate of inflammatory cardiomyopathy and myocarditis in young age (age group of 15 to 49 years) remained stable in 2019 except Eastern Europe. Worryingly, the death toll of inflammatory cardiomyopathy and myocarditis in Eastern Europe is increasing rapidly, especially among middle-aged and older adults (50–69 age group). In addition, in high-income North America, Central Europe, and East Asia, the increase in deaths from inflammatory cardiomyopathy and myocarditis among the elderly (over 70 years old) is equally noteworthy (e-Fig. 2A, C). Only four GBD regions (Central Asia, Eastern Europe, Caribbean, and Oceania) reported increased ASDRs of inflammatory cardiomyopathy and myocarditis, and one GBD region (East Asia) remained stable during the study period; Other GBD regions reported a decrease of ASDRs in inflammatory cardiomyopathy and myocarditis (Table 1).

Observed from 204 countries and regions, ASDRs showed an upward trend in 49 countries and regions, a stable trend in 16 countries and regions, and a downward trend in 139 countries and regions (Fig. 1C). The countries and regions with the highest EAPC are Kazakhstan, Uzbekistan, and Moldova; The countries and regions with the lowest EAPC are Italy, Austria, and Slovenia (e-Table 1).

Our research results show that EAPC had a significant negative correlation with ASDR in 1990 (ρ =-0.3063, $P<0.01$, Pearson correlation analysis), indicating that ASDR in those countries with low baseline disease banks increased faster (Fig. 4A). Similarly, we found a significant negative correlation between the EAPC of ASDR and the HDI in 2019 (ρ = -0.115, $p=0.04$, Pearson correlation analysis), indicating that ASDR increased faster in countries with lower HDI (Fig. 4B).

The DALYs burden of inflammatory cardiomyopathy and myocarditis

In 2019, the global DALY related to inflammatory cardiomyopathy and myocarditis was 9,135,764 (95% UI = 7,864,970–10,039,922), and the high-middle SDI quintile contributed the most. In 2019, the global age-standardized DALY rate was 114.76/100,000 (95 95% UI = 98.69-126.15). The age-standardized DALY rate of the high-middle SDI quintile is also the highest, while the middle-low SDI quintile is the lowest. Among the 21 GBD regions, the highest DALY is in Eastern Europe, followed by high-income North America. The standardized DALY rate is the highest in Eastern Europe, 8.6241/100,000 people, and the lowest in South Asia, 16.22/100,000 people (Table 2). Russia, the United States, China, and Brazil have the highest reported DALY of inflammatory cardiomyopathy and myocarditis in 2019. Russia, Ukraine, and Lithuania have the highest age-standardized DALY rate, while India, Nepal, and Bhutan have the lowest (e- Table 2, e- Fig. 3A, B). Similar to death, the DALYs of inflammatory cardiomyopathy and myocarditis vary greatly between age and sex, and the peak of the DALY curve is about 5 years earlier than the peak of death (e- Fig. 1B).

At the global level, DALYs have increased by 29.39% in the past 30 years. In contrast, the global age-standardized DALY rate dropped from 161.15/100,000 in 1990 (95% UI = 146.73-185.58) to 114.76/100,000 in 2019 (95% UI = 98.69-126.15), and the overall EAPC was – 1.20. We also observed that the age-standardized DALY rate of men was higher, and the age-standardized DALY rate of women decreased more obviously.

As for the analysis of SDI level, except the DALYs of the high SDI quintile decreased slightly, the DALYs of the other SDI quintiles increased, ranging from 0.48 times of the high-middle SDI quintile to 0.19 times of the middle SDI quintile. Accordingly, the age-standardized DALY rate dropped significantly in the high SDI quintile, and the EAPC was – 2.04 (95% UI =–2.16 to–1.93) (Table 2; Fig. 2).

Among the 21 GBD regions, between 1990 and 2019, inflammatory cardiomyopathy and myocardial DALYs in Central Asia increased the most. At the same time, DALYs in western Europe, the high-income Asia-Pacific region, and Oceania have declined significantly. Comparing the data of 2019 with the data of 1990, the DALYs of inflammatory cardiomyopathy and myocarditis in the elderly (over 70 years old) remained stable. Among other areas with more DALYs in inflammatory cardiomyopathy and myocarditis, the DALYs in Eastern Europe is still the most, and the proportion of people aged 15–49 is the largest. The growth in Eastern Europe is obvious, while the decline in Western Europe is obvious (e- Fig. 2B, D). Age-standardized DALY rate only increased in four regions (Central Asia, Eastern Europe, Caribbean, and Oceania) but decreased in all other regions (Table 2).

Observed from 204 countries and regions, the age-standardized DALY rate showed an upward trend in 37 countries and regions, a stable trend in 19 countries and regions, and a downward trend in 148 countries and regions (e- Fig. 3C). The three countries and regions with the highest EAPC in DALYs are Kazakhstan, Moldova,

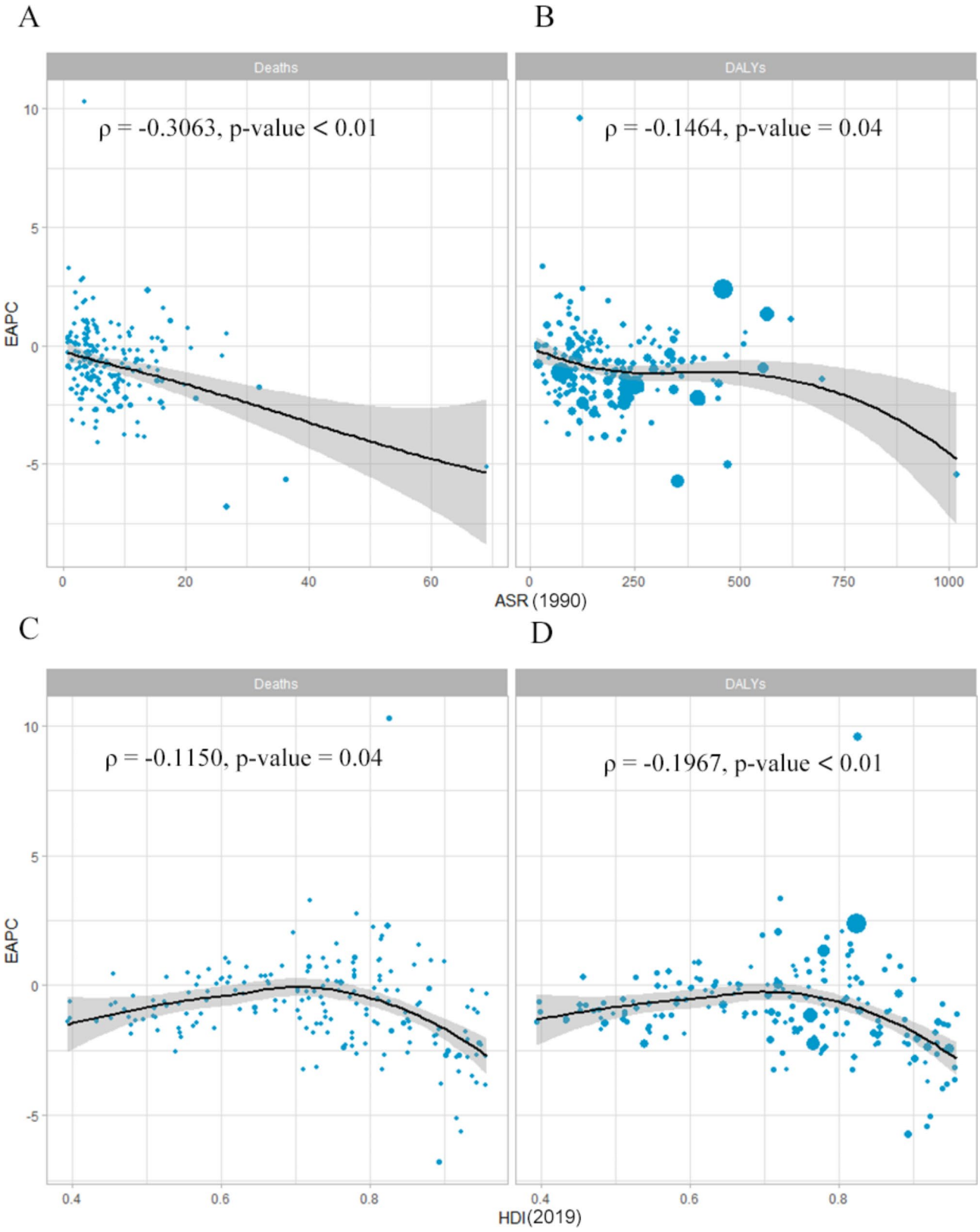

Fig. 4 The correlation between the EAPC of deaths/DALYs and the corresponding ASRs in 1990 (**A**, **B**) and HDI in 2019 (**C**, **D**). The size of circle is increased with the number of death cases of cardiomyopathy and myocarditis. ASR, age-standardized death rate; DALYs, disability-adjusted life years; EAPC, estimated annual percentage change; HDI, human development index

and Uzbekistan; The three countries and regions with the lowest EAPC in DALYs are Austria, Italy, and Slovenia (e-Table 2). The relationship between EAPC of DALYs and age-standardized DALY rate /HDI reflects the same pattern as the dead EAPC (Fig. 4C, D).

Attributable risk factors changes

Regarding risk factors, there are much heterogeneity among different geographical locations, ages, genders, and years. In 21 GBD areas, the death rate of inflammatory cardiomyopathy and myocarditis caused by high systolic blood pressure (SBP) is roughly equal between the sexes. The bad news is that, compared with 1990, in all GBD areas, the number of female deaths caused by alcohol use increased in 2019 (e-Fig. 5A). From different age groups, the proportion of men under 40 who died due to excessive SBP was slightly higher than that of women, and the proportion of women over 40 who died due to excessive SBP was slightly higher than that of men. Among men under 60 and women under 65, the proportion of deaths caused by high SBP in 2019 was lower than that in 1990; Among men over 60 and women over 65, the proportion of deaths caused by high SBP in 2019 was higher than that in 1990 (e-Fig. 5B).

Discussion

Based on GBD 2019, this study comprehensively analyzed the updated global burden of deaths and DALYs and the most relevant risk factors for inflammatory cardiomyopathy and myocarditis from 1990 to 2019. Overall, the absolute deaths and DALYs in inflammatory cardiomyopathy and myocarditis increased while the overall ASR of both decreased. There are significant differences in inflammatory cardiomyopathy and myocarditis burden patterns and trends among different locations, ages and genders, and risk factors. Our research can be regarded as an important extension of previous research and further provide the latest comprehensive information on the epidemiology of inflammatory cardiomyopathy and myocarditis for health decision-makers and policymakers to provide information for strategic development, prevention and treatment plans, and optimization of resource allocation in a health system.

We noted that the global burden of inflammatory cardiomyopathy and myocarditis was heavy in 2019, with 340,349 deaths and 9,135,764 DALYs. For inevitable reasons, these figures more or less underestimate the impact of inflammatory cardiomyopathy and myocarditis [15, 16]. Targeted health policies combined with local conditions may be the key to reducing disease burden. In addition, the high-middle SDI areas where the burden of inflammatory cardiomyopathy and myocarditis is highly concentrated deserve special attention, not only in the absolute number of death and disability-adjusted years but also in the ASRs of both. It is reported that inflammatory cardiomyopathy and acute myocarditis are even the main causes of CVD DALYs in Central and Eastern Europe [17], which is higher than in other parts of the world. Russia, the United States, China, and Brazil have the highest reported deaths and DALYs from inflammatory cardiomyopathy and myocarditis at the national and regional levels. This further emphasizes the necessity of strengthening the understanding of inflammatory cardiomyopathy and myocarditis in these areas.

Understanding the time trend of inflammatory cardiomyopathy and myocarditis burden is also helpful in formulating more targeted public health strategies. Contrary to the death toll increase of 42.84% and DALYs increase of 29.39% in the past 30 years, the ASDR and age-standardized DALY rates of inflammatory cardiomyopathy and myocarditis decreased, indicating that population growth and aging may be one of the reasons for the absolute increase of the global burden of inflammatory cardiomyopathy and myocarditis [18]. In the SDI level analysis, deaths and DALYs from inflammatory cardiomyopathy and myocarditis increased in almost all SDI quintiles, with a sharp increase in deaths in the middle and middle-low SDI quintiles and a sharp increase in DALYs in the high-middle and low SDI quintiles, which were less pronounced in the high SDI quintiles. Correspondingly, the ASDR and age-standardized DALY rates decreased in high SDI quintiles. From a regional perspective, Central Asia and Eastern Europe have seen the greatest increase in burden. In contrast, Western Europe, high-income Asia Pacific, and Oceania have substantially progressed in reducing ASRs. A similar pattern of epidemiological changes has been observed in ASRs for overall cardiovascular disease [16]. Policymakers must take this phenomenon into account and pay attention to the potential public health measures behind the rapid decline of ASRs in Western Europe, the high-income Asia-Pacific region, and Oceania, and implement comprehensive strategies based on health, education, and income in countries with increased burden of inflammatory cardiomyopathy and myocarditis.

We also verified that the magnitude of ASR change from 1990 to 2019, namely EAPC, was significantly negatively correlated with baseline ASR in 1990. For countries and regions with high ASR in 1990, the burden of inflammatory cardiomyopathy and myocarditis is more likely to decrease. One possible reason is that countries and regions with high ASR are more likely to bear a heavier burden of cardiovascular diseases. To solve this problem, these countries and regions have made great public health efforts, such as improving the management of various cardiovascular risk factors, continuous disease surveillance, and preventing complications. These countries are also more likely to regard inflammatory

cardiomyopathy and myocarditis as important parts of disease prevention programs. In addition, we also find that there is a negative correlation between EAPC and HDI. In countries with higher human development indexes, the burden of inflammatory cardiomyopathy and myocarditis seems to be reduced. To some extent, the declining trend of ASR reflects the benefits of sound health systems, which can reduce the burden of inflammatory cardiomyopathy and myocarditis by adjusting risk factors. In addition, improving treatment and management measures in recent years may further promote this trend [19, 20]. These findings confirm that preventing inflammatory cardiomyopathy and myocarditis is no longer the primary task in developed areas. The countries with low/middle HDI are also facing challenges because there is a relatively large increase in ASRs in these countries. Moreover, the health systems in these areas may not be able to cope with the foreseeable increase in the burden of inflammatory cardiomyopathy and myocarditis in the future, which indicates that more active local preventive policy intervention may be needed to cope with various challenges faced by the health care system. In addition, the burden of inflammatory cardiomyopathy and myocarditis in low HDI areas may be underestimated [16, 21], so improving disease surveillance in these areas and promoting the implementation and evaluation of relevant health policies is necessary.

The absolute number of deaths /DALYs and ASR of inflammatory cardiomyopathy and myocarditis in men was significantly higher than in women, and the peak age of burden in men was earlier than in women. These differences partly reflect the distribution of risk factors between men and women. At the same time, the protective effect of estrogen, local differences in vascular hemodynamics, and many other pathophysiological factors may also contribute to sex differences. In addition, it is also possible that these findings are because men are more often diagnosed with myocarditis than women and have a worse prognosis, possibly due to a more pronounced fibrotic response [22]. We also noted a global increase in deaths associated with inflammatory cardiomyopathy and myocarditis in both men and women and a more pronounced decline in ASDR in women. The findings for DALY were consistent with those for death. This suggests that prevention policies and intervention treatment may be more effective for women over the same period.

Due to the widespread use of antihypertensive drugs, the global average blood pressure has remained unchanged or slightly decreased in the past 40 years [23]. In contrast, the global prevalence of hypertension has increased, but the proportion of cognition, treatment, and blood pressure control of hypertension is low [24]. Countries and regions with low SDI, middle-low SDI, and middle SDI quintile are particularly backward. At the same time, our research results also show that the contribution of high SBP to the death of inflammatory cardiomyopathy and myocarditis has increased in these areas. It is urgent to strengthen blood pressure management to correct this trend.

Although the GBD study provides detailed estimates of the global burden and risk factors of inflammatory cardiomyopathy and myocarditis, there are several limitations that affect the current study. First, the data collected by different regions and countries may vary greatly in terms of quality, comparability, accuracy, and degree of missing. Although statistically robust methods have been applied to adjust the data as much as possible, it will inevitably lead to some bias in the estimates. Second, diagnostic criteria may have changed over time, and various nomenclature and classification schemes may exist in different literature [3]. Finally, our analyses of the burden of inflammatory cardiomyopathy and myocarditis were performed at the regional and national levels and did not further examine local characteristics, such as differences between urban and rural areas.

Conclusion

In short, inflammatory cardiomyopathy and myocarditis are still important global public health problems, which will increase the burden on a global scale. It is worth noting that the changing pattern of the burden of inflammatory cardiomyopathy and myocarditis presents a mixed situation: on the one hand, we have achieved the reduction of ASRs in some developed areas with heavy burdens in the past; On the other hand, the death and DALYs caused by inflammatory cardiomyopathy and myocarditis are still an important problem. At the same time, the health problems in those relatively underdeveloped areas may become more important in the near future. In several high-risk areas, it should be emphasized to prevent inflammatory cardiomyopathy and myocarditis caused by government policy intervention in blood pressure control. Further research is needed to expand our knowledge of potential risk factors related to inflammatory cardiomyopathy and myocarditis and to improve the prevention, early detection, and treatment of these diseases.

Supplementary Information

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Supplementary Material 1

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Author contributions
JZ developed the original research idea and study design. WX, GW, SW and CG performed data extraction, and analyses. WX, GW and SW drafted the first version of the manuscript. JZ, GW and WX critically reviewed the manuscript and revised it. CG and SW worked on data validation. WX performed the graphs. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
The datasets supporting the conclusions of this article are included within the article (and its additional files). Data is available on https://ghdx.healthdata.org/.

Declarations

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