

# The Global Burden of Appendicitis in 204 Countries and Territories from 1990 to 2019

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**Objective:** Appendicitis is a common surgical emergency. This study aimed to estimate the worldwide burden and trends of appendicitis from 1990 to 2019.

**Methods:** Data on appendicitis were derived from the Global Burden of Disease 2019. Incidence and disability-adjusted life-years (DALYs) data were analyzed at global, regional, and national levels and stratified by sex, age, and socio-demographic index. The estimated annual percentage change and relative change were used to assess changing trends. Pearson's correlation test was used to assess the correlation between different measures.

**Results:** Global incidence grew by 63.55% between 1990 and 2019, age-standardized incidence rate climbed by an estimated percentage change of 0.58 per year, whereas the number of DALY declined by 31.93% during the same period, with an estimated annual percentage change of -2.77. In 2019, the areas of Andean Latin America and the Caribbean had the highest age-standardized rates of incidence and DALYs. While South Asia saw the largest increase in age-standardized incidence rates, Andean Latin America saw the biggest decline in age-standardized rates of incidence and DALYs. At the national level, Bangladesh, Bhutan, and Peru were the top three countries in terms of age-standardized incidence rates in 2019, and Honduras, Haiti, and the Central African Republic held the highest age-standardized DALY rates. Ethiopia experienced the most age-standardized incidence rate increase, and Peru saw the largest decline in age-standardized rate of incidence and DALYs. Significant negative correlations between age-standardized DALY rates and socio-demographic index, between estimated annual percentage change and age-standardized incidence rates, were observed at the national level.

**Conclusion:** Appendicitis remains a major global health concern. Although the trends in DALYs decreased, the burden of incidence increased from 1990 to 2019. Policymakers should create health policies adapted to local conditions to manage the burden of appendicitis globally.

**Keywords:** appendicitis, global burden, incidence, disability-adjusted life-years, socio-demographic index

## Introduction

Appendicitis is one of the most common surgical emergencies globally and imposes an important burden on modern health systems.<sup>1</sup> Because it is very common among adults and children worldwide, previous studies of appendicitis epidemics have mainly focused on incident cases. Although the pooled incidence of the disease has been decreasing in high-income regions and countries since the 1990s, it has increased in newly industrialized countries.<sup>2-4</sup> While appendicitis is also associated with the risk of morbidity and mortality, disability-adjusted life-years (DALYs), a comprehensive measurement of premature mortality and disability, is a meaningful measure that should be analyzed across geographical areas.

The Global Burden of Disease (GBD) study has estimated a variety of metrics for diseases annually since 1990 and provides a great opportunity for comparable assessments of disease burden and trends at the global, regional, and national levels; however, no study addressing these data on appendicitis has been published.<sup>5,6</sup> A systematic review and meta-analysis reported the incidence of appendicitis in Western countries and several other industrialized countries; however, this study did not report data on mortality and morbidity rates. Additionally, the association between the burden of appendicitis and the socio-economic development of countries, age distribution, and sex differences were also not mentioned.<sup>4</sup> Studies that have

reported the association between socio-economic status and the incidence and severity of appendicitis, in which areas with a lower socio-economic status have much more incidence cases and perforation rates compared to areas with a high socio-economic status, have only used statewide or nationwide data sets.<sup>7-9</sup> Other studies dealing with the epidemiology of appendicitis based on sex and age were also statewide or nationwide population-based studies.<sup>10-12</sup> A study on appendicitis burden referring to the incidence and DALYs at the global level is needed.

In this study, using the data from the Global Burden of Diseases, Injuries, and Risk Factors Study 2019 (GBD 2019), we analyzed the appendicitis burden of incidence and DALYs at the global, regional, and national levels stratified by sex, age, and SDI and in terms of numbers and age-standardized rates (ASRs) from 1990 to 2019. A burden and trend report for different countries and regions will help improve health care administration for appendicitis.

## Materials and Methods

### Data Source

Data on appendicitis burden were collected from the GBD 2019, which systematically analyzed 369 diseases and injuries, 87 risk factors for 204 countries and territories, and 21 regions from 1990 to 2019.<sup>5,6</sup> In the GBD 2019, the countries or territories were classified into five regions, namely, low, low-middle, middle, high-middle, and high, in terms of the socio-demographic index (SDI), and the world was also geographically divided into 21 regions. In this study, data on appendicitis burden were mainly considered in terms of incidence and disability-adjusted life years (DALYs). Data on these appendicitis parameters were derived using the Global Health Data Exchange query tool (<http://ghdx.healthdata.org/gbd-results-tool>).<sup>13</sup> Appendicitis burden data (rates, number of cases) on incidence and DALYs were extracted according to sex, age, SDI areas, geographic regions, and countries/territories from 1990 to 2019, without any inclusion or exclusion criteria. This study adhered to the guidelines for accurate and transparent health estimates reporting (GATHER) statements.<sup>14</sup>

### Statistical Analysis

In this study, the incidence and DALYs number in 204 countries and territories with 95% uncertainty intervals (UIs) were used. To compare populations with different age structures or the same population with changing age structures in different time periods, data were standardized by applying age-specific rates. The age-standardized rate (ASR) did not reflect the actual case number, but was only used to compare the appendicitis burden in different countries, different regions, or different historical periods in the same region, so as to facilitate data comparisons. The method used to calculate ASR has been reported previously.<sup>15,16</sup> Age-standardized rates of incidence and DALYs with 95% UIs were calculated using the following formulae:

$$ASR = \frac{\sum_{i=1}^A a_i W_i}{\sum_{i=1}^A W_i} \times 100,000$$

Where  $a_i$  is the age-specific rate in the  $i^{\text{th}}$  age group,  $w$  is the number of people (or weight) in the  $i^{\text{th}}$  age group from among the selected standard population, and  $A$  represents the number of age groups.

The relative changes (RC) and estimated annual percentage changes (EAPC) with 95% confidence intervals (CIs) were used to quantify the trends of appendicitis from 1990 to 2019. The relative changes are defined as follows:

$$RC = \frac{c1 - c2}{c2} \times 100\%$$

Where  $c_1$  represents the number or ASR in 2019 and  $c_2$  represents the number or ASR in 1990.<sup>17</sup> The EAPC is a widely accepted index for quantifying and describing trends in ASR.<sup>18</sup> EAPC was estimated using a linear regression model that was fitted to the natural logarithm of the ASR.<sup>19</sup> The formulae are as follows:

$$y = \alpha + \beta x + \varepsilon$$

$$EAPC = 100 \times (\exp(\beta) - 1)$$

Where  $y = \ln(\text{ASR})$ ,  $x$  is the calendar year,  $\varepsilon$  represents error term. These trends were assessed as follows: 1) ASR was considered to show an increasing trend with EAPC, and its 95% CI > 0; and 2) ASR was considered to have a decreasing trend with EAPC, and its 95% CI < 0.<sup>15</sup>

The Wilcoxon signed-rank test was used to compare sex differences in the global burden for different age groups.<sup>20</sup> The Wilcoxon signed rank test is a non-parametric statistical hypothesis test used to determine if the population mean ranks of two related samples, matched samples, or repeated measurements on a single sample vary.<sup>21,22</sup> The correlation between ASRs and SDI values and EAPC was assessed using a Pearson's correlation test model. An R of -1 indicates a perfect negative linear relationship, an R of 0 indicates no linear relationship, and an R of 1 indicates a perfect positive linear relationship between variables.<sup>21</sup> In this study, data were analyzed using the R program (Version 3.6.3), and a p-value of < 0.05 was considered statistically significant.

## Results

### Appendicitis Burden at the Global Level

In 2019, there were 17.70 million (95% UI: 14.10–22.32) new cases of appendicitis globally, with an age-standardized incidence rate (ASIR) of 229.86 (95% UI: 180.88–291.0) per 100,000 population (Figures 1A and S1A, Table 1). The incidence increased by 63.55% (95% UI: 58.25–69.45%) and ASIRs increased with an EAPC of 0.58 (95% CI: 0.44–0.71) from 1990 to 2019. Globally, there were 1.50 million (95% UI: 1.24–1.71) DALYs attributed to appendicitis in 2019, representing a decrease of 31.93% (95% UI: -45.59 to -1.88%) from 1990 to 2019 (Figure S1B, Table 2). The global age-standardized DALY rate of appendicitis was 19.35 (95% UI: 15.92–21.98) per 100,000 population in 2019, which represents a decreasing EAPC of -0.77 (95% CI: -2.84 to -2.7) from 1990 to 2019 (Figure 1B and Table 2).

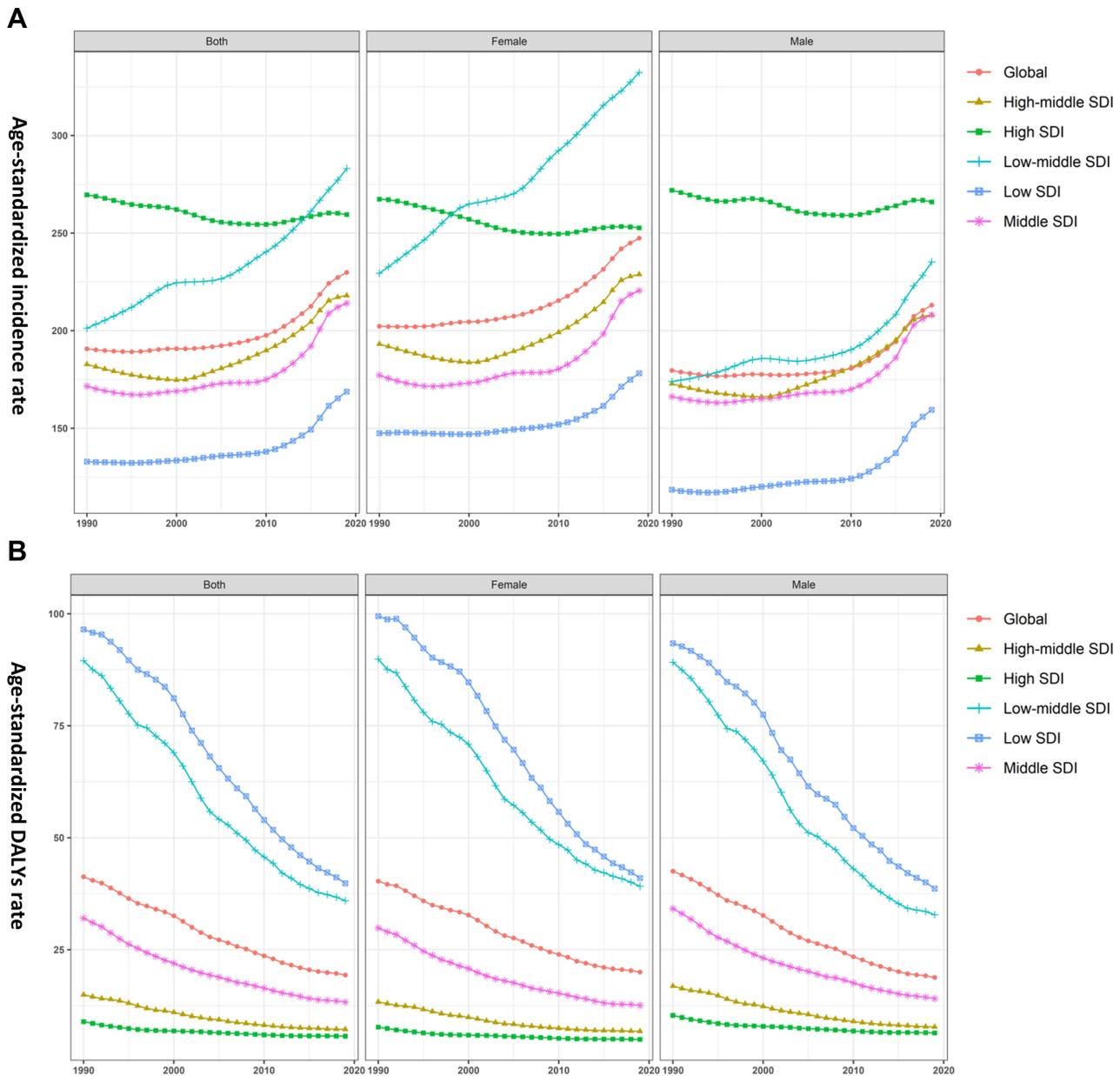
### Appendicitis Burden According to SDI Level

In 2019, the highest ASIR was observed in the low-middle SDI quintiles (283.10 [95% UI: 227.24–354.20] per 100,000 population) among all SDI regions, whereas the lowest ASIR was observed in the low SDI quintiles (168.76 [95% UI: 133.50–214.04] per 100,000 population). From 1990 to 2019, the number of incident cases increased across all SDI quintiles. Among them, the low SDI regions had the greatest increase in incident cases (1.75-fold). Analysis of ASIR according to SDI quintiles showed increasing trends in all SDI areas, except high SDI regions, over the study period. From 1990 to 2019, the sharpest increase in ASIR was also observed in the low-middle SD quintiles, which exhibited an EAPC of 1.05 (95% CI: 0.96–1.14), while the high SDI area had an EAPC of -0.15 (95% CI: -0.2 to -0.1) (Figure 1A and Table 1).

The highest rate of age-standardized DALYs in 2019 was observed in the low SDI quintiles (39.82 [95% UI: 28.82–51.56] per 100,000 population), and the lowest was observed in the high SDI quintiles (5.69 [95% UI: 4.45–7.14] per 100,000 population). The number of DALYs decreased in all SDI quintiles over the study period, with middle SDI regions holding the most pronounced decrease (0.34-fold). A decreasing trend in the age-standardized DALY rates over the study period was observed in all SDI quintiles, and the steepest decreasing trend was found in the low-middle SDI quintiles (EAPC: -3.37 [95% CI: -3.48 to -3.27]) (Figure 1B and Table 2).

### Appendicitis Burden Affected by Sex and Age

In 2019, the burden of incidence and DALYs were higher for women globally (Figure 1, Tables 1 and 2). The Wilcoxon test showed significant differences between sexes in the global incidence burden of numbers and rates among different age groups ( $p < 0.05$ ). Although the number of incident cases and incidence rate all peaked in the 15 to 19 age group for both females and males, the number of incident cases was higher for females in all groups except in the 1 to 4 and 30 to 39 age groups, and incidence rates were higher in females in the age groups younger than 70 years (Figure 2A and B). No statistically significant difference in DALYs between women and men according to age group was observed in 2019. The number of DALY for both sexes and the DALY rates for females also peaked in the 15–19 age group in 2019, while the DALY rate for males increased with age, peaking in the 90–94 age group (Figure 2C and D).



**Figure 1** The age-standardized incidence (A) and disability-adjusted life-year (DALY) (B) rates of global appendicitis burden for sexes and socio-demographic index (SDI) quintiles, 1990–2019.

### Appendicitis Burden at the Regional Level

In 2019, the highest ASIRs were observed in Andean Latin America (852.38 [95% UI: 697.66–1059.42] per 100,000 population), high-income Asia Pacific (448.09 [339.75–572.27] per 100,000 population), and Central Latin America (358.22 [271.11–460.12] per 100,000 population). Andean Latin America has a much higher ASIR than other regions throughout the past three decades. The lowest ASIRs were observed in Oceania (109.19 [85.02–140.31] per 100,000 population), Western Sub-Saharan Africa (120.12 [89.74–158.90] per 100,000 population), and Eastern Sub-Saharan Africa (127.0 [96.73–166.87] per 100,000 population). From 1990 to 2019, the number of incident cases increased across all regions except high-income Asia Pacific, Central Europe, and Eastern Europe. Western sub-Saharan Africa had the highest increase in incident cases (2.62-fold). Increasing trends of ASIR were also observed in most geographic regions from 1990 to 2019, of which the most pronounced was Southern Latin America (EAPC: 1.45 [95% CI: 1.32–1.57]). In

**Table 1** The Burden and Trends on Incidence of Appendicitis from 1990 to 2019

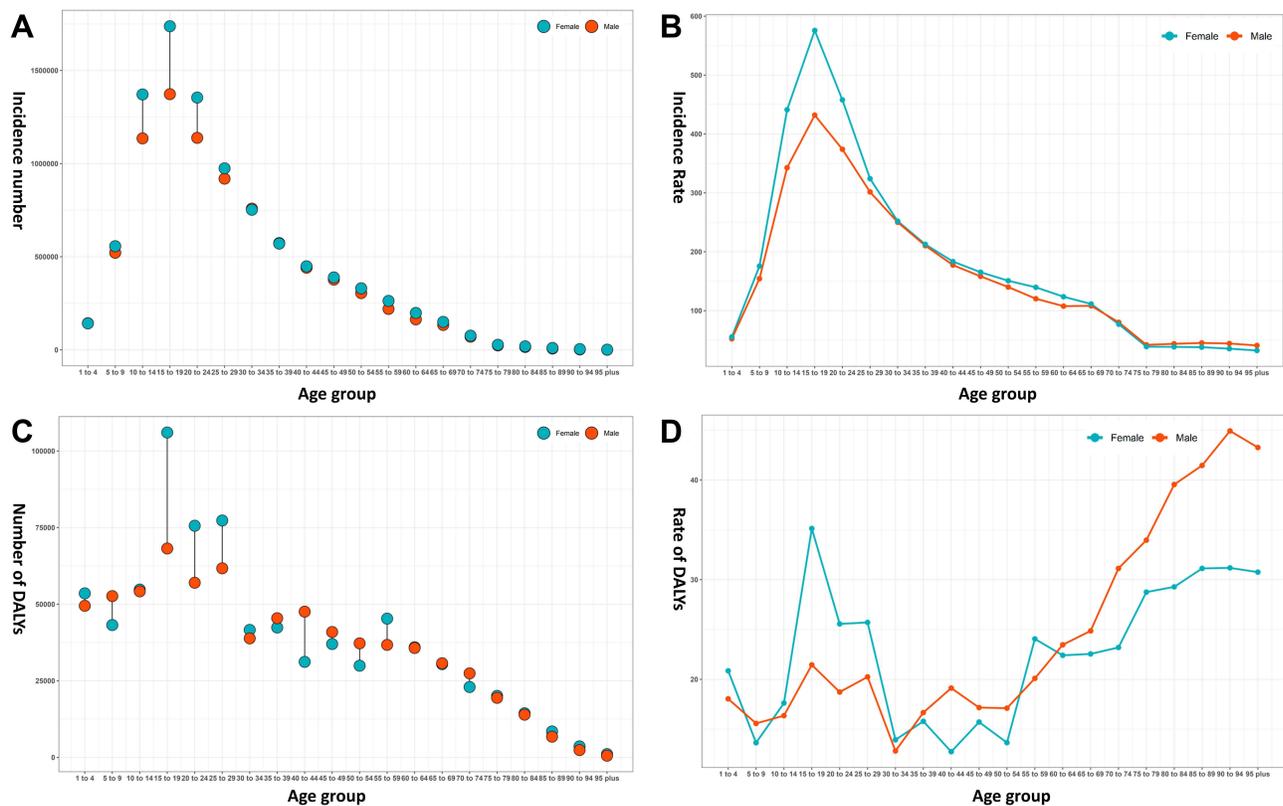
Characteristics	Numbers in 2019 (95% UI)	RC Between 1990 and 2019 (95% UI)	ASIR per 10 <sup>5</sup> in 2019 (95% UI)	EAPC from 1990 to 2019 (95% CI)
<b>Global</b>	17,698,765(14,101,114–22,324,572)	63.55%(58.25%–69.45%)	229.86(180.88–291.00)	0.58(0.44–0.71)
<b>Sex</b>				
Male	8,322,038(6,620,285–10,532,093)	61.62%(56.21%–61.19%)	213.10 (167.68–271.07)	0.49(0.33–0.64)
Female	9,376,726(7,467,261–11,763,257)	65.30%(59.69%–71.62%)	247.41 (196.15–311.16)	0.66(0.54–0.78)
<b>SDI</b>				
High	2,292,170(1,900,644–2,760,932)	7.05%(–0.48%–16.03%)	259.52(210.96–321.16)	–0.15(–0.2–0.1)
High-middle	2,896,601(2,281,587–3,614,229)	32.99%(23.70%–44.13%)	218.04(168.23–277.99)	0.68(0.51–0.84)
Middle	5,079,676(3,968,284–6,454,663)	50.15%(42.49%–59.11%)	214.06(164.03–272.60)	0.69(0.5–0.88)
Low-middle	5,328,706(4,217,801–6,753,992)	113.46%(103.17%–124.24%)	283.10(227.24–354.20)	1.05(0.96–1.14)
Low	2,091,773(1,596,562–2,698,952)	174.73%(164.60%–184.70%)	168.76(133.50–214.04)	0.66(0.5–0.83)
<b>Region</b>				
Andean Latin America	558,662(456,610–696,711)	2.55%(16.08%–6.76%)	852.38(697.66–1059.42)	–1.87(–2.27–1.47)
Australasia	74,147(58,363–94,560)	30.86%(38.31%–22.84%)	283.92(220.06–369.34)	0.12(0.1–0.13)
Caribbean	132,078(102,639–169,890)	56.5%(63.59%–50.33%)	282.90(219.36–361.93)	0.68(0.6–0.77)
Central Asia	233,029(175,238–306,969)	28.58%(36.04%–22.25%)	245.34(184.64–323.50)	0.02(–0.06–0.1)
Central Europe	203,543(167,437–245,338)	–16.37%(–8.24%–23.16%)	220.27(175.18–271.35)	0.13(0.05–0.22)
Central Latin America	900,312(686,867–1,159,909)	49.3%(55.79%–43.1%)	358.22(271.11–460.12)	0.34(0.24–0.44)
Central Sub-Saharan Africa	416,895(315,480–538,242)	230.22%(246.58%–214.94%)	284.29(224.91–361.67)	1.06(0.97–1.15)
East Asia	2,565,267(2,034,140–3,149,307)	17.29%(34.83%–2.85%)	176.20(138.46–219.96)	0.42(0.26–0.59)
Eastern Europe	480,413(370,619–612,175)	–0.73%(5.21%–5.66%)	273.23(202.64–354.62)	0.92(0.59–1.26)
Eastern Sub-Saharan Africa	591,822(432,475–797,031)	228.45%(237.93%–218.72%)	127.0(96.73–166.87)	1.37(1.13–1.6)
High-income Asia Pacific	586,290(463,318–730,184)	–23.52%(–17.72%–28.55%)	448.09(339.75–572.27)	–0.12(–0.2–0.04)
High-income North America	571,783(514,543–636,513)	12.88%(30.35%–2.25%)	162.58(144.89–182.06)	–0.4(–0.51–0.3)
North Africa and Middle East	1,745,503(1,329,173–2,271,525)	151.57%(170.92%–135.67%)	271.58(206.05–350.85)	1.29(1.22–1.36)
Oceania	15,219(11,665–19,748)	137.84%(148.96%–127.66%)	109.19(85.02–140.31)	0.38(0.27–0.49)
South Asia	5,214,009(4,114,157–6,620,999)	152.21%(166.25%–138.42%)	266.74(212.69–334.86)	1.27(1.06–1.48)
Southeast Asia	1,146,656(892,434–1,477,241)	79.06%(90.33%–70.2%)	166.46(129.15–216.33)	0.94(0.88–1)
Southern Latin America	201,955(157,808–254,876)	96.51%(110.95%–82.81%)	305.53(236.30–389.33)	1.45(1.32–1.57)
Southern Sub-Saharan Africa	154,821(116,584–203,979)	74.54%(85.84%–64.99%)	183.03(138.55–241.03)	0.64(0.07–1.21)
Tropical Latin America	298,011(243,250–366,750)	65.35%(77.44%–56.24%)	135.57(109.66–167.80)	0.85(0.8–0.91)
Western Europe	997,135(806,633–1,229,567)	9.66%(17.00%–2.9%)	278.55(220.22–352.76)	0.36(0.29–0.43)
Western Sub-Saharan Africa	611,213(445,004–824,269)	262.28%(276.62%–248.11%)	120.12(89.74–158.90)	1.42(1.14–1.69)

**Abbreviations:** ASIR, age-standardized incident rates; RC, relative change; EAPC, estimated annual percentage change; SDI, socio-demographic index; UI, uncertain interval; CI, confidential interval.

**Table 2** The Burden and Trends on Disability-Adjusted Life-Years (DALYs) of Appendicitis from 1990 to 2019

Characteristics	Numbers in 2019 (95% UI)	RC Between 1990 and 2019 (95% UI)	ASR Per 10 <sup>5</sup> in 2019 (95% UI)	EAPC from 1990 to 2019 (95% CI)
<b>Global</b>	1,501,492(1,236,232–1,705,756)	–31.93%(–1.88%–45.59%)	19.35(15.92–21.98)	–2.77(–2.84–2.7)
<b>Sex</b>				
Male	726,756(552,156–854,949)	–34.92%(–45.83%–3.17%)	18.81(14.32–22.10)	–2.96(–3.02–2.89)
Female	774,736(603,981–897,484)	–28.87%(–48.52%–14.14%)	20.01(15.70–23.17)	–2.59(–2.67–2.52)
<b>SDI</b>				
High	65,652(53,398–80,562)	–15.29%(–1.3%–21.17%)	5.69(4.45–7.14)	–1.39(–1.54–1.25)
High-middle	109,306(92,726–132,526)	–35.17%(–23.78%–43.19%)	7.22(6.01–8.7)	–2.67(–2.83–2.51)
Middle	317,880(265,061–369,324)	–40.72%(–20.54%–52.99%)	13.31(11.07–15.5)	–3.04(–3.15–2.92)
Low-middle	614,999(495,566–709,957)	–34.73%(2.14%–51.05%)	35.94(28.96–41.41)	–3.37 (–3.48–3.27)
Low	392,572(284,827–505,022)	–18.18%(50.28%–40.71%)	39.82(28.82–51.16)	–3.3(–3.46–3.14)
<b>Region</b>				
Andean Latin America	24,903(19,692–31,923)	–80.99%(–71.48%–86.59%)	39.49(31.3–50.62)	–6.92(–7.73–6.1)
Australasia	1,641(1,257–2,143)	13.08%(34.27%–3.51%)	5.15(3.76–7.01)	–0.95(–1.04–0.87)
Caribbean	19,774(14,156–27,771)	–31.73%(–1.84%–51.84%)	43.3(30.29–61.73)	–1.62(–2.19–1.04)
Central Asia	9,684(7,864–12,463)	–50.49%(–23.12%–60.76%)	10.43(8.46–13.43)	–4.01(–4.39–3.63)
Central Europe	9,252(7,565–12,887)	–53.17%(–32.73%–61.27%)	6.56(5.28–8.66)	–2.83(–3.07–2.58)
Central Latin America	79,612(63,718–97,580)	–23.81%(–7.53%–37.41%)	32.18(25.82–39.36)	–1.92(–2.29–1.55)
Central Sub-Saharan Africa	43,183(24,388–69,515)	25.58%(202.26%–19.99%)	36.13(21.15–57.69)	–1.55(–1.72–1.39)
East Asia	68,712(55,191–84,652)	–61.63%(–51.17%–70.43%)	4.37(3.5–5.41)	–4.84(–5.03–4.65)
Eastern Europe	21,213(17,341–30,074)	–49.91%(–20.23%–59.31%)	9.11(7.31–12.41)	–2.58(–2.88–2.27)
Eastern Sub-Saharan Africa	124,840(74,786–195,219)	–2.96%(134.66%–38.68%)	34.19(22.03–56.27)	–2.12(–2.16–2.09)
High-income Asia Pacific	12,236(9,472–15,548)	–39.94%(–33.24%–51.21%)	6.94(4.94–9.53)	–1.53(–1.87–1.19)
High-income North America	22,691(18,436–27,444)	17.53%(29.5%–5.96%)	5.23(4.26–6.29)	–0.73(–0.85–0.6)
North Africa and Middle East	70,903(51,605–87,877)	–5.58%(92.26%–36.57%)	12.43(9.18–15.35)	–2.32(–2.36–2.28)
Oceania	1,674(940–2,395)	71.16%(152.74%–24.36%)	14.33(8.15–20.09)	–0.66(–0.76–0.56)
South Asia	703,819(557,425–836,936)	–31.29%(12.2%–50.83%)	39.77(31.54–47.15)	–3.7(–3.88–3.52)
Southeast Asia	102,875(75,572–121,780)	–42.57%(5.82%–60.09%)	15.69(11.73–18.65)	–3.09(–3.17–3)
Southern Latin America	8,121(6,663–10,668)	–19.63%(10.77%–33.11%)	11.32(9.22–14.76)	–1.85(–2.24–1.46)
Southern Sub-Saharan Africa	14,079(11,730–17,255)	9.23%(52.16%–16.12%)	18.08(15.12–22.14)	–0.89(–1.4–0.38)
Tropical Latin America	49,542(38,112–58,203)	21.72%(45.85%–14.74%)	21.48(16.54–25.26)	–0.43(–0.61–0.26)
Western Europe	28,489(23,147–37,211)	–23.25%(4.1%–31.86%)	5.5(4.17–7.14)	–1.33(–1.44–1.22)
Western Sub-Saharan Africa	84,249(53,617–120,589)	–12.44%(37.64%–41.9%)	19.32(13.53–25.96)	–3.2(–3.43–2.97)

**Abbreviations:** DALY, disability-adjusted life-year; ASR, age-standardized rates; RC, relative change; EAPC, estimated annual percentage change; SDI, socio-demographic index; UI, uncertain interval; CI, confidential interval.



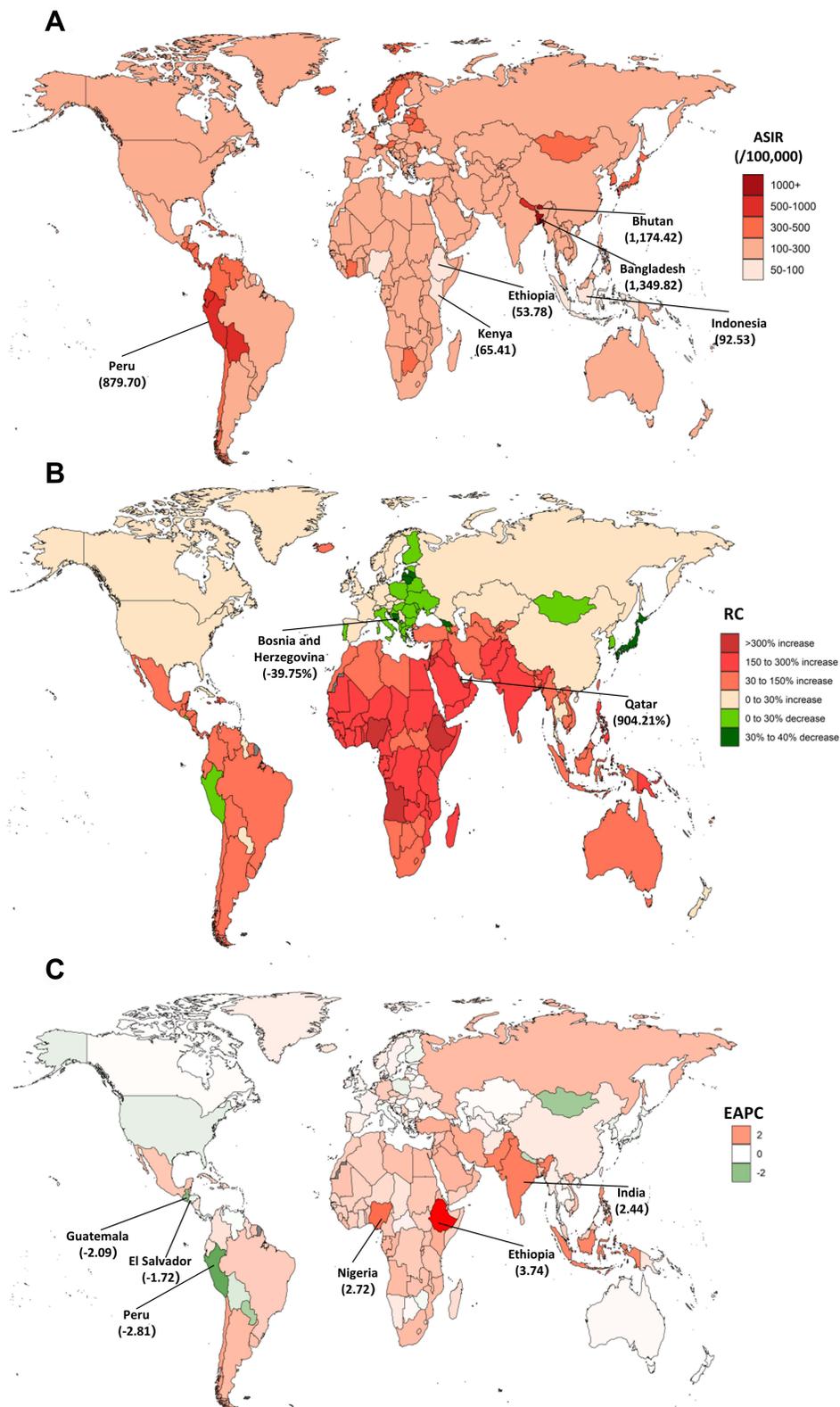
**Figure 2** Number and rate of incidence and DALYs according to sex and age groups in 2019. Male and female are represented by the Orange and blue points, respectively. (A) Number of incident cases for females and males in different age groups; (B) Rate of incidence for females and males in different age groups; (C) Number of DALYs for females and males in different age groups; (D) Rate of DALYs for females and males in different age groups.

contrast, only three regions exhibited downward trends in ASIR, including Andean Latin America (EAPC:  $-1.87$  [95% CI:  $-2.27$  to  $-1.47$ ]), high-income North America (EAPC:  $-0.4$  [95% CI:  $-0.51$  to  $-0.3$ ]), and high-income Asia Pacific (EAPC:  $-0.12$  [95% CI:  $-0.2$  to  $-0.04$ ]) from 1990 to 2019 (Table 1).

In 2019, the Caribbean had the highest age-standardized DALYs rates (43.30 [95% UI: 30.29–61.73] per 100,000 population), whereas East Asia had the lowest age-standardized DALYs rate (4.37 [3.50–5.41] per 100,000 population). During the study period, the number of DALYs decreased in most of the geographic regions. Among them, Andean Latin America had the greatest decrease of 80.99% (95% UI:  $-86.59$  to  $-71.48$ %). Downward trends in age-standardized DALYs rates were observed in all geographic regions from 1990 to 2019, especially in Andean Latin America (EAPC:  $-6.92$  [95% CI:  $-7.73$  to  $-6.1$ ]), East Asia (EAPC:  $-4.84$  [95% CI:  $-5.03$  to  $-4.65$ ]), and Central Asia (EAPC:  $-4.01$  [95% CI:  $-4.39$  to  $-3.63$ ]) (Table 2).

## Appendicitis Burden at the National Level

The top three countries in terms of appendicitis ASIR in 2019 were Bangladesh (1349.82 [95% UI: 1092.20–1673.12] per 100,000 population), Bhutan (1174.42 [942.11–1459.63] per 100,000 population), and Peru (879.70 [95% UI: 687.99–1137.55] per 100,000 population). In contrast, Ethiopia (53.78 [95% UI: 38.75–73.33] per 100,000 population), Kenya (65.41 [95% UI: 47.39–88.72] per 100,000 population), and Indonesia (92.53 [95% UI: 68.72–121.79] per 100,000 population) had the lowest ASIRs in 2019 (Figure 3A and Table S1). At the national level, the most pronounced changes in incident cases from 1990 to 2019 were observed in Qatar (increase, 904.21% [95% UI: 823.83–999.03%]) and Bosnia and Herzegovina (decrease,  $-39.75$ % [95% UI:  $-44.45$  to  $-34.11$ %]) (Figure 3B and Table S1). The changes in ASIRs from 1990 to 2019 varied greatly between countries, with the highest increases in Ethiopia (EAPC: 3.74 [95% CI: 2.61–4.87]), Nigeria (EAPC: 2.72 [95% CI: 2.12–3.32]), and India (EAPC: 2.44 [95% CI: 1.8–3.09]); and greatest



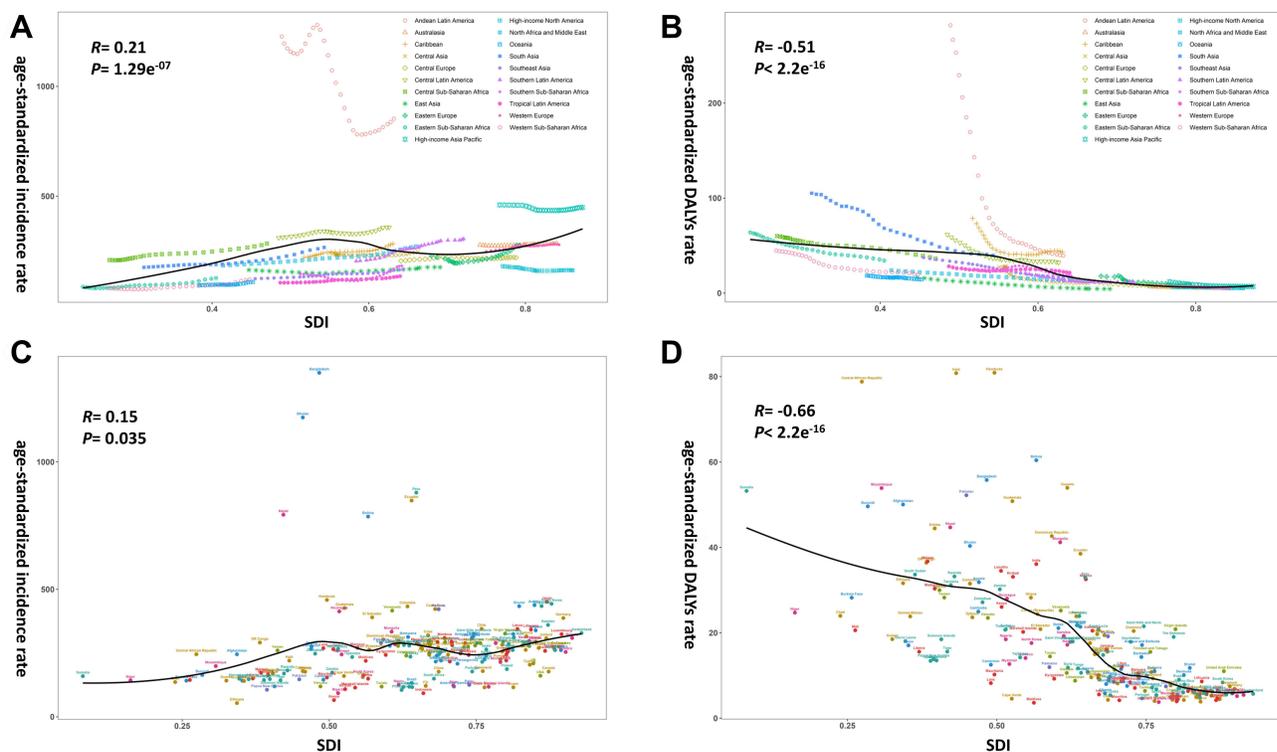
**Figure 3** The distribution of age-standardized rates (ASR), relative changes (RC) in number of cases, and estimated annual percentage changes (EAPCs) of appendicitis incidence at the national level, 1990–2019. **(A)** the ASR of incidence in 2019; **(B)** the relative percentage changes in number of incidence cases between 1990 and 2019; **(C)** the EAPCs in countries and territories from 1990 to 2019.

decreases in Peru (EAPC:  $-2.81$  [95% CI:  $-3.37$  to  $-2.24$ ]), Guatemala (EAPC:  $-2.09$  (95% CI:  $-2.72$  to  $-1.46$ )), and El Salvador (EAPC:  $-1.72$  [95% CI:  $-2.24$  to  $-1.21$ ]) (Figure 3C and Table S1).

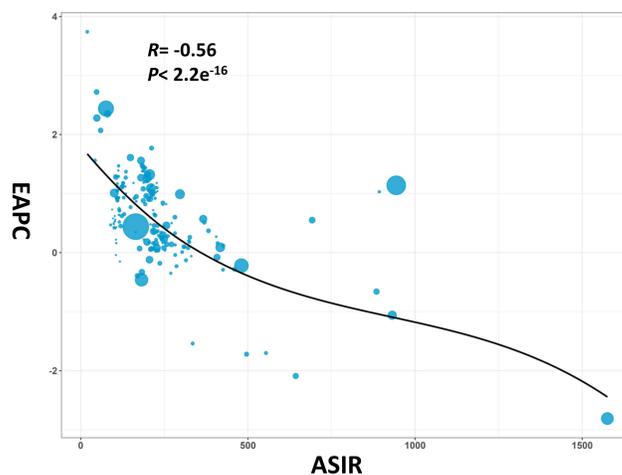
The top three countries in terms of appendicitis-associated age-standardized DALY rates in 2019 were Honduras (80.91 [95% UI: 56.97–112.85] per 100,000 population), Haiti (80.82 [95% UI: 32.64–137.78] per 100,000 population), and the Central African Republic (78.82 [95% UI: 27.05–137.34] per 100,000 population). In contrast, the lowest age-standardized DALYs rates were in the Maldives (3.63 [95% UI: 2.48–5.25] per 100,000 population), Northern Mariana Islands (95% UI: 3.79 [3.01–4.82] per 100,000 population), and Cyprus (3.89 [95% UI: 2.91–5.19] per 100,000 population) (Figure S2A and Table S2). Similarly, the most pronounced changes in the number of DALYs from 1990 to 2019 were also observed in Qatar (increase, 489.18% [95% UI: 251.42–909.11%]) and Peru (decrease,  $-88.47\%$  [95% UI:  $-92.62$  to  $-80.74\%$ ]) (Figure S2B and Table S2). The age-standardized DALY rates showed a decreasing trend in all countries except Zimbabwe, Fiji, Georgia, Mexico, and Greenland over the study period. The DALY rates of Peru (EAPC:  $-8.7$  [95% CI:  $-9.76$  to  $-7.62$ ]), El Salvador (EAPC:  $-6.48$  [95% CI:  $-7.69$  to  $-5.26$ ]), and Guatemala (EAPC:  $-6.32$  [95% CI:  $-7.03$  to  $-5.61$ ]) decreased most rapidly (Figure S2C and Table S2).

## Correlation Between ASRs and Both SDI and EAPC

Overall, a slightly positive correlation was found between ASIR and SDI in global regions from 1990 to 2019, while a prominent negative correlation was observed between age-standardized DALY rates and SDI (Figure 4A and B). Andean Latin America, High-income Asia Pacific, Central Latin America, and Central Sub-Saharan Africa showed higher than expected levels of ASIR during the study period, while Andean Latin America and the Caribbean showed higher than expected levels of age-standardized DALY rates. Similarly, a slightly positive correlation between ASIR and SDI and a significant negative correlation between age-standardized DALY rates and the SDI were observed at the national level, suggesting a higher incidence burden but a lower DALY burden with higher socio-economic development (Figure 4C and D). In addition, a negative correlation between EAPC and ASIR was found, which indicated that appendicitis cases increased more rapidly in lower-incidence countries than in higher-incidence countries (Figure 5).



**Figure 4** Age-standardized rates (ASR) of incidence and disability-adjusted life-years (DALYs) according to socio-demographic index (SDI) in 21 regions and 204 countries and territories. Expected levels based on SDI and ASRs were shown as the black line. (A) ASIR for 21 regions by SDI from 1990 to 2019; (B) ASR of DALYs for 21 regions by SDI from 1990 to 2019; (C) ASR of incidence for 204 countries and territories by SDI in 2019; (D) ASR of DALYs for 204 countries and territories by SDI in 2019.



**Figure 5** Correlation between estimated annual percentage change (EAPC) and age-standardized incidence rate (ASIR) for 204 countries and territories. The size of the circle increased with the incidence case of appendicitis. A significant negative correlation was found between the EAPC and ASIR in 1990.

## Discussion

This study analyzed the substantial burden of appendicitis worldwide over the past three decades. We reported the overall and age-standardized appendicitis incidence and DALY burden at the global, regional, and national levels from 1990 to 2019. Although DALYs decreased over the study period, the burden of incidence increased. Globally, the incidence of new cases was 17.70 million, and the ASIR was 229.86 per 100,000 population in 2019, both increasing from 1990. The number of DALYs was 1.50 million and the ASR of DALYs was 19.35 per 100,000 population in 2019, both decreasing from 1990.

The increased burden of incidence from 1990 to 2019 may be related to population growth, whereas the decreased number and rate of DALYs reflected an improvement in medical management and treatment, especially in diagnosis and operation. In recent years, the use of imaging and scoring systems has improved the efficiency of clinical diagnosis, which will not delay treatment and add the risk of perforation.<sup>23</sup> As phlegmonous and gangrenous appendicitis seem to be separate entities, one of which may resolve spontaneously and another that progresses to gangrene and perforation, diagnostic improvements in CT and the application of artificial intelligence and advanced combinatorial tools for distinguishing these two entities, especially in middle-income countries, helped in choosing treatment and reduced the perforation rate and adverse events.<sup>24–27</sup> Surgical advances have begun to reduce complications, and the promoted laparoscopic appendectomy is reported to be associated with a lower incidence of wound infection and post-intervention morbidity, shorter hospital stay, and better quality of life scores than open appendectomy.<sup>28–30</sup> In addition, endoscopic retrograde appendicitis therapy, which is a new and minimally invasive technique, has emerged as a promising non-invasive treatment for acute uncomplicated appendicitis.<sup>31</sup> Compared to laparoscopic appendectomy, endoscopic retrograde appendicitis therapy holds the advantages of rapid postoperative abdominal pain relief, preservation of the appendix, fast recovery, and a lower rate of adverse events for acute uncomplicated appendicitis patients.<sup>32</sup>

Differences were found between different age groups and sexes. We found that the incidence rate was significantly higher in the 15–19 year age group, which is similar to that reported in previous studies that appendicitis is most common between the ages of 10 and 20 years.<sup>33,34</sup> In addition, the burden for females was heavier than that of males, and ASIRs were higher for females under 70 years of age. As previous studies reported that the appendicitis incidence rate was higher in males even with a male to female ratio of 1.4:1, they all drew conclusions from data from the United States, while this study made the analysis at the global level.<sup>10,33</sup> We found that older individuals, especially older males, have increasing DALY rates with increasing age. As appendicitis in the elderly is associated with higher rates of complicated appendicitis, morbidity, and mortality, the DALY rate has increased.<sup>35–37</sup>

At the regional level, Andean Latin America had the highest ASIRs and the steepest decrease in ASIR from 1990 to 2019. The ASIR in this region was far higher than those of other regions across the three decades. The three countries in this region, Peru, Ecuador, and Bolivia, all had high ASIRs. Other Latin American regions, such as Central and Southern Latin America, also had high ASIRs. Geographic and ethnic variations in appendicitis incidence have been reported in previous studies.<sup>33,38,39</sup>

Appendicitis was less common in non-white groups than in white and Hispanic individuals.<sup>40</sup> A Swedish cohort study on immigrant populations and international adoptees reported that individuals of South American origin have the highest appendicitis incidence rate compared to individuals from other regions, which is in accordance with our findings.<sup>41</sup> Although the reasons for the geographical and ethnic differences are not known, environmental and genetic differences may partially explain this. Studies have reported a predominantly seasonal incidence rate of acute appendicitis during the summer, which may be statistically associated with ambient temperature.<sup>42</sup> Individuals with a family history of appendicitis tend to have an increased risk for appendicitis.<sup>43</sup> A multi-institutional genome-wide association study identified SNVs within the NEDD4L gene as being associated with acute appendicitis, which presented individuals with a genetic predisposition.<sup>44</sup>

This study provides several novel insights. First, we conducted a comprehensive analysis of the appendicitis burden and global trends. While there have been nationwide studies on appendicitis epidemics, worldwide reports are lacking. Although there has been a systematic review of population-based studies reporting the incidence of appendicitis across the world, it only mentioned several regions and could not evaluate the burden in 204 countries and territories.<sup>4</sup> Moreover, it only analyzed incidence. Second, we investigated the association between the burden of appendicitis and SDI using regression modeling instead of just presenting estimates separately for each SDI quintile. A positive association between ASIR and SDI quintiles was found, which differs from previous reports.<sup>7-9</sup> As this study dealt with global data, it may be influenced by environmental and ethnic factors compared to previous reports that only dealt with statewide or nationwide burdens. Our findings of a negative association between SDI and DALYs, in accordance with the analysis that the highest age-standardized DALYs were observed in the low SDI quintiles and the lowest age-standardized DALYs were observed in the high SDI quintiles, which reflected great variation in the presentation, severity of disease, diagnosis, and surgical management of patients related to country socio-economic status.<sup>45</sup> This result may be due to better healthcare and treatment conditions in high SDI regions and countries. Although the highest age-standardized DALY rates occurred in the low-middle and low SDI regions during this study period, there was still an improvement in the management and treatment of appendicitis, leading to the steepest decrease in these regions.

This study has some limitations. First, the quality and quantity of the input data used in the DisMod-MR 2.1 model may have influenced the GBD 2019 estimates. As data were absent or sparse in many regions and countries, and only a few countries or territories provided actual national data globally, the burden estimates were heavily dependent on the modeled data instead of typical data. Second, in the GBD 2019, acute and chronic appendicitis data were combined, and there was no differentiation between the subtypes of perforated appendicitis and non-perforated appendicitis, which differed in DALYs. To clarify the burden of appendicitis, stratification of appendicitis subtypes is needed in the future.

## Conclusion

Appendicitis remains a major public health problem worldwide with a large burden of incidence. The number and rate of incidence have increased, while the number and rate of DALYs have decreased globally. Our findings may be valuable for policymakers to establish effective prevention and management strategies that are adaptable to local conditions.

## Data Sharing Statement

Data used in this study were derived from the Global Burden of Diseases, Injuries, and Risk Factors Study 2019 (GBD 2019).

## Ethics Approval and Informed Consent

This study did not contain identifiable data of living individual, and animal subjects were not involved in the study. An ethics-approval waiver was consented to by the ethics committee of the Second Hospital of Jilin University.

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## Disclosure

The authors report no conflicts of interest in this work.

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