Global, regional, and national burden of allergic disorders and their risk factors in 204 countries and territories, from 1990 to 2019: A systematic analysis for the Global Burden of Disease Study 2019

1 **Global, regional, and national burden of allergic disorders and its risk**

2 **factors in 204 countries and territories, 1990–2019: a systematic analysis**

3 **for the Global Burden of Disease Study 2019**

4 **Running head:** Global disease burden of asthma and atopic dermatitis, 1990–2019

5

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Summary

Background: Asthma and atopic dermatitis (AD) are chronic allergic conditions that constitute the "atopic march" and cause significant morbidity both to children and adults. This study aimed to describe the global, regional, national and temporal trends of the burden of asthma and AD from 1990 to 2019 and analyze their associations with geographic, demographic, social, and clinical factors.

Methods: Using data from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019, we assessed the age-standardized prevalence, incidence, mortality, and disability-adjusted life years (DALYs) of asthma and AD from 1990 to 2019, stratified by geographic region, age, sex, and socio-demographic index (SDI). DALYs were calculated as the sum of years lived with disability and years of life lost to premature mortality. Additionally, the disease burden of asthma attributable to high body mass index, occupational asthmagens, and smoking was described.

Results: In 2019, there were a total of 262 million [224–309] cases of asthma and 171 million total cases of AD globally; age-standardized prevalence rates were 3,416 and 2,277 [2.192–2.369] per 100,000 population for asthma and AD, respectively, a 24.1% [27.2–20.8] decrease for asthma and 4.3% [4.8–3.8] decrease for AD. Both asthma and AD had similar trends according to age, with age-specific prevalence rates peaking at age 5-9 and rising again in adulthood. The prevalence and incidence of asthma and AD were both higher for individuals with higher SDI; however mortality and DALYs rates of individuals with asthma had a reverse trend, with higher mortality and DALYs rates in those in the lower SDI quintiles. Of the three risk factors, high body mass index contributed to the highest DALYs and deaths due to asthma, accounting for a total of 3.65 million [2.14–5.60] asthma DALYs

55 and 75,377 [40,615–122,841] asthma deaths.

56 **Conclusion:** Asthma and AD continue to cause significant morbidity worldwide, having

57 increased in total prevalence and incidence worldwide, but having decreased in age-

58 standardized prevalence rates from 1990 to 2019. Although both are more frequent in the

59 younger ages and prevalent in high-SDI countries, each condition has distinct temporal and

60 regional characteristics. Understanding the temporospatial trends in the disease burden of

61 asthma and AD could guide future policies and interventions to better manage these diseases

62 worldwide as well as to achieve equity in prevention, diagnosis and treatment.

65

66 **Key words**

67 Asthma; atopic dermatitis; epidemiology; mortality; disability-adjusted-life-years; global

68 burden.

69

70 **Abbreviations**

71 AD, Atopic dermatitis; DALYs, disability-adjusted-life-years; GBD, Global Burden of

72 Disease; ICD, International Classification of Disease; SDI, socio-demographic index; 95% UI,

73 95% uncertainty interval; YLD, Years of healthy life lost due to disability; YLLs, Years of

74 life lost.

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76 **Word count: 4178**

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INTRODUCTION

Although frequently dismissed as diseases of childhood, allergic disorders such as asthma and atopic dermatitis (AD) are chronic diseases that can cause significant morbidity having long-term effects even into adulthood[1]. The prevalence of these physician-diagnosed allergic diseases has increased drastically over the years as reported in multiple studies[2,3], now affecting approximately 10% to 30% of the population worldwide[2,3]. Not only do asthma and AD incur great healthcare-related economic costs, they also cause significant indirect costs due to decreases in quality of life and missed work, school, and productivity[4].

Asthma and AD were once characterized as diseases being frequent in high-income countries, with affluent countries reporting higher prevalence rates and the "hygiene hypothesis" suggesting that maternal and childhood exposure to pathogens in low-resource settings could sensitize individuals to allergens[4]. However, the hypothesis that unhygienic conditions protect individuals against allergic illness has been criticized and expanded to encompass a complex interplay between genetic predisposition and the range of environmental exposures[5]. Further, on an individual level, lower socioeconomic status has been associated with higher disease burden – increased severity and poorer control of asthma and AD[6]; racial and ethnic disparities also exist[6,7]. Health equity regarding these diseases have been further accentuated recently, as novel and targeted treatment options, such as the use of biologics, has been gaining evidence and popularity, and numerous reports have called attention to disparities in access and efficacy of these emerging options[8]. As both asthma and AD are now recognized as major public health problems that greatly impact developing countries as well as developed countries[6,7], it is important to provide evidence integrating data from around the world and across sociodemographic levels.

5

101   Against this backdrop, it is critical at this time to comprehensively analyze data to

102   paint a global picture regarding the disease burden and time trends of allergic diseases

103   (asthma and AD). There have been isolated studies detailing the global prevalence and

104   disease burden of asthma and AD using the Global Burden of Disease (GBD) 2017[9,10], but

105   there has not yet been an up-to-date study encompassing both asthma and AD utilizing

106   recently released dataset, both ends of the atopic march. Moving forward from scattered

107   systematic reviews regarding the global distribution of these allergic diseases[11], the present

108   study aimed to provide a bird's eye view of the global distribution of asthma and AD by

109   analyzing data from the GBD study from 1990 to 2019 and discussing temporospatial trends

110   in association with country-level socioeconomic development to aid future public health

111   interventions.

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METHODS

Overview

Data utilized in this paper were obtained from the GBD 2019 Results Database, provides data in 204 countries and territories from 1990 to 2019. Our analysis was performed as part of the GBD Collaborator Network and complied with the Guidelines for Accurate and Transparent Health Estimates Reporting (Supplementary Method). Comprehensive methodology for the estimation models have been published elsewhere[12]. R software version 3.6.2 (R Foundation, Vienna, Austria) was used to generate all tables.

Case Definition

In the GBD 2019 list of causes, asthma corresponds to the International Classification of Disease 10th revision (ICD-10) codes J45 and J56 and ICD-9 code 493.[10,13,14] Asthma was defined as a chronic lung disease involving bronchospasms and shortness of breath due to allergic reactions or hypersensitivity, adjudicated by physician diagnosis and wheezing in the past year. AD, consistent with ICD-10 code L20, was defined as relapsing dermatitis, either localized or widespread, associated with pruritus, elevated serum immunoglobulin E, and immune dysregulation.[1,9] Cases were selected through literature review with physical exam and claims data, then further stratified into three severity levels with different disability weights according to physical deformity and pain/itch.

Data acquisition and processing

Main data inputs for assessing the prevalence of asthma and AD were population representative surveys, limited prevalence investigations in the literature described by a

138 systematic review of the literature, health service visits, surveillance data, survey data, and

139 medical claims information. Estimates for prevalence, incidence, and disease burden were

140 modeled through three main standardized tools, namely, (1) Cause of Death Ensemble model

141 (CODEm), an optimized tool for analyzing cause of death by collecting an ensemble of

142 different modeling methods with varying choices of covariates for high predictive validity; (2)

143 Spatiotemporal Gaussian Process Regression (ST-GPR), a model for analyzing and

144 comparing temporal and regional estimates between different groups; and (3) DisMod-MR

145 2.1, a Bayesian meta-regression tool, utilized to provide consistency between epidemiological

146 parameters including prevalence, incidence, remission, and mortality by adjusting variations

147 of heterogeneous datasets from various modeling methods[12].

148

Estimators of disease burden

150 For this study, we obtained the publication estimates of incidence, prevalence, mortality,

151 years of life lost (YLLs), years lived with disability (YLDs), and disability-adjusted life years

152 (DALYs) for asthma and AD, respectively, for each 5-year age group, sex, year, and location

153 from GBD 2019. Briefly, age-standardized rates per 100,000 population were computed by

154 the direct method to the GBD population standard. YLLs were defined as the product of the

155 number of deaths and the remaining life expectancy per age group, as per the GBD standard

156 life table; YLDs were calculated as the product of the prevalence estimate and disability

157 weights for that specific condition, in this case asthma and AD. DALYs were computed by

158 the summation of YLL and YLD, representing the health loss due to a specific cause; in this

159 case, asthma and AD. Estimates for disease burden were reported with 95% uncertainty

160 intervals (UIs), defined as the 25th and 975th values of 1,000 samples drawn for each variable.

161   A detailed description of the methods can be found in the literature[15].

162

163   *Socio-demographic index*

164   The development status of each country was graded based on the socio-demographic index

165   (SDI) as defined in the GBD study since 2017, which is a composite score from 0 to 1 based

166   on the total fertility under age 25, average education in those over age 15, and lag-distributed

167   income per person[12,15]. In our analysis, we classified countries into quintiles of ranked SDI

168   values as low, low-middle, middle, high-middle, and high SDI as obtained from the GBD

169   2019 data.

170

171   *Risk factors*

172   DALYs and deaths for asthma attributable for three risk factors: namely, high body mass

173   index (BMI), occupational asthmagens, and smoking, as classified in GBD 2019[31], were

174   obtained and further stratified by region and sex. Attributable risk factors for AD could not be

175   evaluated from the current GBD database at this time.

176

177   *Role of the funding source*

178   The funders of this study had no role in study design, data collection, data analysis, data

179   interpretation, or the writing of the report.

RESULTS

Global and regional burden of asthma

The age-standardized prevalence rates of asthma are mapped at the country level on Figure 1. Globally, the total number of patients with asthma increased slightly from 227 million [95% UI 195–270] in 1990 to 262 million [224–309] in 2019 (Figure 2 and Table S1). However, age-standardized prevalence rates had a 24.1% [20.8–27.2] decrease, from 4,497 [3,914–5,224] per 100,000 population in 1990 to 3,416 [2,899–4,066] per 100,000 population in 2019. Incidence rates of asthma showed similar trends, with total incident cases having increased from 32.2 million [25.8–40.5] to 37.0 million [29.6–45.9], whereas age-standardized incidence rates having decreased from 580.1 per 100,000 population [474.7–715.0] to 504.3 per 100,000 population [400.6–633.3] in 1990 and 2019, respectively (Table S2).

Asthma accounted for a total of 0.461 million [0.367–0.559] deaths in 2019, resulting in an age-standardized mortality rate of 5.8 per 100,000 population; this was a 51.3% decrease since 11.9 in 1990. Both the total number of DALYs and age-standardized DALYs rates due to asthma decreased from 1990 to 2019 (Figure 2 and Table S3 and S4). In particular, age-standardized DALYs rates underwent a steep dive of 42.5% [48.5–36.6] from 1990 and 2019, with DALYs rates of 476.3 per 100,000 population [378.5–579.6] in 1990 to 273.6 [216.7–343.4] per 100,000 population in 2019.

High-income North America and Australasia regions had the highest and second-highest age-standardized prevalence of asthma at 9,848 [8,624–11,312] and 8,393 [6,909–10,347] per 100,000 population, respectively, in 2019. Notably, the high-income North America region had a 9.6% [1.2–19.2] increase from 1990, with the United States

203   contributing most of the increase at 10.9% [2.0–21.4] from 1990 to 2019; Australasia,

204   consistent with most regions and the global trend, had a 30.6% [40.6 –18.5] decrease from its

205   prevalence rate in 1990.

206   East, Central, and South Asia were the regions with the lowest age-standardized

207   prevalence of asthma, at 2,026 [1,577–2,631], 2,277 [1,883–2,788], and 2,443 [2,030–2,910]

208   per 100,000 population, respectively, in 2019. The lowest age-standardized prevalence rates

209   of asthma were reported in Nepal and Bangladesh, at 1,073 [932–1,215] and 1,391 [1,217–

210   1,574] per 100,000 population.

211   DALYs rates showed a somewhat different regional trend, with Oceania reporting

212   the highest DALYs rates of 1,102 [864–1431] per 100,000 population, and East Asia

213   reporting the lowest DALYs rates of 106.4 [75.3–152.1] per 100,000 population.

214   In most countries, age-standardized DALYs rates had a precipitous decrease over time, the

215   drop in DALYs rates being as large as 72.3% [60.8–79.2] in the Republic of Korea; the only

216   exceptions were Montenegro, the United States, and Paraguay, with 6.7% [-1.3–15.9], 4.4%

217   [-3.4–12.9], and 3.1% [7.8–13.7] increase in DALYs from 1990 to 2019.

218

219   *Global and regional burden of AD*

220   In 2019, the number of prevalent cases of AD worldwide was 171 million [165–178], an

221   increase from 133 million [128–138] cases in 1990; in contrast, global age-standardized rates

222   of AD had a slight decrease of -4.3% [-4.8 to -3.8] to 2,277 [2.192–2.369] per 100,000

223   population in 2019 (Figure 1 and Table S5). Similarly, total incident cases rose from 19.2

224   million [18.3–20.2] in 1990 to 24.4 million [23.3–25.6] in 2019, but age-standardized

225   incidence rates dropped slightly (-4.2% [-4.8 to -3.6] change; Table S6).

11

226   As there were no deaths directly attributable to AD, DALYs for AD was the same as

227   the YLDs. DALYs rates due to AD showed the same trend as prevalence and incidence; the

228   total number of DALYs rose steeply from 5.827 million [3.090–9.784] in 1990 to 7.480

229   million [3.987–12.58] in 2019, age-standardized rates had a slight drop of 4.1% [3.5–4.8] to

230   99.7 per 100,000 population (Table S7 and S8).

231   The prevalence rates of AD did not vary as drastically between regions as those of

232   asthma, but there were still some regional trends. The highest prevalence rates of AD were

233   reported in the High-income Asia Pacific region at 4,876 [4,639–5,113] per 100,000

234   population and Central Asia at 4,678 [4,210–5,192] per 100,000 population; the lowest

235   prevalence rates of AD were reported in African countries, including Central, Eastern,

236   Southern, and Western Sub-Saharan Africa, with 1,081 [1,009–1,162], 1,082 [1,035–1,132],

237   1,083 [1,027–1,140], and 1,102 [1,054–1,149] per 100,000 population. In most regions,

238   prevalence rates of AD remained stable over 1990–2019; the steepest increase was seen in

239   Kenya at merely 5.3% [2.0–8.2], and the largest drop was seen in the Maldives at a similar

240   percentage of 6.6% [6.0–7.2]. DALYs rates of AD had a similar regional distribution with

241   prevalence rates of AD, with highest DALYs rates in the High-income Asia Pacific region

242   and lowest DALYs rates in the Sub-Saharan Africas.

243

244   *Trends according to demographic factors*

245   Consistently throughout 1990–2019, the total number of incident cases and age-standardized

246   incidence rates of asthma were similar between females and males, whereas those of AD

247   were substantially higher in females than males (Figure 3). Both total incidence and incidence

248   rates of asthma down-trended slightly from 1990 to 2005, then increased from 2005 to 2019,

249 drawing a slight V-shape over time. In contrast, the total incidence of AD increased steadily

250 from 1990 to 2019, while age-standardized rates decreased slightly over the same period.

251 Time trends were similar in both sexes.

252   Stratified by age, in 2019, the total number of prevalent cases peaked at age 5-9,

253 down-trended to reach a plateau at age 25-69, then decreased in the older age groups (Figure

254 4). In contrast, the age-specific prevalence rate of asthma had an N-shaped distribution, with

255 prevalence rates peaking in age 5-9, reaching a lowest point at age 25-29, then subsequently

256 rising well into the oldest age group (≥95 years). Total age-specific prevalent cases and

257 prevalence rates of asthma were higher for males up to the 15-19 age group; afterwards, the

258 trend reversed with higher prevalence in females.

259   Total prevalent cases of AD according to age groups showed similar trends as that of

260 asthma, having a distribution heavily skewed in infancy and early childhood with a high peak

261 in the 5-9 age group and a steep decrease thereafter (Figure 4). Age-specific prevalence of

262 AD was characterized by an earlier peak in age groups 1-4 and 5-9 and a later trough at age

263 35-44. For AD, both age-specific prevalence rates and total number of prevalent cases were

264 higher for females in all age groups, with the difference almost twofold in young adulthood

265 (ages 25-45).

266

267 ***Burden of asthma and AD in accordance with SDI***

268 Age-standardized DALYs rates of asthma decreased steadily from 1990 to 2005 over all SDI

269 quintiles, with the exception of the High SDI quintile, for which the DALYs rates increased

270 slightly since 2005 (Figure 5). Higher SDI levels tended to have lower DALYs rates, with

271 High, High-middle, and Middle SDI quintiles having substantially lower DALYs rates than

272 Low and Low-middle quintiles consistently over the study period, and with the Low SDI

273 quintile having the highest, and the High-middle quintile having the lowest DALYs rates

274 throughout 1990 to 2019 (553.9 [434.7–726.8] and 158.3 [114.0–220.2] per 100,000

275 population, respectively, in 2019). On the other hand, the High SDI quintile had the highest

276 age-standardized prevalence, incidence, and YLDs rates of asthma across the study period,

277 compared to lower SDI quintiles (Figure S4–S6). The highest SDI quintile had a prevalence

278 rate of 6,855 [5,877–8,058] per 100,000 population; at the same time, the High and High-

279 middle SDI quintiles experienced the largest decrease in asthma prevalence of 17.7% [14.2–

280 20.9] and 26.8% [22.2–32.1], respectively, over the study period. The discrepancy in

281 associations with SDI could be explained by the mortality rate; although the mortality rate

282 decreased for all SDI quintiles over the study period, lower SDI was associated with higher

283 mortality in all timeframes (Figure S3).

284   Age-standardized DALYs rates of AD were stagnant across time in all SDI levels,

285 and the association between DALYs and SDI was reversed in AD. Higher SDI levels had

286 higher DALYs rates of AD throughout 1990–2019, with the High SDI quintile having more

287 than double the DALYs rates of the Low SDI quintile (155.5 [83.5–262.0] and 59.7 [32.0–

288 100.1] per 100,000 population, respectively, in 2019). This trend was replicated in prevalence

289 and incidence rates of AD; the High SDI quintile had the highest prevalence rate of 3,540

290 [3,376–3,685] per 100,000 population, whereas the Low SDI quintile had the lowest

291 prevalence rate of 1,359 [1,301–1,424] per 100,000 population in 2019 (Figures S1 and S2).

292

293 ***Burden of asthma attributable to risk factors***

294 We also analyzed the DALYs of asthma attributable to three different risk factors, namely

295   BMI, occupational asthmagens, and smoking (Figure 6).

296   Globally, high BMI contributed to the most DALYs and deaths due to asthma in

297   2019, followed by smoking and occupational asthmagens, with a total of 3.65 million [2.14–

298   5.60], 2.12 million [1.13–3.01], and 1.90 million [1.51–2.33] asthma DALYs, and total

299   75,377 [40,615–122,841], 54,849 [29,149–78,006] and 34,395 [27,828–42,614] deaths

300   attributable to each risk factor, respectively (Figure S25 and S27). In both men and women,

301   South Asia had the highest number of asthma DALYs attributable to all three risk factors

302   (0.910 million [0.447–1.587] for high BMI, 0.622 million [0.475–0.818] for occupational

303   asthmagens, and 0.689 million [0.333–1.044] for smoking), mirroring the number of total

304   DALYs due to asthma. South Asia was followed by North Africa and Middle East, High-

305   income North America, and Southeast Asia, for highest asthma DALYs due to high BMI; the

306   trend was slightly different for occupational asthmagens and smoking, for which the second

307   and third-highest asthma DALYs occurred in Southeast Asia and Eastern Sub-Saharan Africa

308   for occupational asthmagens, and Southeast Asia and East Asia for smoking, respectively

309   (Figure S25).

310   Consistent with the high absolute numbers of attributable DALYs, high BMI

311   accounted for nearly 30% of asthma DALYs in the North Africa and Middle East (27.9%

312   [18.3–38.8]) and Southern Sub-Saharan Africa (27.7% [18.3–38.0]), but only 9.6% [5.0–6.6]

313   in the High-income Asia Pacific. In most regions, females had a higher proportion of asthma

314   DALYs attributable to high BMI, with the exception of the high-income Asia Pacific and East

315   Asia regions. These two regions also had the lowest percentages of DALYs due to high BMI.

316   Eastern, Western, and Central Sub-Saharan Africa had a substantially higher

317   percentage of asthma DALYs due to occupational asthmagens compared to other regions,

318   which were 13.3% [11.8–14.8], 11.9% [10.5–13.3], and 10.8% [9.0–12.4], respectively.

319   Further, the percentage of asthma DALYs attributable to occupational asthmagens were

320   higher in males than in females in all regions.

321   The highest asthma DALYs attributable to smoking occurred in Central Europe (12.7%

322   [7.2–17.8]) and Western Europe (12.2% [6.7–17.0]), and lowest in Andean Latin America

323   (1.3% [0.5–2.1]). Notably, the percentage of DALYs attributable to smoking was

324   substantially higher in males in most regions with the exception of High-income North

325   America, Southern Latin America, and Australasia; these countries had some of the highest

326   proportions of DALYs due to smoking in females nearing 10%.

327

DISCUSSION

328

329 Asthma and AD increased in total prevalent and incident cases worldwide, but have

330 decreased in age-standardized prevalence rates from 1990 to 2019. Both have strong

331 associations with age, being most prevalent at age 5-9 but the prevalence increasing in later

332 adulthood. These diseases tend to have higher prevalence in countries with higher SDI, but

333 for asthma, lower SDI was associated with higher mortality and DALYs rates; further, disease

334 burden varied substantially across geographic region. Further epidemiologic studies of

335 asthma and AD spanning the globe are warranted to mitigate the high disease burden due to

336 these allergic diseases and achieve equity in prevention, diagnosis and treatment.

337 Asthma and AD are atopic diseases that can affect individuals throughout the life

338 course, having major repercussions both in population health and in the global economy.

339 However, reflecting heightened awareness from early in life, improved diagnostic resources,

340 and perceptions that affluent populations are prone to allergic diseases, many studies have

341 been focused on high-income countries, such as the United Kingdom, the European Union,

342 and the United States[16,17]. Furthermore, as these diseases have been considered as pediatric

343 conditions, most studies have leaned towards children[3]. To provide a global bird's eye view

344 regarding the true public health impact of these diseases across the lifespan, we investigated

345 the most up-to-date data from the GBD 2019 study to describe the global prevalence,

346 incidence, and disease burden of asthma and AD and analyzed their associations with

347 geographic region, demographic characteristics, SDI, and risk factors.

348 In 2019, there were 262 million total cases (2.4%) of asthma globally across all ages,

349 the percentage lower than other studies from the World Health Survey (4.3% in adults),

350 Global Asthma Network (10.4% in adolescents and 9.9% in children), and the International

17

351   Study of Asthma and Allergies in Childhood (13.7% in age 13–14 and 11.6% in age 6–

352   7)[2,18,19]. This discrepancy could be explained by the difference in included countries and age

353   groups, especially considering the significant variation in asthma prevalence between

354   countries and along the life course evident in the GBD data and in the other worldwide

355   studies. While the total number of patients with asthma increased, age-standardized

356   prevalence rates had a large decrease of 24.1% globally, with incident cases and incidence

357   rates mirroring the same trend, which suggests that the increase in number was in part due to

358   population expansion. Likewise, the prevalence rate of asthma decreased in most regions.

359   However, few regions, such as the United States, had a rise in asthma prevalence; this

360   increase could be attributed to increased awareness and diagnostic availability of asthma due

361   to public health campaigns such as the National Asthma Education and Prevention Program

362   and, in part, overdiagnosis[20].

363   The disease burden of asthma represented by age-standardized DALYs rates and

364   mortality rates also underwent a steep decrease of 42.5% and 51.3% from 1990 to 2019,

365   respectively. This could reflect the establishment of cornerstone guidelines (e.g., the National

366   Heart, Lung, and Blood Institute guidelines, first issued in 1991, and the Global Initiative for

367   Asthma guidelines, first published in 1995), heightened awareness and better management of

368   asthma globally, and the development and popularization of different treatment options[21,22].

369   For example, the decrease in asthma DALYs were especially precipitous in some countries,

370   reaching 72.3% in the Republic of Korea; this could reflect various initiatives and cohorts

371   that took place since the early 2000s, such as the Cohort for Reality and Evolution of Adult

372   Asthma, the Korea Asthma Allergy Foundation, and the Seoul Atopy-Asthma-friendly

373   School Project[23]. However, as there still exist wide variations in DALYs and mortality rates

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374   around the globe and within regions, it is critical to continue efforts for better prevention and

375   control of asthma, especially in under-resourced settings[6].

376   For AD, there were 171 million total cases globally, approximately 2.23% of the

377   population. Although the absolute number of prevalent and incident cases rose from 1990 to

378   2019, age-standardized prevalence and incidence rates stayed relatively stable over time,

379   undergoing only a slight drop of 4.3% and 4.2%, respectively. Between regions, the

380   prevalence and DALYs rates of AD did not vary as drastically between countries and regions

381   as those of asthma; however, the highest prevalence and DALYs rates were reported in the

382   High-income Pacific region, and the lowest rates were reported in the Sub-Saharan Africa

383   regions. The low reported disease burden in African countries may be partly ascribed to

384   differences in diet and environment, but may also be a result of under-reporting, especially as

385   AD prevalence has recently been increasing in these developing countries[24]. Therefore,

386   additional epidemiologic studies should take place to delineate complex factors associated

387   with the changes in different parts of the world and efforts to boost awareness and diagnostic

388   capability in under-resourced settings should be continued.

389   Consistent with the literature and common perceptions, this study found that both

390   asthma and AD peaked in the younger ages, typically ages 5-9[18,21]; however, we also found

391   that age-standardized rates increased past adulthood well into older ages. As asthma and AD

392   in older populations may be difficult to diagnose and treat due to their traditional

393   misconceptions as "pediatric diseases", different clinical presentations (i.e., phenotypes)and

394   functional characteristics, and multiple comorbidities associated with aging, physicians

395   should be vigilant in the recognition and multi-dimensional management of these conditions

396   in older adults[25].

397   Higher SDI levels tended to have higher prevalence of asthma and AD, as reported in

398   numerous international studies previously[3,18,26]. Notably, however, mortality and DALYs

399   rates had the reverse trend, with lower SDI quintiles having substantially higher DALYs and

400   higher mortality. Low-resource settings have been associated with worse outcomes of asthma,

401   mediated by socioeconomic factors such as income and education, environmental allergens or

402   pollutants, psychosocial stressors, and lack of access to healthcare[6,27]. Likewise, many inner-

403   city populations in low- and middle-income countries have very high prevalence of asthma

404   but limited access and affordability for essential medications for persistent asthma[28]; under-

405   treatment in these countries causes significant morbidity and mortality[29]. Further, the high

406   incidence of acute respiratory infections in low- and middle-income countries can lead to

407   asthma exacerbations as well as under-diagnosis and thus under-treatment of asthma, leading

408   to a relatively lower reported prevalence and higher morbidity[30]. These trends suggest a large

409   potential for global and community initiatives to improve asthma outcomes in low-resource

410   populations[27,31].

411   The present study was the first to systematically assess the disease burden of asthma

412   and AD across regions and throughout the lifespan using the most recent GBD data. However,

413   there are some limitations to our study. First, the definition of asthma and AD were made

414   mainly through physician diagnosis and symptom data, the stringency of which could have

415   been heterogeneous across regions – for example, different countries using different terms to

416   describe symptoms of asthma or AD – and thus resulted in a discrepancy of prevalence

417   statistics. Second, as this study was driven by data from the GBD study, it includes the

418   limitations of the GBD dataset, mainly, that some regions had low availability and quality of

419   data, for which statistics had to rely on predictive covariates. Furthermore, as we compared

420   country-level aggregate data, the trends and associations we found are subject to ecological

421   bias. Lastly, we could only assess the attributable risk for asthma on three risk factors (high

422   BMI, occupational asthmagens, and smoking); more research is necessary to investigate

423   associations with different demographic and clinical factors, and also for AD.

424   In summary, asthma and AD are both allergic diseases that have increased in total burden

425   worldwide but have decreased in age-standardized prevalence rates from 1990 to 2019.

426   Although both are more frequent in the younger ages and prevalent in high-SDI countries,

427   each condition has distinct temporal and regional trends. This study will help assess regional

428   and temporal trends regarding the distribution and disease burden of asthma and AD, and

429   guide interventions to better manage these diseases worldwide as well as to attain equity in

430   prevention, diagnosis and treatment.

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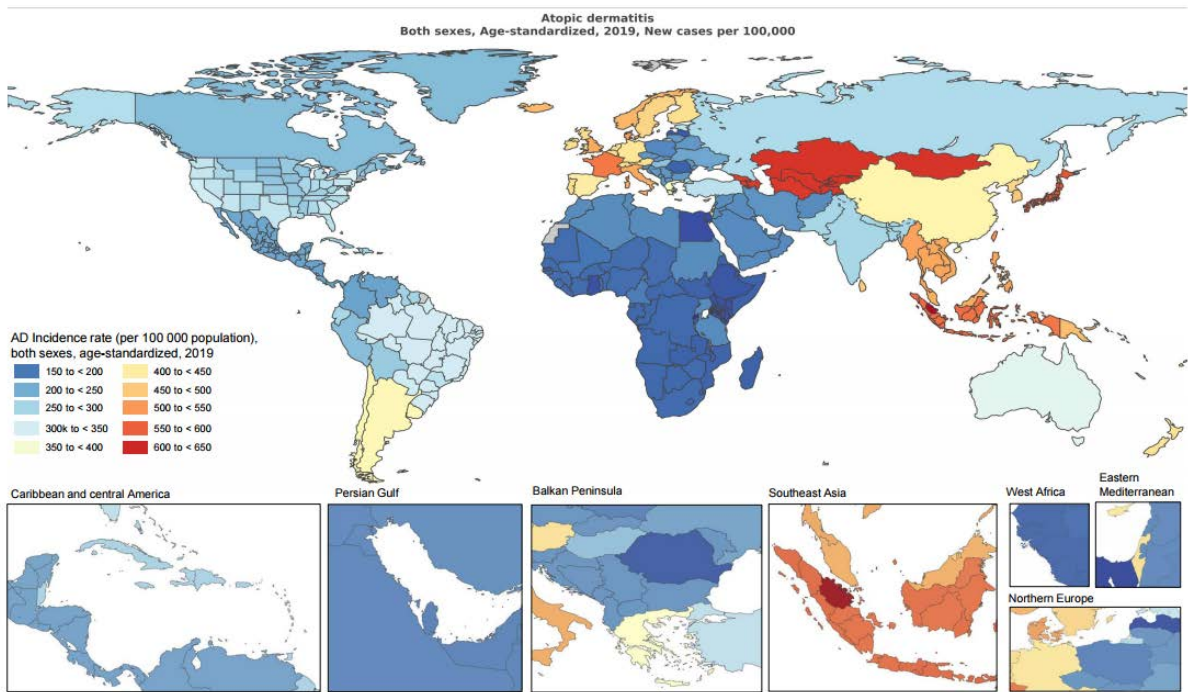8.   Inselman JW, Jeffery MM, Maddux JT, Shah ND, Rank MA. Trends and Disparities

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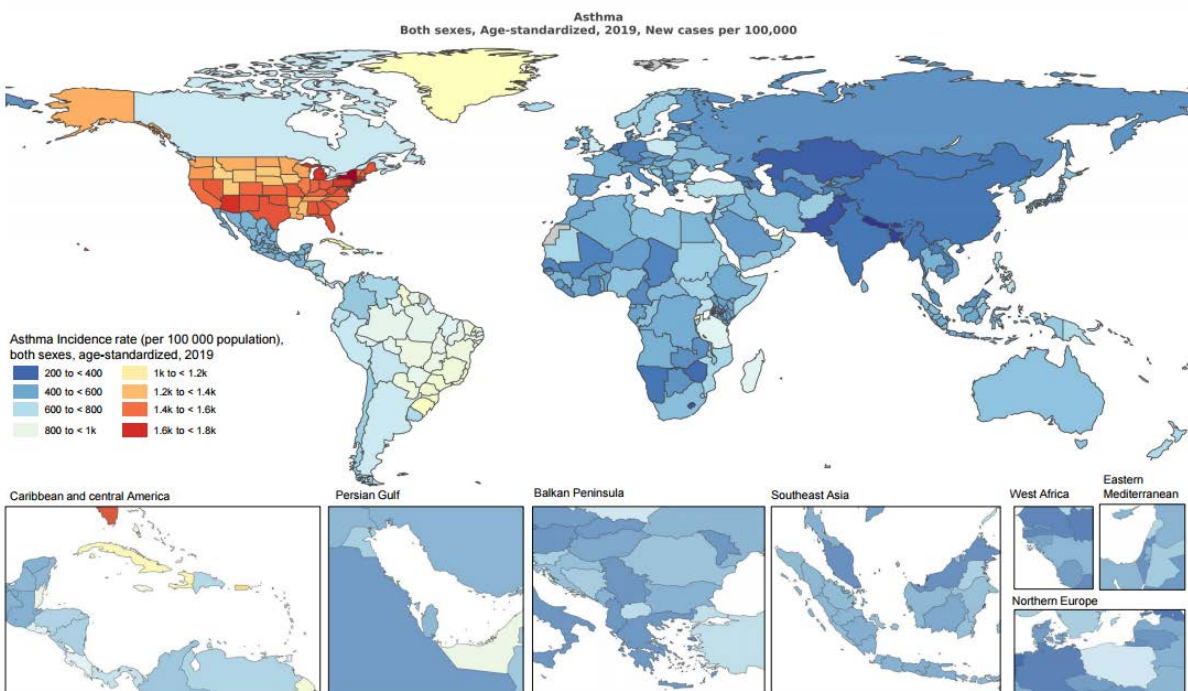
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547 **Figure 1.** Global distribution of the age-standardized prevalence rates of asthma (A) and AD

548 (B). AD, atopic dermatitis.

Atopic dermatitis
Both sexes, Age-standardized, 2019, New cases per 100,000

AD Incidence rate (per 100 000 population), both sexes, age-standardized, 2019

150 to < 200	400 to < 450
200 to < 250	450 to < 500
250 to < 300	500 to < 550
300k to < 350	550 to < 600
350 to < 400	600 to < 650

Caribbean and central America — Persian Gulf — Balkan Peninsula — Southeast Asia — West Africa — Eastern Mediterranean — Northern Europe

549

Asthma
Both sexes, Age-standardized, 2019, New cases per 100,000

Asthma Incidence rate (per 100 000 population), both sexes, age-standardized, 2019

200 to < 400	1k to < 1.2k
400 to < 600	1.2k to < 1.4k
600 to < 800	1.4k to < 1.6k
800 to < 1k	1.6k to < 1.8k

Caribbean and central America — Persian Gulf — Balkan Peninsula — Southeast Asia — West Africa — Eastern Mediterranean — Northern Europe
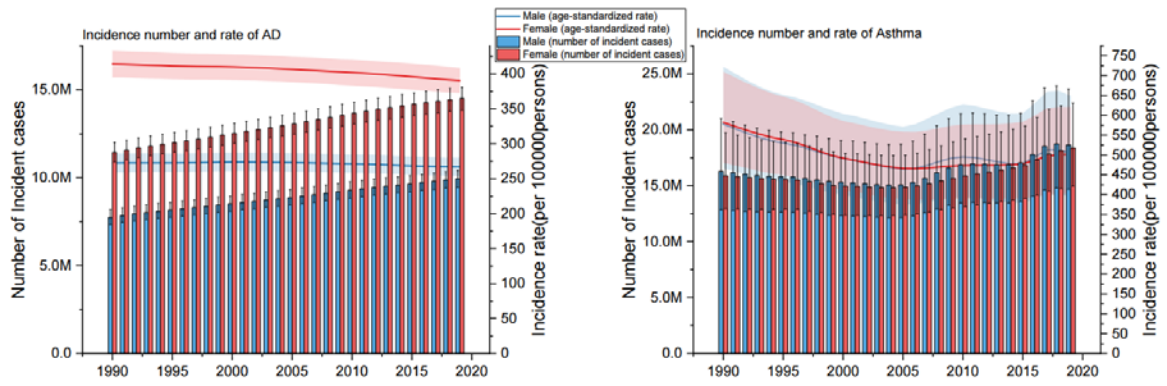
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552   **Figure 2.** Global prevalence and DALYs of asthma (A and B) and AD (C and D), 1990–2019.

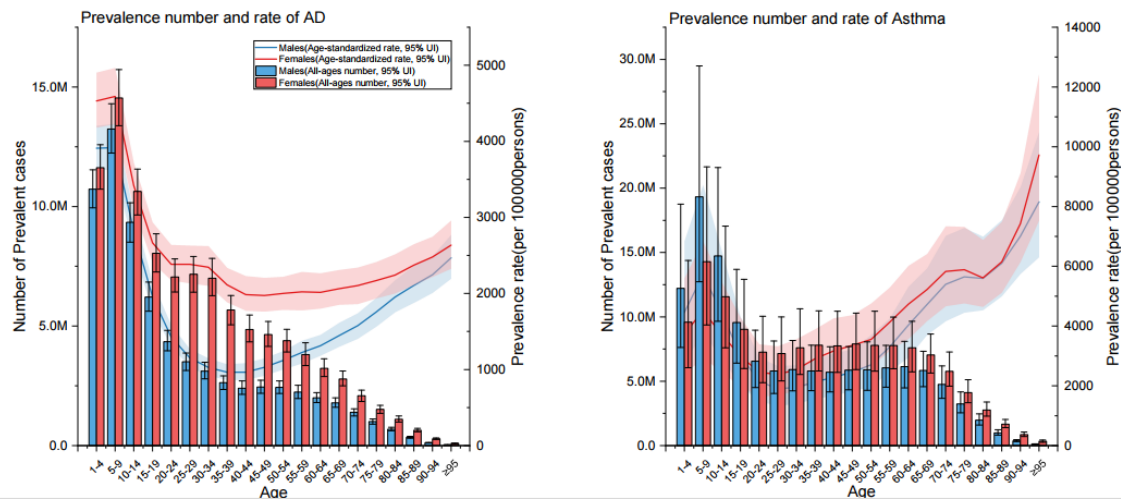553   AD, atopic dermatitis; DALY, disability-adjusted life-years.
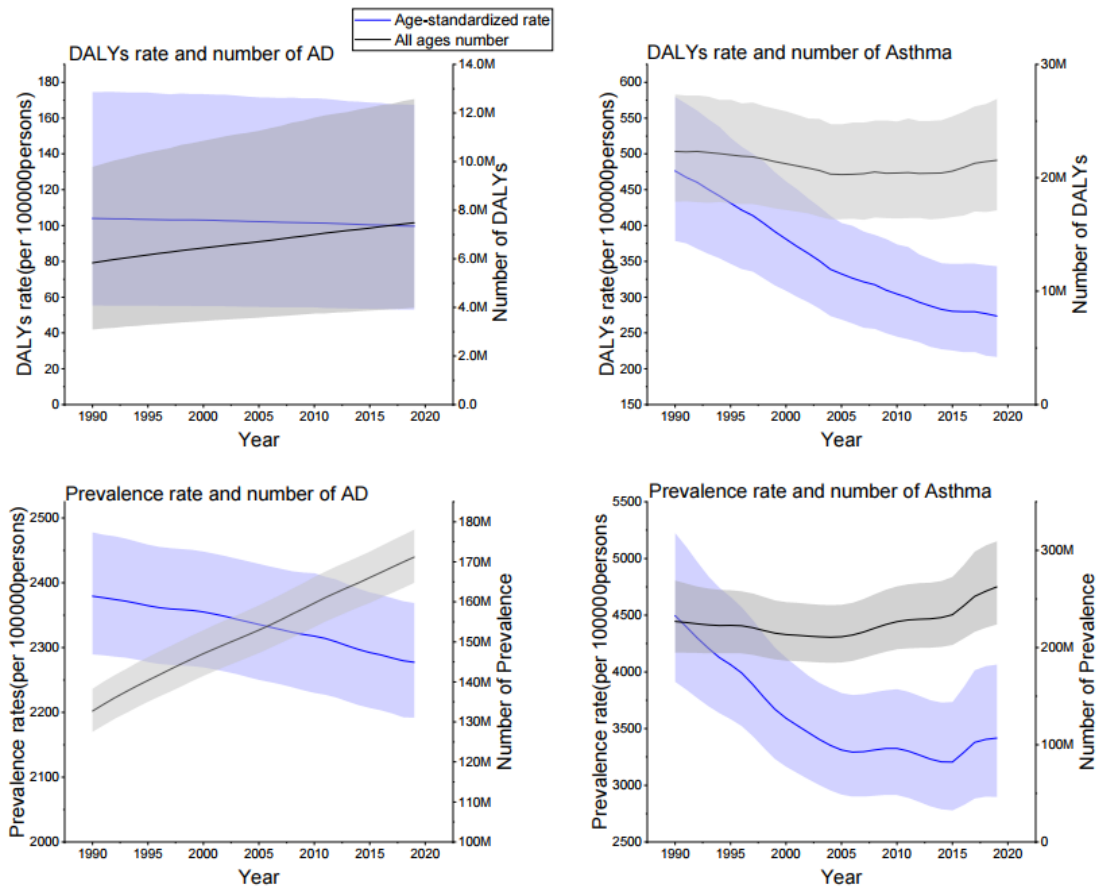
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557 **Figure 3.** Total number of incident cases and global incidence rates of asthma (A) and AD (B)
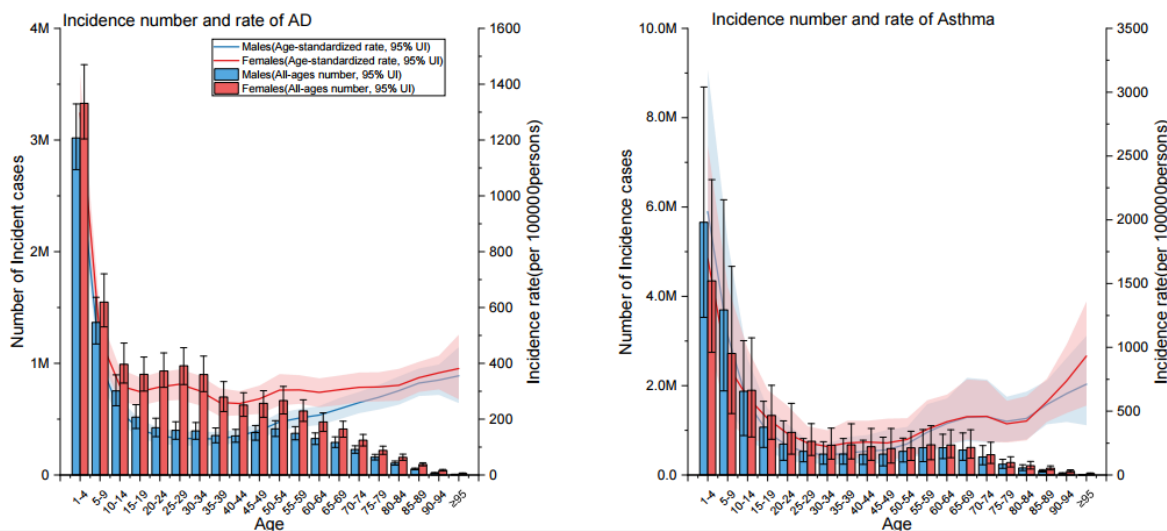
558 by sex, 1990–2019.

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561　**Figure 4.** Total number of prevalent cases and global prevalence rates of asthma (A) and AD
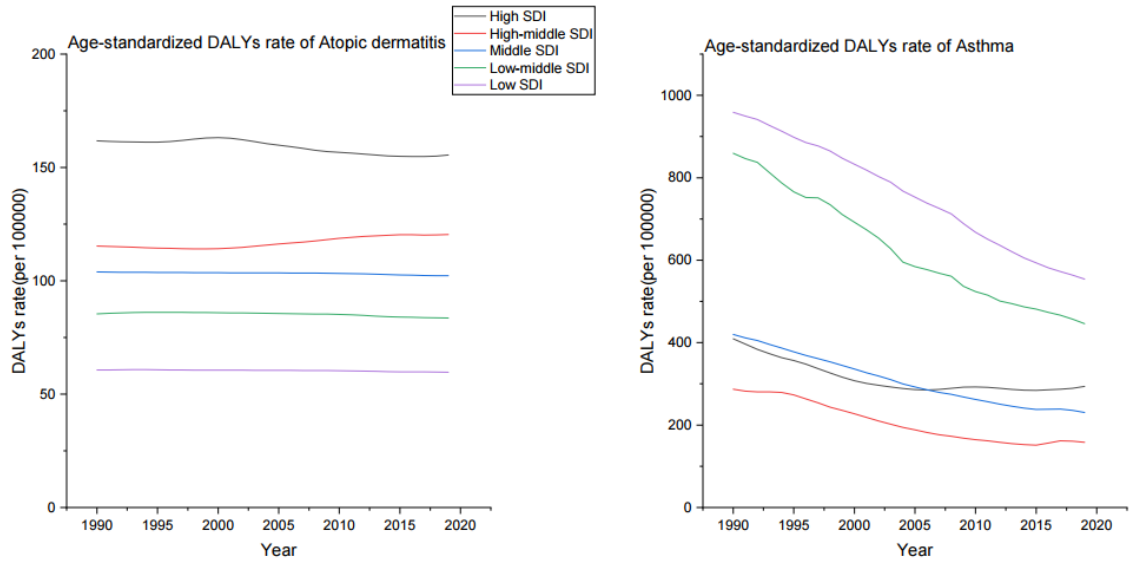
562　(B) by age, 1990–2019.

Figure 5. Age-standardized DALYs rates of asthma (A) and AD (B) according to SDI, 1990–

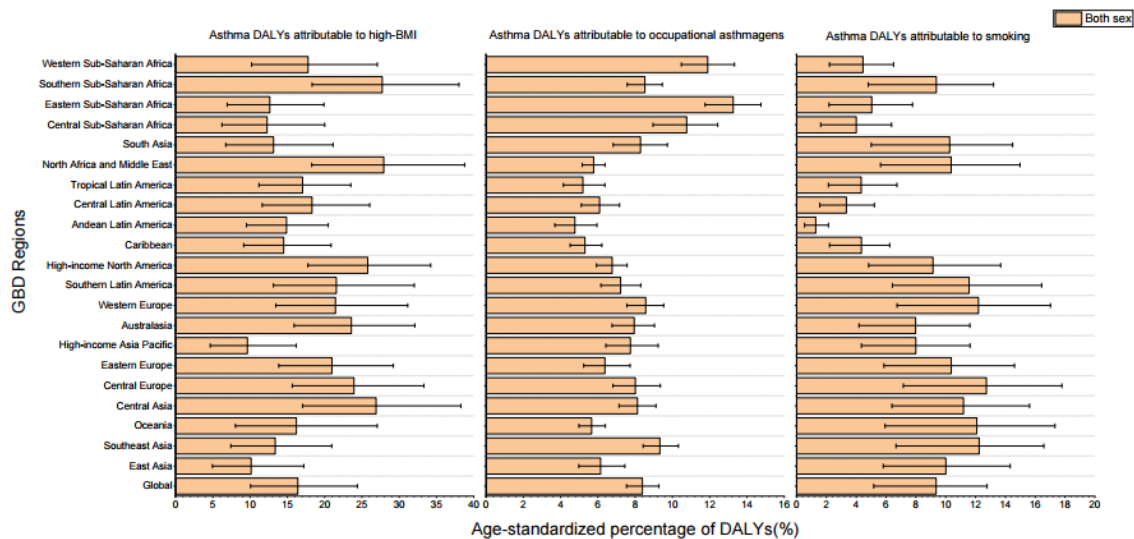2019. AD, atopic dermatitis; DALY, disability-adjusted life-years; SDI, socio-demographic
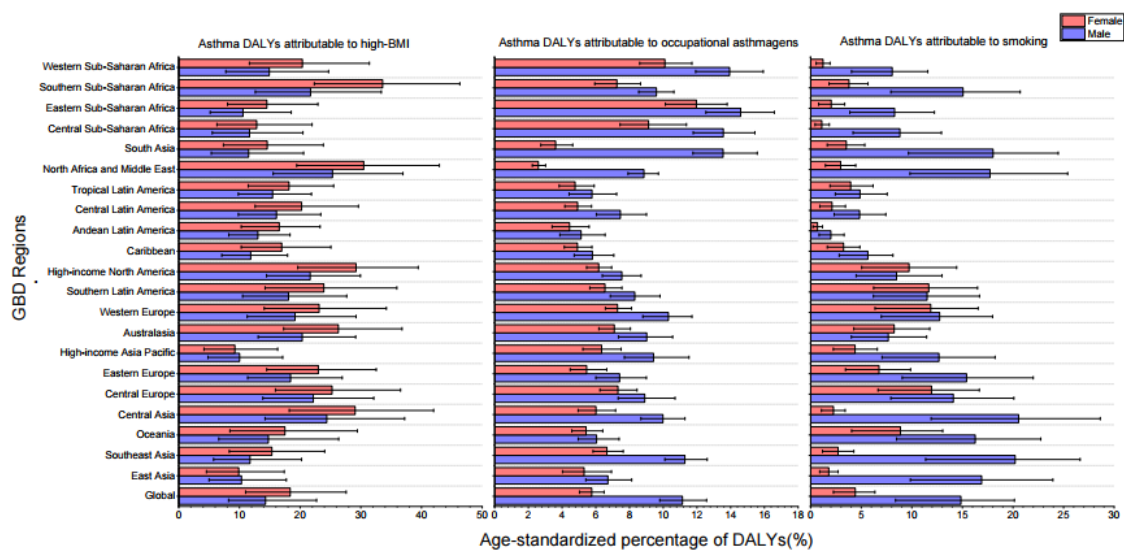
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573   **Figure 6.** Percentage of age-standardized DALYs rates of asthma attributable to high BMI,

574   occupational asthmagens, and smoking by geographic region, total (A) and sex-stratified (B).

575   BMI, body mass index; DALY, disability-adjusted life-years.

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