Epidemiology of patients with severe asthma in Japan: a nationwide descriptive study

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From a national database of ⩾99% of the Japanese population, the proportion of severe asthma declined from 5.6% to 4.3% in the last decade, while approximately 45% of patients with asthma remained uncontrolled https://bit.ly/49GTAwr

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Abstract

Background The 2014 European Respiratory Society/American Thoracic Society guidelines defined severe asthma based on treatment intensity and estimated the proportion of severe asthma among all asthma cases to be 5–10%. However, data supporting the estimate and comprehensive and sequential data on asthma cases are scarce. We aimed to estimate the national prevalence and proportion of severe asthma during the last decade.

Methods Using a Japanese national administrative database, which covers ⩾99% of the population, we evaluated the prevalence and proportion of severe asthma in 2013, 2015, 2017 and 2019. Additionally, we elucidated the demographic characteristics, treatments and outcomes of patients with asthma.

Results The national prevalence of mild–moderate and severe asthma in 2019 was 800 and 36 per 100 000 persons, respectively. While the prevalence of mild–moderate asthma remained almost constant in the study years, the prevalence of severe asthma decreased, resulting in a reduction in the proportion of severe asthma from 5.6% to 4.3%. Although treatment modalities have evolved, such as the increased use of combination inhalers and asthma biologics, approximately 15% of mild–moderate and 45% of severe asthma cases were still considered "uncontrolled". The number of deaths from asthma decreased in patients with both mild–moderate and severe asthma.

Conclusions This study revealed that the prevalence of severe asthma in Japan decreased during the study period and fell below 5% in the most recent data. Despite treatment evolution, a substantial proportion of patients with both mild–moderate and severe asthma still have poor asthma control.

Introduction

The 2014 European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines defined severe asthma as 1) asthma that requires treatment with high-dose inhaled corticosteroids (ICS) plus a second controller and/or systemic corticosteroids to prevent it from becoming "uncontrolled", or 2) asthma that remains "uncontrolled" despite this therapy [1]. The guidelines estimated the proportion of severe asthma to be 5–10% of all asthma cases. This high-burden condition is problematic on an individual level because frequent exacerbations related to severe asthma can impair quality of life and systematic corticosteroids for controlling it can cause additional complications [2–5]. This condition is also problematic on a societal level because the economic burden is correlated with the severity of asthma [6–8].

The reported proportion of severe asthma among all patients with asthma varied widely in previous studies (2.7–36.2%), depending on their criteria for defining severe asthma [9–13]. When the studies are limited to

those that used the definition of severe asthma from the ERS/ATS guidelines, the estimates were 4.5–7.8% [9, 11]. Although these estimates have provided substantial insight, they are potentially biased because of the limited study populations.

We aimed to clarify the prevalence and proportion of severe asthma based on the definition from the ERS/ATS guidelines using a national administrative claims database that covers 99% of the hospitals in Japan [14]. We also aimed to explore the demographic characteristics, treatments and outcomes stratified by asthma severity. We present the data in a manner consistent with our previous project on severe childhood asthma [15].

Methods

Data source

We used data from the National Database of Health Insurance Claims and Specific Health Checkups (NDB). The NDB was developed by the Ministry of Health, Labour and Welfare in Japan and covers more than 126 million people and 1.9 billion electronic claims annually, with data from 99% of the hospitals in Japan [16]. The information included in the NDB was: unique identifiers and demographic characteristics for each patient; diagnoses based on diagnostic codes [17]; and data on examinations, treatments and hospitalisations. The details of the database are described elsewhere [14, 16].

The study was approved by the Institutional Review Board of the University of Tokyo (approval number 11187-(8); approval date: 22 February 2023) and was performed in accordance with the tenets of the Declaration of Helsinki. The requirement for written informed consent was waived because of the anonymous nature of the data.

Study population

Figure 1 shows the step-by-step process used to identify the study population. In the NDB from January 2013 through December 2020, we identified all patients with prescriptions for asthma-related medications for at least 2 months, combined with the diagnostic code for asthma in 2013, 2015, 2017 and 2019 [18]. Asthma-related medications included ICS, a combination of ICS and long-acting β_2-agonist (LABA), a combination of ICS, LABA and long-acting muscarinic antagonist (LAMA), leukotriene receptor antagonist (LTRA), and xanthine and asthma biologics (omalizumab, mepolizumab, benralizumab and dupilumab). The index date was defined as the date of the first prescription for either ICS, ICS–LABA or ICS–LABA–LAMA in the year. If these medications were not prescribed, we set the date of the first prescription for the other asthma-related medications (LTRA, xanthine and asthma biologics) in the year.

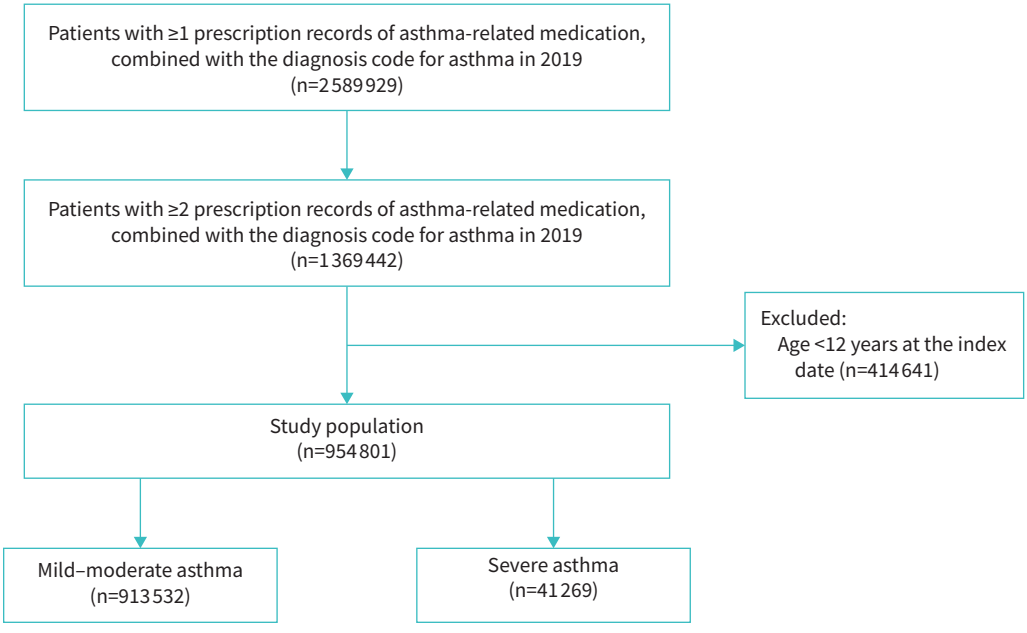

FIGURE 1 Flow diagram of patient recruitment.

The analysis was limited to patients aged ⩾12 years at the index date because asthma guidelines have different treatment recommendations for patients aged ⩾12 and <12 years [1].

Study design

This was a cross-sectional study. We gathered patient data from either the index date to 365 days after the index date or until the date of death (the observational period), whichever came first (supplementary figure S1). To exclude any seasonal change in asthma symptoms and medication prescriptions, a data-gathering period of 365 days was chosen.

Definition of the severity of asthma

Based on the definition from the ERS/ATS guidelines [1], patients with severe asthma were defined as patients who had a prescription for a high-dose ICS (⩾1000 µg·day^{-1} fluticasone equivalent) plus at least one other controller (LABA, LAMA, LTRA, xanthine and asthma biologics), or patients who had a prescription for systemic corticosteroids ⩾183 days or over half of the observational period in cases where the patient was deceased before 365 days. To calculate the average daily dose of ICS equivalent to fluticasone, we adopted an algorithm developed elsewhere (supplementary table S1) [13, 19]. In this study, patients with asthma who did not meet the definition of severe asthma were classified as having mild–moderate asthma.

Definition of controlled asthma

Based on the definition of controlled asthma in the ERS/ATS guidelines [1], we defined uncontrolled asthma as any of the following three criteria: 1) high short-acting β_2-agonist (SABA) use (a prescription of ⩾600 doses of SABA) [13, 20]; 2) at least two prescriptions for ⩾3 days use of oral corticosteroids (OCS) (⩾15 mg·day^{-1} prednisolone equivalent) or injectable corticosteroids [9]; or 3) hospitalisation for asthma. As for 2), prescriptions for OCS or injectable corticosteroids within 14 days were treated as one. Regarding 3), we defined hospitalisation for asthma as cases where the primary diagnostic code for hospitalisation was asthma, or when it could not be identified, if systemic corticosteroids were used within 2 days of hospitalisation. Further details are provided in the supplementary material.

Demographic characteristics, treatments and outcomes

We evaluated demographic characteristics, treatments and outcomes, stratified by the severity of asthma (severe or mild–moderate). Demographic characteristics were analysed in terms of age, sex and comorbidities. Treatments included medications, procedures, hospitalisations and outpatient clinic visits. Outcomes included controlled status of asthma, exposure to corticosteroids, total healthcare costs and deaths. Age was calculated based on the index date. Comorbidities, medications, procedures, hospitalisations, outpatient clinic visits, controlled asthma, total healthcare costs and deaths were evaluated based on the data in the observational period. Comorbidities were identified by the presence of corresponding diagnostic codes for each comorbidity (supplementary table S2) at least twice within the observational period. Medications were identified by the presence of at least one claim for each medication. Procedures were identified by the presence of at least one claim for home oxygen therapy or bronchial thermoplasty. Because information regarding the specific cause of death is not included in the NDB, deaths were from all causes. However, we defined deaths from asthma as those that occurred during hospitalisation for asthma.

Data analysis

The prevalence of severe or mild–moderate asthma in each year was calculated as the total number of patients with severe or mild–moderate asthma in the year divided by the total number of the estimated population in Japan in that year [21]. The prevalence in each year was calculated. The prevalence of all asthma cases and the proportion of severe asthma among all asthma cases in 2019 were visualised by choropleth mapping for nine geographical regions. Additionally, the proportion of severe asthma was calculated as the total number of severe asthma cases divided by all asthma cases. Demographic characteristics, treatments and outcomes were also provided for each year. We present continuous variables (parametric) as mean and standard deviation, continuous variables (nonparametric) as median and interquartile range (IQR), and categorical variables as number and percentage.

The data were analysed using PostgreSQL version 15 (www.postgresql.org) and Python version 3.7 (www.python.org). The choropleth mapping was created by QGIS (www.qgis.org).

Exploratory analysis

We performed some exploratory analyses. First, we determined patient characteristics classified by their asthma control status. Second, we calculated the proportion of patients treated with asthma biologics among regular OCS users. Third, we identified the characteristics of deceased patients stratified by asthma severity.

Results

Prevalence of mild–moderate or severe asthma and demographic characteristics

Table 1 shows the prevalence of mild–moderate and severe asthma. The prevalence of mild–moderate asthma remained consistent from 2013 to 2019, with values of 802, 809, 776 and 800 per 100 000 persons for each respective year. The prevalence of severe asthma decreased during the same period, with values of 48, 42, 37 and 36, respectively. Consequently, the proportion of severe asthma among all asthma cases decreased, with values of 5.6%, 4.9%, 4.6% and 4.3%, respectively. The decreasing trend in the prevalence of severe asthma was observed in all sex and age categories. Females accounted for approximately 60% of both mild–moderate and severe asthma patients (table 2). In mild–moderate asthma, the median (IQR) age was 58 (41–74) years, with approximately 15% each in the 40–49, 50–59, 60–69, 70–79 and ⩾80 years age groups. For severe asthma, the median (IQR) age was 71 (57–81) years, and the proportion increased in the older age categories, with the highest proportion observed in the ⩾80 years age group (28%). In mild–moderate asthma, females were predominant in all age groups except the 12–19 and ⩾80 years age groups (figure 2). Similarly, in severe asthma, females were predominant in all age groups except for the group aged ⩾80 years.

The proportion of severe asthma among all asthma cases ranged between 3.8% and 5.3% in the nine geographical regions (supplementary figure S2). The proportions were higher in the northern (Hokkaido and Tohoku) and southern (Chugoku, Kyusyu, and Okinawa) regions.

Supplementary table S3 shows the patients' comorbidities, which were classified into six categories (type 2 inflammation-related diseases, lifestyle diseases, diseases that can cause chronic cough, chronic infectious diseases, steroid-related diseases and others). Patients with severe asthma exhibited a higher prevalence of comorbidities of any category compared to those with mild–moderate asthma.

Treatments

Supplementary table S4 shows treatments regarding medications and procedures. The most commonly prescribed controller medications (prescribed in ⩾10% of patients) in mild–moderate asthma were ICS

TABLE 1 Sex and age distribution of the prevalence of mild–moderate and severe asthma per year

	Prevalence of mild–moderate asthma				Prevalence of severe asthma			
	2013	2015	2017	2019	2013	2015	2017	2019
Total	801.6 (799.9–803.2)	809.1 (807.5–810.8)	775.9 (774.3–777.5)	800.2 (798.6–801.8)	47.8 (47.4–48.2)	41.5 (41.1–41.9)	37.3 (36.9–37.6)	36.1 (35.8–36.5)
Sex								
Male	701.5 (699.3–703.7)	694.0 (691.9–696.2)	657.2 (655.1–659.3)	666.9 (664.8–669.1)	43.5 (43.0–44.1)	36.8 (36.3–37.3)	32.3 (31.8–32.8)	30.8 (30.4–31.3)
Female	895.2 (892.8–897.6)	917.0 (914.6–919.4)	887.3 (884.9–889.7)	925.2 (922.7–927.6)	51.9 (51.3–52.5)	45.9 (45.4–46.4)	41.9 (41.4–42.4)	41.1 (40.6–41.7)
Age group (years)								
12–19	655.7 (650.6–660.9)	686.7 (681.5–692.0)	631.0 (625.9–636.1)	667.5 (662.2–672.9)	10.6 (10.0–11.3)	8.8 (8.2–9.4)	6.4 (5.9–6.9)	5.8 (5.3–6.3)
20–29	436.3 (432.7–439.9)	444.2 (440.5–447.9)	408.3 (404.8–411.8)	422.2 (418.6–425.8)	9.6 (9.1–10.1)	8.1 (7.6–8.6)	6.3 (5.9–6.7)	5.8 (5.4–6.2)
30–39	639.3 (635.4–643.1)	665.1 (661.1–669.2)	624.2 (620.3–628.2)	680.5 (676.2–684.8)	18.1 (17.5–18.8)	14.9 (14.3–15.5)	12.4 (11.9–13.0)	12.0 (11.4–12.5)
40–49	660.8 (657.1–664.5)	697.0 (693.3–700.8)	672.9 (669.2–676.6)	727.2 (723.4–731.1)	26.1 (25.3–26.8)	21.9 (21.2–22.5)	19.1 (18.4–19.7)	19.6 (19.0–20.3)
50–59	688.6 (684.5–692.7)	721.2 (717.1–725.5)	724.9 (720.7–729.1)	774.3 (770.0–778.6)	36.9 (36.0–37.9)	32.6 (31.7–33.5)	29.9 (29.1–30.8)	29.8 (29.0–30.6)
60–69	818.0 (813.9–822.1)	818.5 (814.4–822.6)	822.5 (818.3–826.7)	865.8 (861.3–870.3)	54.7 (53.6–55.8)	46.6 (45.6–47.6)	43.8 (42.8–44.8)	44.0 (43.0–45.0)
70–79	1224.7 (1219.0–1230.5)	1167.4 (1161.8–1173.0)	1065.3 (1060.0–1070.6)	1011.4 (1006.5–1016.3)	109.0 (107.3–110.7)	90.4 (88.9–92.0)	77.6 (76.1–79.0)	70.5 (69.2–71.8)
⩾80	1552.8 (1544.9–1560.8)	1438.4 (1431.1–1445.8)	1330.5 (1323.7–1337.4)	1247.3 (1240.8–1253.8)	148.9 (146.5–151.4)	129.0 (126.8–131.3)	112.4 (110.4–114.4)	101.8 (99.9–103.6)

Data are presented as prevalence (95% CI) per 100 000 persons. 95% confidence intervals were calculated by the Wilson confidence interval for the binomial distribution.

TABLE 2 Sex and age distribution of the prevalence of mild–moderate and severe asthma patients in 2019

	Mild–moderate asthma cases	Severe asthma cases	Prevalence of mild–moderate asthma (95% CI)[#]	Prevalence of severe asthma (95% CI)[#]	Estimated population in 2019
Total	913 532 (100.0)	41 269 (100.0)	800.2 (798.6–801.8)	36.1 (35.8–36.5)	114 165 000
Sex					
Male	368 589 (40.3)	17 042 (41.3)	666.9 (664.8–669.1)	30.8 (30.4–31.3)	55 265 000
Female	544 943 (59.7)	24 227 (58.7)	925.2 (922.7–927.6)	41.1 (40.6–41.7)	58 901 000
Age group (years)					
12–19	60 264 (6.6)	523 (1.3)	667.5 (662.2–672.9)	5.8 (5.3–6.3)	9028.000
20–29	53 310 (5.8)	734 (1.8)	422.2 (418.6–425.8)	5.8 (5.4–6.2)	12 627 000
30–39	97 323 (10.7)	1710 (4.1)	680.5 (676.2–684.8)	12.0 (11.4–12.5)	14 302 000
40–49	134 672 (14.7)	3635 (8.8)	727.2 (723.4–731.1)	19.6 (19.0–20.3)	18 519 000
50–59	126 039 (13.8)	4848 (11.7)	774.3 (770.0–778.6)	29.8 (29.0–30.6)	16 278 000
60–69	140 530 (15.4)	7143 (17.3)	865.8 (861.3–870.3)	44.0 (43.0–45.0)	16 232 000
70–79	161 098 (17.6)	11 230 (27.2)	1011.4 (1006.5–1016.3)	70.5 (69.2–71.8)	15 928 000
⩾80	140 296 (15.4)	11 446 (27.7)	1247.3 (1240.8–1253.8)	101.8 (99.9–103.6)	11 248 000

Data are presented as n (%) or n, unless otherwise stated. [#]: data are presented as prevalence (95% CI) per 100 000 persons. 95% confidence intervals were calculated by the Wilson confidence interval for the binomial distribution.

(15–21%), ICS–LABA (48–59%), LTRA (58–65%) and xanthine (28–43%). In severe asthma, the most commonly prescribed controller medications were ICS (29–46%), ICS–LABA (49–62%), LAMA (13–16%), LTRA (52–59%), xanthine (35–49%), asthma biologics (2–12%) and regular OCS (59–76%). Regarding controller inhaler medications, there was a decreasing trend in monotherapy (ICS, LABA and LAMA) and an increasing trend in combination therapy (ICS–LABA and LABA–LAMA). While xanthine decreased, LTRA increased. Asthma biologics increased in both mild–moderate and severe asthma, and in 2019, the value in severe asthma reached 12%. Notably, regular OCS in patients with severe asthma increased from 59% to 76%.

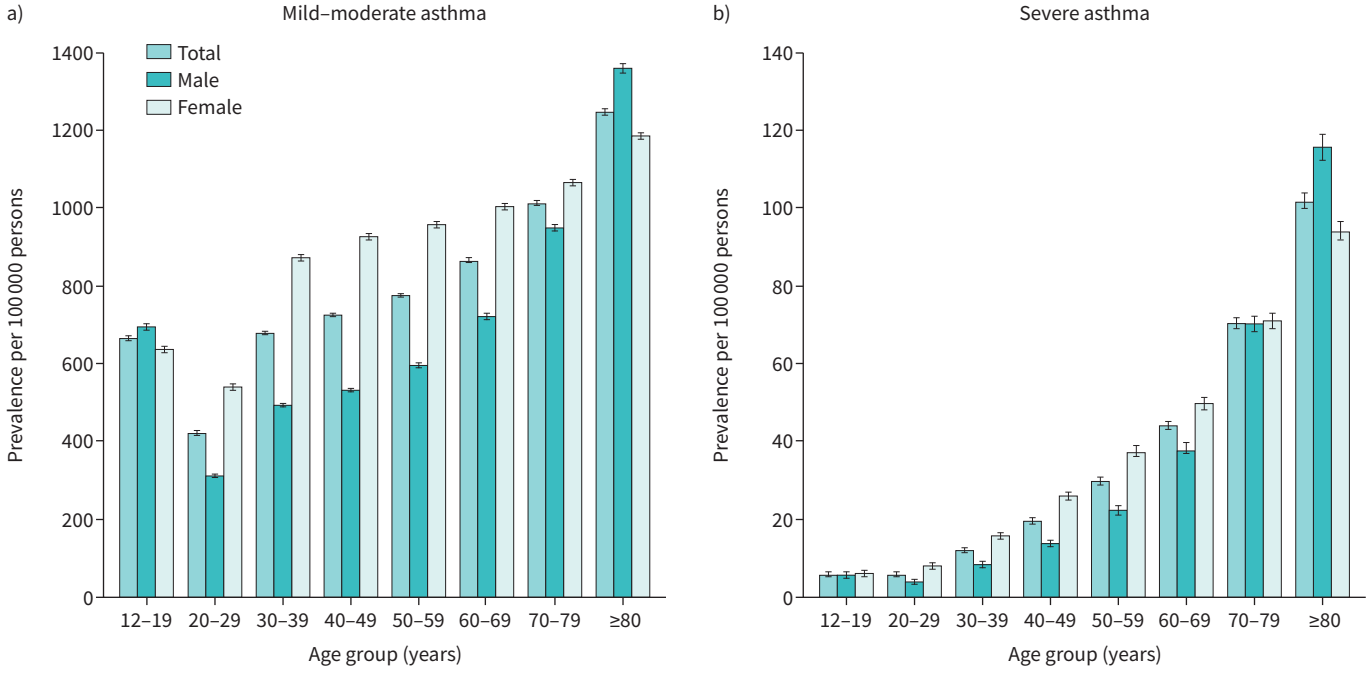

FIGURE 2 Prevalence rate of a) mild–moderate and b) severe asthma in 2019, by sex and age group. The prevalence (95% CI) per 100 000 persons is presented. 95% confidence intervals were calculated by the Wilson confidence interval for the binomial distribution.

TABLE 3 Controlled status of asthma in mild–moderate and severe asthma patients

	Mild–moderate asthma				Severe asthma			
	2013	2015	2017	2019	2013	2015	2017	2019
Total	917 238 (100.0)	927 280 (100.0)	887 733 (100.0)	913 532 (100.0)	54 737 (100.0)	47 557 (100.0)	42 632 (100.0)	41 269 (100.0)
Uncontrolled status of asthma	169 405 (18.5)	163 272 (17.6)	151 021 (17.0)	144 122 (15.8)	25 137 (45.9)	21 414 (45.0)	19 615 (46.0)	18 272 (44.3)
SABA ⩾600 doses	44 640 (4.9)	37 709 (4.1)	32 087 (3.6)	28 562 (3.1)	6960 (12.7)	5197 (10.9)	4302 (10.1)	3888 (9.4)
OCS/IVS ⩾2 times	128 845 (14.0)	127 979 (13.8)	120 625 (13.6)	116 693 (12.8)	20 155 (36.8)	17 405 (36.6)	16 090 (37.7)	15 013 (36.4)
Hospitalisation for asthma	16 224 (1.8)	15 087 (1.6)	13 136 (1.5)	11 664 (1.3)	5842 (10.7)	5006 (10.5)	4495 (10.5)	3999 (9.7)

Data are presented as n (%). SABA: short-acting β_2-agonist; OCS: oral corticosteroids; IVS: injectable (intravenous) corticosteroids.

Supplementary table S5 shows hospitalisations and outpatient clinic visits. The proportion of patients hospitalised for asthma showed a decreasing trend during the study period in both mild–moderate (1.8% to 1.3%) and severe (10.7% to 9.7%) asthma cases. The number of outpatient clinic visits remained stable in both groups.

Outcomes

Table 3 shows the trends for controlled status of asthma. The proportion of patients with uncontrolled asthma was approximately 15% and 45% in the mild–moderate and severe asthma groups, respectively. Both mild–moderate and severe asthma showed higher proportions of uncontrolled status among older age groups (figure 3). The proportions of severe asthma in younger age groups were as high as 30–40%.

Table 4 shows exposure to corticosteroids. Regarding ICS amounts, the value remained stable in mild–moderate asthma, but in severe asthma, it decreased. As for systemic corticosteroid amounts, the value showed a slight decreasing trend, but in severe asthma, it remained stable. The median amount of systemic corticosteroids in mild–moderate asthma was zero, except in the group aged 12–19 years. The median amount of systemic corticosteroids in severe asthma varied depending on the age group (supplementary figure S3).

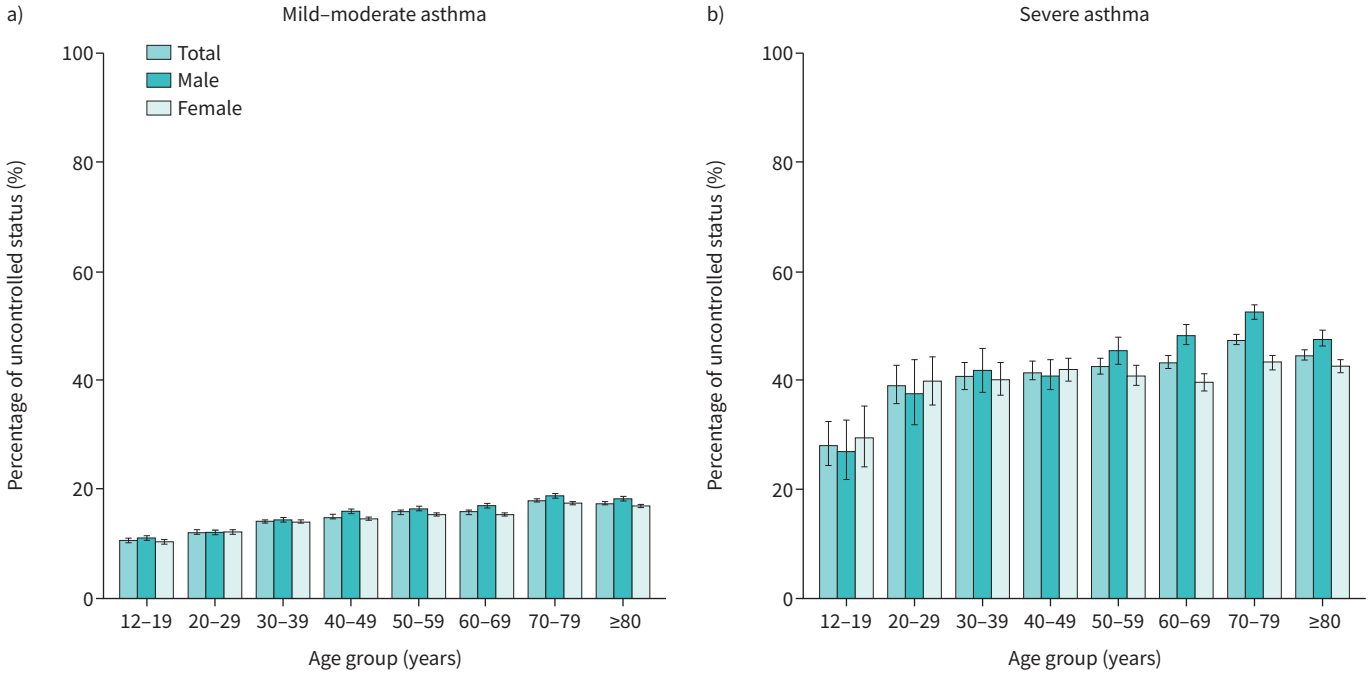

FIGURE 3 Control status in patients with a) mild–moderate and b) severe asthma in 2019, by sex and age group. The percentages (95% CI) of uncodntrolled asthma status are presented. 95% confidence intervals were calculated by the Wilson confidence interval for the binomial distribution.

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TABLE 4 Exposure to corticosteroids in mild–moderate and severe asthma patients

	Mild–moderate asthma				Severe asthma			
	2013	2015	2017	2019	2013	2015	2017	2019
Total	917 238 (100.0)	927 280 (100.0)	887 733 (100.0)	913 532 (100.0)	54 737 (100.0)	47 557 (100.0)	42 632 (100.0)	41 269 (100.0)
Users of ICS-containing medications[#]	573 639 (62.5)	605 030 (65.2)	589 594 (66.4)	621 439 (68.0)	45 288 (82.7)	39 413 (82.9)	35 155 (82.5)	34 055 (82.5)
Users of OCS[#]	130 435 (14.2)	134 495 (14.5)	130 222 (14.7)	136 943 (15.0)	37 520 (68.5)	34 014 (71.5)	32 938 (77.3)	33 494 (81.2)
Users of IVS[#]	239 475 (26.1)	235 234 (25.4)	219 025 (24.7)	212 097 (23.2)	24 424 (44.6)	20 796 (43.7)	18 904 (44.3)	17 503 (42.4)
Users of systemic corticosteroids (OCS/IVS)	301 483 (32.9)	301 512 (32.5)	285 285 (32.1)	286 252 (31.3)	41 721 (76.2)	37 070 (77.9)	35 215 (82.6)	35 146 (85.2)
Total amount of ICS[¶] (µg)	48 000 (17 500–107 266)	45 000 (15 000–100 437)	45 000 (15 000–97 596)	44 636 (15 000–96 000)	380 164 (135 000–782 143)	309 412 (111 087–644 739)	201 429 (91 269–480 000)	180 000 (84 850–405 989)
Total amount of OCS[+] (mg)	120 (60–280)	120 (60–280)	120 (60–280)	120 (60–275)	1790 (950–2904)	1805 (997–2955)	1797 (1005–2910)	1790 (1015–2874)
Total amount of IVS[+] (mg)	50 (21–200)	50 (20–177)	50 (20–165)	49 (17–156)	248 (50–1115)	248 (50–1147)	225 (50–1063)	201 (50–938)
Total amount of systemic corticosteroids[§] (mg)	90 (25–295)	88 (25–276)	83 (25–266)	80 (25–250)	1826 (890–3443)	1844 (940–3483)	1844 (984–3400)	1830 (1016–3315)

Data are presented as n (%) or median (interquartile range). Values are per patient year and are limited to those patients using the corresponding medication. ICS: inhaled corticosteroids; OCS: oral corticosteroids; IVS: injectable (intravenous) corticosteroids. [#]: users of ICS-containing medications, OCS or IVS were defined as those who used these medications at least once during the observational period; [¶]: the amount of ICS equivalent to fluticasone; [+]: the amount of OCS/IVS equivalent to prednisolone; [§]: systemic corticosteroids included OCS and IVS.

Table 5 shows the outcomes. While the median yearly costs decreased from USD 2735 to USD 2392 in mild–moderate asthma, they increased from USD 9543 to USD 13 284 in severe asthma. The trend of higher total healthcare costs with increased age was common in both asthma groups, but it was more pronounced in the severe asthma group (supplementary figure S4). In mild–moderate asthma, the proportion of all-cause deaths decreased from 2.56% to 2.01%, and there was also a decrease in asthma-related deaths from 0.16% to 0.10%. In severe asthma, although the proportion of all-cause deaths was stable between 10.29% and 11.20%, there was a decrease in asthma-related deaths from 1.94% to 1.46%. The number of patients who died from asthma in 2013, 2015, 2017 and 2019 was 2557, 2163, 1804 and 1477, respectively. Among these deceased patients, the proportion of severe asthma cases was stable at around 40%.

Exploratory analyses

Supplementary table S6 presents patient characteristics classified by their asthma control status. The patients with uncontrolled asthma were older, had a higher prevalence of severe asthma, and used a greater proportion of medications and procedures across all categories compared with those with controlled asthma.

The proportion of those treated with asthma biologics among regular OCS users in 2013, 2015, 2017 and 2019 was 2.8% (902/33 372), 3.3% (1005/30 430), 6.3% (1885/30 125) and 13.5% (4211/31 145), respectively.

The deceased patients were older (median (IQR) age in the deceased *versus* all patients with mild–moderate asthma: 84 (77–90) *versus* 58 (41–74) years; in those with severe asthma: 81 (74–87) *versus* 71 (57–81) years), more likely to be male patients and less frequently used ICS-containing controller inhalers. However, they more often used LABA- or LAMA-containing controller inhalers (table 2, and supplementary tables S4 and S7).

Discussion

Using the national administrative claims database (NDB), which covers 99% of the hospitals in Japan, we reported on the national prevalence of severe asthma. Over the past decade, severe asthma prevalence decreased from 48 to 36 per 100 000 persons, while mild–moderate asthma prevalence remained stable at around 800 per 100 000 persons. As a result of these trends, the proportion of patients with severe asthma decreased from 5.6% to 4.3%. These values were within the range of the predicted values (5–10%) according to the ERS/ATS guidelines [1]. While a clear reason regarding the decreasing trend in the prevalence of severe asthma cannot be obtained from this study, the widespread use of advanced asthma treatments (such as combination controller inhalers, asthma biologics, thermoplasty, *etc.*), as confirmed in this study, offers a plausible explanation. As advancements in asthma treatments continue and our understanding of personalised medicine based on phenotypes/endotypes improves [22], the prevalence of severe asthma may further decrease if these advancements are effectively implemented in the real world.

On the other hand, there are several issues identified in this study. First, asthma patients in Japan were older than those from other countries [11, 12, 23]. Because elderly asthma patients have an increased number of comorbidities and lower treatment responsiveness compared to younger asthma patients [24, 25], management of asthma in Japan, the country with the highest aged population, may be more challenging than in other countries. Physicians in Japan, as well as those in other countries that will experience the ageing of asthma patients, need to pay careful attention to the comorbidities (particularly COPD) and treatment responsiveness of older patients to deliver better outcomes. Second, the proportion

TABLE 5 Outcomes in mild–moderate and severe asthma patients

	Mild–moderate asthma				Severe asthma			
	2013	2015	2017	2019	2013	2015	2017	2019
Total	917 238 (100.0)	927 280 (100.0)	887 733 (100.0)	913 532 (100.0)	54 737 (100.0)	47 557 (100.0)	42 632 (100.0)	41 269 (100.0)
Total healthcare costs (USD)	2735 (1208–6395)	2265 (1041–5153)	2439 (1155–5560)	2392 (1146–5443)	9543 (3528–27 387)	8642 (3166–23 770)	10 684 (3830–28 077)	13 284 (4338–32 778)
All-cause deaths	23 517 (2.56)	21 470 (2.32)	19 899 (2.24)	18 329 (2.01)	5999 (10.96)	5324 (11.20)	4727 (11.09)	4247 (10.29)
Deaths from asthma	1493 (0.16)	1267 (0.14)	1079 (0.12)	873 (0.10)	1064 (1.94)	896 (1.88)	725 (1.70)	604 (1.46)

Data are presented as n (%) or median (interquartile range).

of patients with uncontrolled asthma was high in both mild–moderate and severe asthma, with values of 15% and 45%, respectively. Uncontrolled asthma is problematic because it impairs health-related quality of life and leads to increased healthcare resource utilisation and lung function decline [26–29]. The high prevalence of uncontrolled asthma in the real world, despite advancements in treatments, indicates that serious unmet needs exist for patients with uncontrolled asthma. To meet these needs, increasing both patients' awareness (including adherence [30]) and physicians' knowledge (including treatment options) is crucial. Third, the number of systemic corticosteroid users remained stable despite the great advancements in asthma control medications. In particular, the number of regular OCS users with severe asthma was consistent at around 30 000, even though the number of patients with severe asthma decreased. It has been established that the frequency and amount of exposure to systemic corticosteroids increase the risk of complications such as osteoporosis, glucose metabolism changes and susceptibility to infections [4, 5, 31]. Reducing the number of regular OCS users with severe asthma and minimising their exposure to systemic corticosteroids is an essential issue that needs to be addressed. While asthma biologics have shown promise in reducing the frequency and amount of systemic corticosteroids in some randomised controlled trials [32–35], their prescriptions were as low as 14%, even in 2019. Therefore, there is room to consider prescribing asthma biologics for regular OCS users. However, as severe asthma patients often have other comorbid diseases that affect asthma symptoms, and as asthma biologics are expensive medications, they should only be considered for prescription after thoroughly managing other comorbidities that may worsen respiratory symptoms and confirming good adherence to asthma medications. In addition, since these biologics are expensive medications, their costs may be a barrier to treatment with them, as suggested by their low usage rates even among regular OCS users. The barrier to treatments that would reduce regular OCS use should be explored in future research. Fourth, about 60% of patients who died from asthma were classified as having mild–moderate asthma. This highlights the potential for further reducing asthma-related deaths through a re-evaluation of asthma management practices (*e.g.* appropriate use of ICS-containing controller inhalers) [36], although the effect on survival might have been minimal due to the advanced age of the deceased patients with mild–moderate asthma. However, it is also important to note that the proportion of deaths from asthma among all deaths was small for both mild–moderate and severe asthma. This and the high prevalence of comorbidities such as lifestyle diseases in both groups suggest the need for comprehensive management that addresses both asthma and other comorbidities affecting the entire body. Fifth, although the ICS amounts showed a decreasing trend, the amounts of systemic corticosteroid remained stable. The specific reasons behind the decrease in the ICS amounts were not identifiable through the NDB, as it lacks information on this aspect. Nonetheless, it is crucial for physicians to closely monitor asthma control status in their patients during attempts to decrease ICS amounts. Furthermore, rather than decreasing the ICS amounts, efforts should be made to reduce OCS amounts among regular OCS users, where feasible.

This study has several limitations. First, the diagnostic code for asthma has not been validated due to restrictions on linking the NDB with other databases, preventing a validation study of the diagnostic codes [37]. Therefore, we adopted the definition of asthma patients based on previous research that identified asthma patients more reliably by combining asthma medication with the diagnostic code for asthma rather than relying solely on the diagnostic code for asthma [18]. The Ministry of Health, Labour and Welfare reports the number of asthma deaths based on death certificates every year using codes from the "International Statistical Classification of Diseases, Injuries, and Causes of Death", and in 2017, the codes used by the Ministry were updated to the latest edition. The reported numbers after the update were 1794 deaths in 2017 and 1481 deaths in 2019 [21], which were very close to the asthma death counts of 1804 in 2017 and 1477 in 2019 from our study data. The close similarity of these values suggests that the combination of diagnostic code and medication to define asthmatic patients, along with our definitions of asthma-related hospitalisation and death from asthma, may be valid. Second, the NDB does not include data on pulmonary function tests, which is one of the criteria for uncontrolled asthma as defined by the ERS/ATS guidelines [1]. Accordingly, we were unable to consider the pulmonary function test criterion, and there is a possibility that the proportion of uncontrolled asthma we presented might be underestimated. However, our definition was similar to the definitions used in previous studies [9, 13]. Third, almost all patients in this study were of Japanese ethnicity. Further research is needed to generalise the results to other ethnicities. Fourth, our data were restricted to the period up to 2019, prior to the coronavirus disease 2019 (COVID-19) era. Therefore, the trends identified in this study (*e.g.* the decreasing trend of the prevalence of severe asthma) might have changed during the COVID-19 era. Further research is required to verify these changes.

Conclusions

Over the past decade, the national prevalence and proportion of severe asthma decreased, while that of mild–moderate asthma remained stable. Approximately 15% of patients with mild–moderate asthma and

45% of patients with severe asthma still have uncontrolled asthma. In severe asthma, the number of regular OCS users and the exposure amounts to systemic corticosteroids were stable, which must be addressed to minimise side-effects. Although the number of deaths from asthma decreased, over half of patients who died from asthma were in the mild–moderate asthma group, suggesting that a re-evaluation of asthma management practices and an appropriate distribution of newly developed asthma treatment are necessary to improve mortality from asthma.

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References

1 Chung KF, Wenzel SE, Brozek JL, *et al.* International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43: 343–373.
2 Hiles SA, Harvey ES, McDonald VM, *et al.* Working while unwell: workplace impairment in people with severe asthma. *Clin Exp Allergy* 2018; 48: 650–662.
3 McDonald VM, Gibson PG. Exacerbations of severe asthma. *Clin Exp Allergy* 2012; 42: 670–677.
4 Lefebvre P, Duh MS, Lafeuille MH, *et al.* Acute and chronic systemic corticosteroid-related complications in patients with severe asthma. *J Allergy Clin Immunol* 2015; 136: 1488–1495.
5 Sweeney J, Patterson CC, Menzies-Gow A, *et al.* Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry. *Thorax* 2016; 71: 339–346.
6 Cisternas MG, Blanc PD, Yen IH, *et al.* A comprehensive study of the direct and indirect costs of adult asthma. *J Allergy Clin Immunol* 2003; 111: 1212–1218.
7 Godard P, Chanez P, Siraudin L, *et al.* Costs of asthma are correlated with severity: a 1-yr prospective study. *Eur Respir J* 2002; 19: 61–67.
8 Serra-Batlles J, Plaza V, Morejón E, *et al.* Costs of asthma according to the degree of severity. *Eur Respir J* 1998; 12: 1322–1326.
9 Nagase H, Adachi M, Matsunaga K, *et al.* Prevalence, disease burden, and treatment reality of patients with severe, uncontrolled asthma in Japan. *Allergol Int* 2020; 69: 53–60.
10 Mincheva R, Ekerljung L, Bossios A, *et al.* High prevalence of severe asthma in a large random population study. *J Allergy Clin Immunol* 2018; 141: 2256–2264.
11 Hekking PW, Wener RR, Amelink M, *et al.* The prevalence of severe refractory asthma. *J Allergy Clin Immunol* 2015; 135: 896–902.
12 Chastek B, Korrer S, Nagar SP, *et al.* Economic burden of illness among patients with severe asthma in a managed care setting. *J Manag Care Spec Pharm* 2016; 22: 848–861.
13 von Bülow A, Kriegbaum M, Backer V, *et al.* The prevalence of severe asthma and low asthma control among Danish adults. *J Allergy Clin Immunol Pract* 2014; 2: 759–767.
14 Yasunaga H. Real world data in Japan: chapter I NDB. *Ann Clin Epidemiol* 2019; 1: 28–30.

15 Kimura Y, Suzukawa M, Jo T, *et al.* Epidemiology of severe childhood asthma in Japan: a nationwide descriptive study. *Allergy* 2024; 79: 1598–1602.
16 Okumura Y, Sakata N, Takahashi K, *et al.* Epidemiology of overdose episodes from the period prior to hospitalization for drug poisoning until discharge in Japan: an exploratory descriptive study using a nationwide claims database. *J Epidemiol* 2017; 27: 373–380.
17 Hatano K, Ohe K. Information retrieval system for Japanese Standard Disease-Code Master using XML Web Service. *AMIA Annu Symp Proc* 2003; 2003: 859.
18 Pont LG, van der Werf GT, Denig P, *et al.* Identifying general practice patients diagnosed with asthma and their exacerbation episodes from prescribing data. *Eur J Clin Pharmacol* 2002; 57: 819–825.
19 Breton MC, Beauchesne MF, Lemière C, *et al.* Risk of perinatal mortality associated with inhaled corticosteroid use for the treatment of asthma during pregnancy. *J Allergy Clin Immunol* 2010; 126: 772–777.
20 Schatz M, Zeiger RS, Vollmer WM, *et al.* Validation of a beta-agonist long-term asthma control scale derived from computerized pharmacy data. *J Allergy Clin Immunol* 2006; 117: 995–1000.
21 Statistics Bureau, Ministry of Internal Affairs and Communications. e-Stat: Official Statistics Portal. 2003. www.e-stat.go.jp/en/stat-search Date last accessed: 12 May 2023.
22 Schoettler N, Strek ME. Recent advances in severe asthma: from phenotypes to personalized medicine. *Chest* 2020; 157: 516–528.
23 Moore WC, Bleecker ER, Curran-Everett D, *et al.* Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *J Allergy Clin Immunol* 2007; 119: 405–413.
24 Gibson PG, McDonald VM, Marks GB. Asthma in older adults. *Lancet* 2010; 376: 803–813.
25 Hanania NA, King MJ, Braman SS, *et al.* Asthma in the elderly: current understanding and future research needs – a report of a National Institute on Aging (NIA) workshop. *J Allergy Clin Immunol* 2011; 128: S4–S24.
26 Gonzalez-Barcala FJ, de la Fuente-Cid R, Tafalla M, *et al.* Factors associated with health-related quality of life in adults with asthma. A cross-sectional study. *Multidiscip Respir Med* 2012; 7: 32.
27 Kerkhof M, Tran TN, Soriano JB, *et al.* Healthcare resource use and costs of severe, uncontrolled eosinophilic asthma in the UK general population. *Thorax* 2018; 73: 116–124.
28 Ortega H, Yancey SW, Keene ON, *et al.* Asthma exacerbations associated with lung function decline in patients with severe eosinophilic asthma. *J Allergy Clin Immunol Pract* 2018; 6: 980–986.
29 Soremekun S, Heaney LG, Skinner D, *et al.* Asthma exacerbations are associated with a decline in lung function: a longitudinal population-based study. *Thorax* 2023; 78: 643–652.
30 Murphy AC, Proeschal A, Brightling CE, *et al.* The relationship between clinical outcomes and medication adherence in difficult-to-control asthma. *Thorax* 2012; 67: 751–753.
31 Bleecker ER, Menzies-Gow AN, Price DB, *et al.* Systematic literature review of systemic corticosteroid use for asthma management. *Am J Respir Crit Care Med* 2020; 201: 276–293.
32 Bel EH, Wenzel SE, Thompson PJ, *et al.* Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014; 371: 1189–1197.
33 Nair P, Wenzel S, Rabe KF, *et al.* Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med* 2017; 376: 2448–2458.
34 Rabe KF, Nair P, Brusselle G, *et al.* Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med* 2018; 378: 2475–2485.
35 Siergiejko Z, Świebocka E, Smith N, *et al.* Oral corticosteroid sparing with omalizumab in severe allergic (IgE-mediated) asthma patients. *Curr Med Res Opin* 2011; 27: 2223–2228.
36 Torjesen I. Two thirds of deaths from asthma are preventable, confidential inquiry finds. *BMJ* 2014; 348: g3108.
37 Hirose N, Ishimaru M, Morita K, *et al.* A review of studies using the Japanese National Database of Health Insurance Claims and Specific Health Checkups. *Ann Clin Epidemiol* 2020; 2: 13–26.