BMJ Open

Global, regional and national burden of asthma attributable to NO_2 from 1990 to 2021: an analysis from the Global Burden of Disease Study 2021

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To cite: Li J, Zhang C, Qin E, *et al*. Global, regional and national burden of asthma attributable to NO_2 from 1990 to 2021: an analysis from the Global Burden of Disease Study 2021. *BMJ Open* 2025;**15**:e095210. doi:10.1136/bmjopen-2024-095210

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-095210).

Received 17 October 2024
Accepted 16 January 2025

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ABSTRACT

Objectives This study aims to systematically assess the global, regional, and national burden of asthma attributable to nitrogen dioxide (NO_2) pollution.

Design and setting Analysis of population-level data from 1990 to 2021 obtained from the Global Burden of Disease Study 2021, covering 204 countries and territories.

Participants Participants included patients with asthma attributable to NO_2 pollution.

Main outcomes and measures Asthma-related disability-adjusted life-years (DALYs) and age-standardised DALY rates (ASDR) attributable to NO_2 pollution across 204 countries and territories. The estimated annual percentage change (EAPC) was used to assess temporal trends to identify regions with increasing or decreasing asthma burdens.

Results In 2021, NO_2 pollution contributed to approximately 176.73 thousand DALYs globally, with an ASDR of 2.48 per 100 000 population (95% uncertainty interval (UI) −2.26 to 10.30). The global ASDR declined significantly from 1990 to 2021, with an EAPC of −1.93% (95% CI −2.14% to −1.72%). High-income North America had the highest ASDR (10.74 per 100 000; 95% UI 10.12 to 46.56), while Australasia experienced the most significant reduction in ASDR over the study period (EAPC −3.92%; 95% CI −4.46% to −3.37%). In contrast, Oceania and Southeast Asia showed increasing trends in asthma burden, with EAPCs of 2.33% (95% CI 1.57% to 3.10%) and 1.14% (95% CI 0.81% to 1.47%), respectively. The 5–9 age group carried the highest asthma burden, reflecting the vulnerability of younger children to NO_2 exposure. A positive correlation between ASDR and sociodemographic index (SDI) was observed ($R=0.637$, $p<0.001$), indicating a greater asthma burden in higher SDI regions.

Conclusion The findings highlight significant regional and demographic disparities in asthma burden attributable to NO_2 pollution. Tailored public health strategies are needed to address the rising burden in vulnerable regions. Future research should focus on identifying effective interventions to reduce NO_2 exposure and improve asthma outcomes, especially in rapidly developing areas.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study uses data from the Global Burden of Disease Study 2021, which incorporates standardised methods across 204 countries and territories over a 31-year period (1990–2021).
- ⇒ Age-standardised disability-adjusted life-year rates and estimated annual percentage change metrics were used to account for differences in age structures and ensure robust trend analysis.
- ⇒ The methodology allows stratification of results by age, sex and sociodemographic index, ensuring detailed insights into demographic disparities.
- ⇒ Nitrogen dioxide (NO_2) exposure data in some low-income and middle-income regions rely on satellite-based estimates, which may introduce potential biases due to limited ground-level monitoring data.
- ⇒ The analysis excludes copollutants such as PM2.5 and ozone, which may interact with NO_2 and confound asthma-related outcomes.

INTRODUCTION

Asthma is a chronic respiratory disease affecting millions of individuals worldwide, characterised by recurrent episodes of wheezing, breathlessness, chest tightness and coughing.[1] The Global Burden of Disease (GBD) Study 2019 ranked asthma among the leading causes of disability-adjusted life-years (DALYs) for non-communicable diseases, underscoring its significant public health burden.[2] Despite substantial advances in asthma management, the prevalence and morbidity associated with asthma remain high, particularly in low-income and middle-income countries.[3 4]

Air pollution, particularly nitrogen dioxide (NO_2), has been identified as a critical environmental risk factor exacerbating respiratory diseases, including asthma.[5 6] NO_2, a byproduct of fossil fuel combustion in vehicles and industrial processes, is known to contribute to the development and worsening of asthma symptoms.[7] Several epidemiological studies have established a positive correlation between NO_2 exposure and increased hospital admissions for asthma, especially in urban areas with high traffic-related air pollution.[8]

Recent studies have further highlighted the association between NO_2 and asthma exacerbations.[9,10] For instance, during the COVID-19 pandemic, lockdown measures resulted in a significant reduction in vehicular traffic, leading to decreased NO_2 levels and a corresponding decline in asthma-related hospital admissions. This quasi-natural experiment provided compelling evidence linking NO_2 reduction with improved asthma outcomes, reinforcing the need for stringent air quality regulations.[9]

However, while the short-term effects of NO_2 on asthma have been well documented, there remains a paucity of comprehensive analyses quantifying the long-term burden of asthma attributable to NO_2 exposure on a global scale. The GBD Study offers a unique opportunity to address this gap by providing standardised estimates of NO_2-attributable asthma burden across different regions and time periods. NO_2 was selected for this study because it is a well-recognised marker of traffic-related air pollution and has been consistently linked to asthma exacerbations in epidemiological studies,[8,11] making it a robust focus for analysis.

This study aims to systematically evaluate the global, regional and national burden of asthma attributable to NO_2 from 1990 to 2021. By integrating data from the GBD Study 2021, this analysis seeks to provide a comprehensive overview of the impact of NO_2 on asthma, thereby informing public health policies aimed at reducing exposure to harmful air pollutants.

METHODS

Data resources

Data on the global burden of asthma attributed to NO_2 pollution were extracted on the Global Health Data Exchange (GHDx) platform (http:// ghdx.healthdata.org/gbd-results-tool). According to our study purpose, the data on asthma-related DALYs and deaths attributable to NO_2 pollution were collected at global, regional and national levels, disaggregated by age, sex and location from 1990 to 2021. The GHDx, a global database, offers extensive health and demographic data, including surveys, indices, registrations, health records and economic health statistics. This open-access resource has been extensively used in numerous research studies. Asthma was defined based on a confirmed medical diagnosis and the presence of wheezing in the past year, following the International Classification of Diseases (ICD) coding system (J45–J46 in ICD-10 and 493 in ICD-9). Additionally, four supplementary asthma definitions were considered: self-reported asthma within the past year, lifetime self-reported asthma, physician-diagnosed asthma in the past year and wheezing episodes reported in the past year. Exposure to NO_2 pollution is defined as the population-weighted annual average ambient concentration of NO_2 gas measured in parts per billion. The NO_2 exposure modelling process for the GBD Study 2021 combines multiple and varied input data sources. These data sources include ground-based measurements, satellite column observations, satellite-derived surface concentration estimates, land-use regression models for surface concentrations, urbanisation data and population estimates. To address variations in data quality across countries, urban areas primarily used the Larkin dataset,[12] while rural areas relied on OMI satellite data adjusted with chemical transport models.[13] Uncertainty was assessed using metrics like mean absolute error to ensure reliability in global comparisons.

Burden of asthma attributed to NO_2 pollution was assessed using metrics including numbers of DALYs, sociodemographic Index (SDI) and age-standardised DALY rate (ASDR). DALYs were determined by combining years of life lost (YLLs) due to premature mortality with years lived with disability, using a reference life expectancy and standardised disability weights specific to each health condition. The disability weights used for YLL calculations were sourced from surveys conducted in the general population. The SDI is a composite measure ranging from 0 (worst) to 100 (best), and it incorporates the total fertility rate of individuals under 25 years (TFU25), the average educational level of those aged 15 and above (EDU15+) and lagged per capita income. Based on SDI scores, 204 countries and territories were classified into five categories: low, low-middle, middle, high-middle and high SDI. Additionally, the GBD collaborators categorised these locations into 21 geographical regions, including high-income North America, Australasia, East Asia, Central Europe and Oceania.

Statistical analysis

To minimise the impact of heterogeneity from variations in population age structures, GBD 2021 computed percentage changes using point estimates of age-standardised rates (ASR, per 100 000 population). The estimates in this study are expressed in absolute numbers and ASRs, accompanied by 95% uncertainty intervals (UIs), defined as the 2.5th and 97.5th percentiles of 1000 model iterations. All rates were age-standardised using the direct method with the GBD global age structure. ASR was used to compare DALY rates between countries with different demographic characteristics. A linear model was fitted between the natural logarithm of the rate and time: $y=\alpha+\beta x+\varepsilon$, where xxx represents calendar year and $y=\ln(\text{rate})$. The estimated annual percentage change (EAPC) was calculated as $100\times(e\beta-1)$ with a 95% CI. An increase in ASR was indicated when both the EAPC value and the lower 95% CI limit were greater than 0, while a decrease was indicated when both the EAPC and the upper 95% CI limit were less than 0; otherwise, the ASR was deemed stable. The correlation between ASR and SDI was visualised using Gaussian process regression with a locally estimated scatterplot smoothing (LOESS) smoother and evaluated using Spearman rank

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correlation. Data processing, analysis and visualisation were performed using R V.4.2.3.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting or dissemination plans of our research.

RESULTS

Global spatial and temporal patterns of asthma burden attributable to NO_2 pollution

Globally, in 2021, NO_2 pollution contributed to approximately 176.73 thousand DALYs due to asthma, with an ASDR of 2.48 (95% UI −2.26 to 10.30) per 100 000 population. Males accounted for 98.22 thousand DALYs (95% UI −88.65 to 411.65), while females accounted for 78.51 thousand DALYs (95% UI −71.81 to 323.41). The ASDR was 2.67 (95% UI −2.42 to 11.20) per 100 000 for males and 2.27 (95% UI −2.08 to 9.35) per 100 000 for females, resulting in a male-to-female ratio of approximately 1.2 for both DALYs and ASDR. Over the past three decades, there was a significant decline in the global burden of asthma attributable to NO_2 pollution, with an EAPC in ASDR of −1.93 (95% CI −2.14 to −1.72) (table 1).

For SDI regions, the burden of asthma attributable to NO_2 pollution in 2021 varied considerably across different SDI levels. Compared with 1990, the low SDI region was the only SDI region where the number of asthma DALYs attributable to NO_2 pollution increased, rising from 10.12 thousand in 1990 to 15.24 thousand in 2021. In 2021, as the SDI level increased from low to high, both the DALYs and ASDR of asthma attributable to NO_2 pollution increased progressively across the regions. Among these SDI regions, the middle SDI region had the highest number of asthma DALYs (57.15 thousand), while the high SDI region experienced the greatest reduction in ASDR, with an EAPC of −2.77 (95% CI −3.10 to −2.43). In contrast, the low SDI region showed the lowest reduction in ASDR, with an EAPC of −0.59 (95% CI −1.13 to −0.05), indicating a less pronounced decrease in the burden (table 1).

For the GBD region, asthma burden attributable to NO_2 pollution showed marked geographical variability among the GBD regions. In 2021, high-income North America had the highest ASDR at 10.74 (95% UI −10.12 to 46.56) per 100 000 population, followed by Andean Latin America (7.80, 95% UI −6.68 to 30.07) and Tropical Latin America (6.36, 95% UI −5.45 to 24.79). High-income North America also recorded the highest number of asthma DALYs at 25.75 thousand (95% UI −23.95 to 111.17). In contrast, Oceania had the lowest ASDR at 0.11 (95% UI −0.07 to 0.66) per 100 000 population. Trends in the burden of asthma attributable to NO_2 pollution also varied across regions. The largest decline in ASDR occurred in Australasia, with an EAPC of −3.92 (95% CI −4.46 to −3.37), followed closely by high-income North America, which had the second-largest reduction in ASDR with an EAPC of −3.52 (95% CI −3.90 to −3.13). In contrast, Oceania and Southeast Asia were the only regions showing an increase in ASDR, with EAPCs of 2.33 (95% CI 1.57 to 3.10) and 1.14 (95% CI 0.81 to 1.47), respectively (table 1).

At the country level, the USA, People's Republic of China and Republic of India ranked top three in the number of asthma DALYs attributable to NO_2 pollution in 2021 (figure 1A; online supplemental table S1). Lebanese Republic, Republic of Peru, State of Qatar were the top three in ASDR in 2021 (figure 1B; online supplemental table S2). However, the fastest increase ASDR occurred in Bahrain, Bermuda and Barbados, with EAPCs 31.05 (95% CI 22.77 to 39.89), 29.81 (95% CI 22.67 to 37.36) and 27.50 (95% CI 20.61 to 34.78) 9.02, respectively (figure 1C; online supplemental table S3).

Global asthma burden attributable to NO_2 pollution by age and sex

Figure 2 shows the contribution of different age groups to the number and rate of DALYs of asthma attributable to NO_2 pollution globally and across 21 GBD regions in 1990 and 2021. In 1990 (figure 2A),the 5–9 years age group had the highest proportion of asthma DALYs, followed by the under 5 years age group, indicating a significant burden among younger populations. By 2021 (figure 2A), this pattern remained consistent, with the 5–9 years and under 5 years age groups continuing to account for the largest shares of asthma DALYs attributable to NO_2 pollution globally and across most regions. Notably, the contribution of the 5–9 years age group slightly increased from 1990 to 2021, reflecting a persistent and growing burden in this demographic over time. In 2021, these age groups were particularly impacted in regions such as East Asia and Western sub-Saharan Africa. The rate of DALYs in 1990 and 2021 (figure 2B) also followed a similar pattern, with the highest rates observed in the 5–9 years and under 5 years age groups. The lowest contribution came from the 15–49 years age group, which consistently had the smallest share of DALYs and the lowest rates, highlighting a different pattern of exposure and susceptibility compared with younger populations.

Figure 3 illustrates the age-specific numbers and rates of global asthma DALYs attributable to NO_2 pollution in 2021. In the population younger than 14 years, the age-specific numbers and rates of asthma DALYs in males were higher than those in females, while were almost the same as that in females older than 15 years old. It should be noted that, due to data limitations in the GBD database, age-specific data for asthma attributable to NO_2 pollution are only available for the age group 0–49 years, and thus, analysis for populations older than 50 years is not feasible.

Temporal trends in asthma burden attributable to NO_2 pollution

Figure 4 illustrates the trends in the ASDR of asthma attributable to NO_2 pollution from 1990 to 2021 globally and across five SDI categories. Globally, the ASDR followed a

Table 1 Global and regional DALYs of asthma attributable to nitrogen dioxide pollution in 1990 and 2021, and EAPC of ASDR from 1990 to 2021

Location	1990		2021		1990–2021
	DALYs No.×1000 (95% UI)	ASDR per 10 000 (95% UI)	DALYs No.×1000 (95% UI)	ASDR per 10 000 (95% UI)	EAPC in ASDR (95% CI)
Global	292.26 (–260.88 to 1079.99)	4.80 (–4.29 to 17.75)	176.73 (–160.46 to 734.86)	2.48 (–2.26 to 10.30)	–1.93 (–2.14 to –1.72)
Male	160.92 (–140.58 to 599.70)	5.16 (–4.51 to 19.20)	98.22 (–88.65 to 411.65)	2.67 (–2.42 to 11.20)	–1.94 (–2.14 to –1.73)
Female	131.34 (–120.36 to 480.18)	4.42 (–4.06 to 16.19)	78.51 (–71.81 to 323.41)	2.27 (–2.08 to 9.35)	–1.93 (–2.16 to –1.71)
SDI region					
Low SDI	10.12 (–7.64 to 54.10)	1.32 (–0.99 to 7.02)	15.24 (–12.29 to 74.95)	0.96 (–0.78 to 4.73)	–0.59 (–1.13 to –0.05)
Low-middle SDI	34.94 (–27.27 to 168.36)	2.16 (–1.69 to 10.42)	29.22 (–23.71 to 128.84)	1.42 (–1.15 to 6.24)	–0.97 (–1.49 to –0.44)
Middle SDI	79.08 (–69.71 to 312.63)	3.88 (–3.42 to 15.34)	57.15 (–50.14 to 231.57)	2.82 (–2.49 to 11.44)	–0.68 (–1.08 to –0.28)
High-middle SDI	49.89 (–43.11 to 186.23)	5.04 (–4.37 to 18.86)	28.75 (–26.65 to 114.51)	3.47 (–3.24 to 13.89)	–0.84 (–1.14 to –0.53)
High SDI	117.97 (–128.86 to 389.89)	17.48 (–19.16 to 57.81)	46.22 (–44.83 to 193.34)	7.35 (–7.18 to 30.90)	–2.77 (–3.10 to –2.43)
GBD region					
Andean Latin America	6.92 (–5.56 to 24.86)	13.44 (–10.81 to 48.37)	4.95 (–4.24 to 19.00)	7.80 (–6.68 to 30.07)	–1.73 (–2.48 to –0.97)
Australasia	1.37 (–1.20 to 5.09)	8.06 (–7.07 to 30.09)	0.58 (–0.52 to 3.00)	2.84 (–2.56 to 14.49)	–3.92 (–4.46 to –3.37)
Caribbean	2.11 (–1.79 to 9.09)	5.23 (–4.43 to 22.57)	2.04 (–1.77 to 9.22)	5.04 (–4.38 to 22.71)	–1.06 (–1.39 to –0.74)
Central Asia	2.70 (–2.32 to 10.08)	3.17 (–2.70 to 11.73)	2.11 (–1.92 to 8.63)	2.24 (–2.03 to 9.12)	–0.94 (–1.83 to –0.04)
Central Europe	7.92 (–7.55 to 27.90)	7.50 (–7.10 to 26.54)	2.83 (–2.50 to 13.96)	4.50 (–4.01 to 21.97)	–1.97 (–2.62 to –1.31)
Central Latin America	16.41 (–15.27 to 58.63)	7.35 (–6.85 to 26.28)	7.52 (–6.41 to 30.16)	3.29 (–2.83 to 13.27)	–2.58 (–2.96 to –2.19)
Central Sub-Saharan Africa	0.96 (–0.76 to 3.82)	1.12 (–0.88 to 4.46)	1.39 (–1.19 to 6.09)	0.69 (–0.59 to 3.04)	–0.47 (–1.30 to 0.37)
East Asia	34.92 (–32.57 to 148.87)	2.92 (–2.70 to 12.43)	21.78 (–19.97 to 97.48)	2.26 (–2.07 to 10.05)	–0.04 (–0.67 to 0.60)
Eastern Europe	14.25 (–15.70 to 46.23)	7.74 (–8.54 to 25.13)	4.50 (–4.19 to 16.99)	3.53 (–3.30 to 13.42)	–2.70 (–3.07 to –2.34)
Eastern Sub-Saharan Africa	2.12 (–1.62 to 14.25)	0.69 (–0.53 to 4.64)	2.83 (–2.24 to 19.25)	0.46 (–0.36 to 3.12)	–0.70 (–1.21 to –0.19)
High-income Asia Pacific	10.51 (–9.54 to 39.43)	7.90 (–7.18 to 29.90)	4.87 (–4.48 to 17.71)	5.93 (–5.52 to 21.84)	–0.29 (–0.89 to 0.30)
High-income North America	68.72 (–76.52 to 217.85)	31.52 (–35.11 to 100.03)	25.75 (–23.95 to 111.17)	10.74 (–10.12 to 46.56)	–3.52 (–3.90 to –3.13)
North Africa and Middle East	26.40 (–20.26 to 97.13)	5.45 (–4.19 to 20.03)	23.55 (–18.48 to 87.95)	3.67 (–2.88 to 13.73)	–0.94 (–1.35 to –0.53)
Oceania	0.01 (–0.00 to 0.04)	0.06 (–0.04 to 0.44)	0.02 (–0.01 to 0.11)	0.11 (–0.07 to 0.66)	2.33 (1.57 to 3.10)
South Asia	27.87 (–21.49 to 141.92)	1.90 (–1.46 to 9.70)	26.68 (–22.61 to 116.71)	1.44 (–1.21 to 6.28)	–0.07 (–0.84 to 0.71)
Southeast Asia	8.62 (–6.94 to 50.12)	1.45 (–1.17 to 8.46)	12.26 (–10.81 to 52.47)	2.00 (–1.76 to 8.55)	1.14 (0.81 to 1.47)
Southern Latin America	3.68 (–3.27 to 13.40)	7.03 (–6.26 to 25.59)	3.03 (–2.73 to 11.69)	5.74 (–5.19 to 22.19)	–0.31 (–0.69 to 0.07)
Southern Sub-Saharan Africa	0.52 (–0.47 to 3.06)	0.73 (–0.65 to 4.28)	0.48 (–0.42 to 2.63)	0.56 (–0.49 to 3.11)	–0.37 (–0.93 to 0.20)
Tropical Latin America	20.98 (–17.06 to 80.93)	11.30 (–9.17 to 43.61)	11.31 (–9.67 to 44.03)	6.36 (–5.45 to 24.79)	–1.85 (–2.08 to –1.63)
Western Europe	31.65 (–32.16 to 101.42)	11.58 (–11.84 to 37.14)	10.69 (–10.30 to 44.71)	4.24 (–4.10 to 17.65)	–3.34 (–3.69 to –2.98)
Western Sub-Saharan Africa	3.62 (–3.02 to 17.36)	1.23 (–1.03 to 5.95)	7.54 (–6.21 to 35.84)	1.03 (–0.85 to 4.88)	–0.24 (–0.65 to 0.18)

ASDR, age-standardised DALY rate; DALYs, disability-adjusted life-years; EAPC, estimated annual percentage change; SDI, sociodemographic index; UI, uncertainty interval.

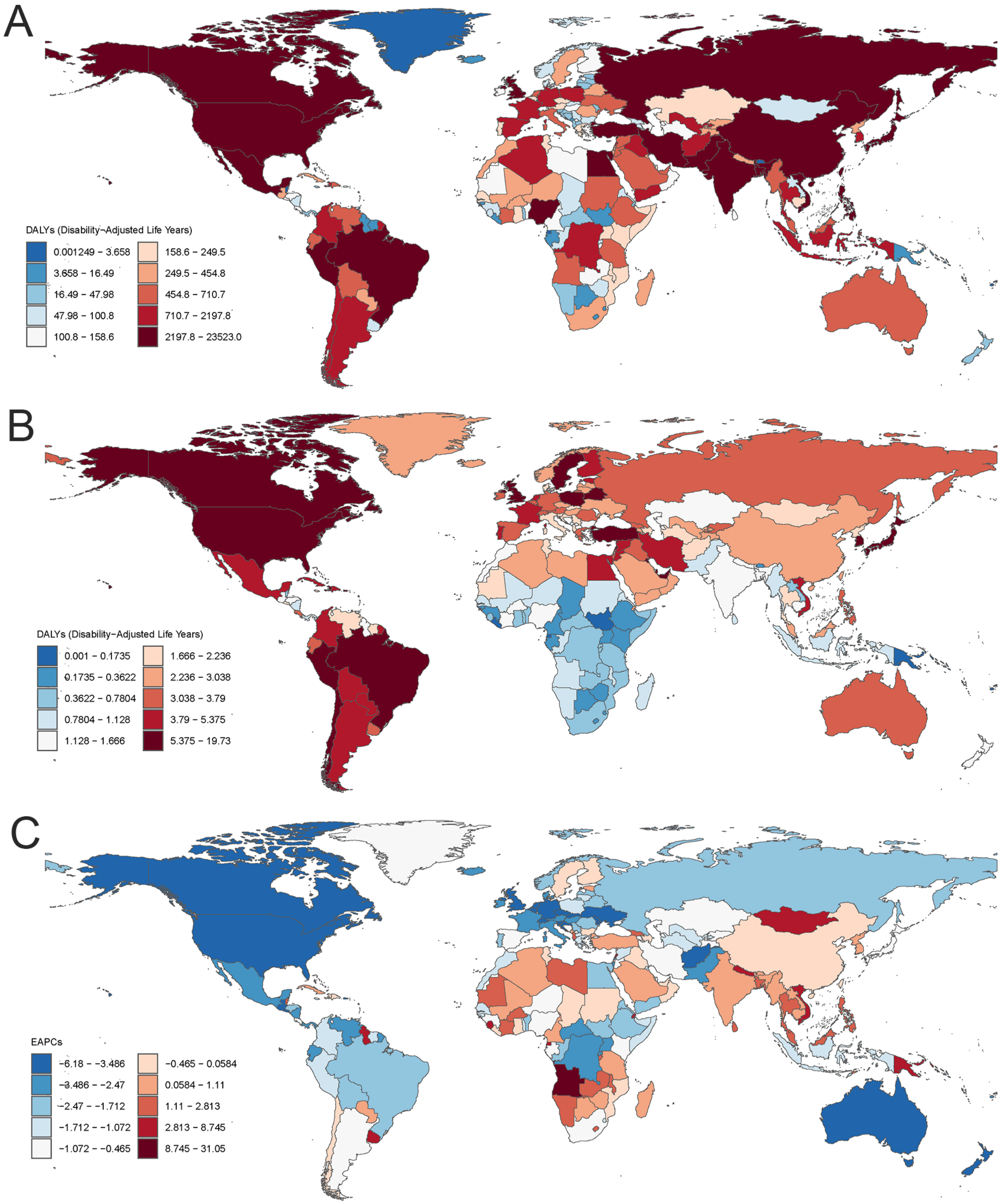

Figure 1 The spatial distribution of asthma ASDR attributable to NO_2 pollution in 204 countries and territories. (A) The number of asthma DALYs attributable to NO_2 pollution in 2021, (B) The asthma ASDR attributable to NO_2 pollution in 2021, (C) The EAPC of asthma ASDR attributable to NO_2 pollution from 1990 to 2021. ASDR, age-standardised DALYs rate; DALYs, disability-adjusted life-years; EAPC, estimated annual percentage change; NO_2, nitrogen dioxide.

'declining-rising-declining' pattern over the past 30 years, characterised by an initial decrease, a subsequent increase and a final decline, with an overall AAPC of −0.076% (95% CI −0.079% to −0.072%) (figure 4A). This fluctuating trend was also observed across low-middle, middle and high-middle SDI regions, where ASDR exhibited a similar 'declining-rising-declining' pattern. These regions experienced significant variability in asthma burden attributable to NO_2 pollution, with initial reductions, mid-period increases and subsequent declines. The overall AAPCs were −0.026% (95% CI −0.027% to −0.025%) for low-middle SDI (figure 4C), −0.040% (95% CI −0.043% to

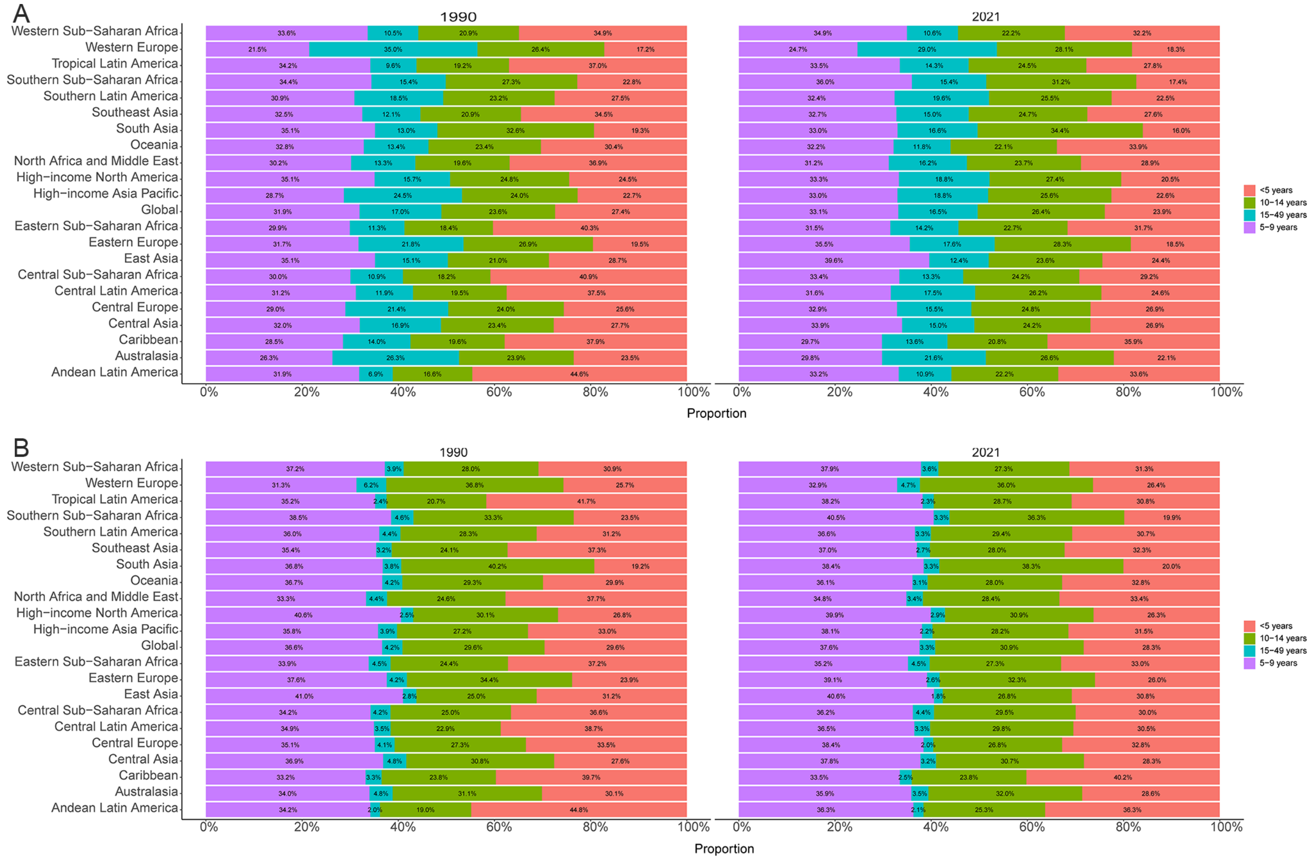

Figure 2 Contribution of different ages in number and rate of DALYs of asthma attributable to NO_2 pollution among global and 21 GBD regions in 1990 and 2021. (A) Number of DALYs in 1990 and 2021; (B) Rate of DALYs in 1990 and 2021. DALYs, disability-adjusted life years; GBD, Global Burden of Disease Study; NO_2, nitrogen dioxide.

−0.037%) for middle SDI (figure 4D) and −0.054% (95% CI −0.060% to −0.049%) for high-middle SDI regions (figure 4E). In contrast, the low SDI regions (figure 4B) demonstrated a ‘declining-rising-plateau’ trend, with an initial decrease in ASDR until around 2005, followed by an increase up to approximately 2010, after which the rate stabilised. This trend indicates a temporary improvement in asthma burden attributable to NO_2 pollution, followed by a worsening and then a stabilisation. The overall AAPC was −0.012% (95% CI −0.013% to −0.011%), reflecting

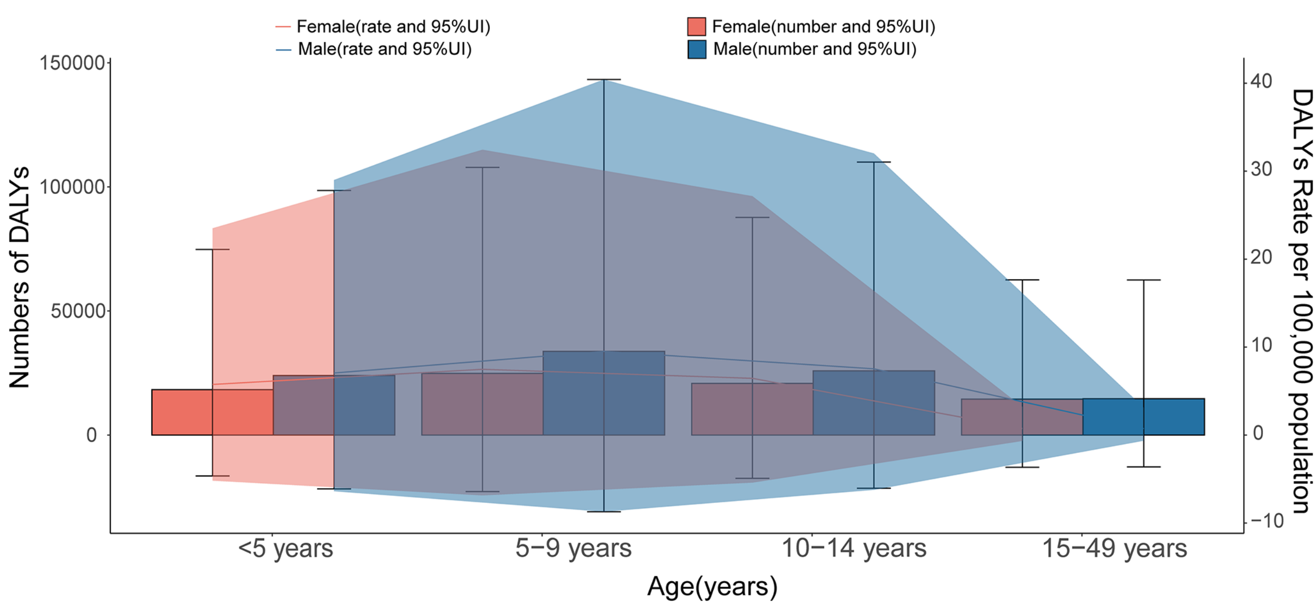

Figure 3 Age-specific numbers (bar plot) and rates (line plot) of DALYs of asthma attributable to NO_2 pollution in 2021 by Sex. DALY, disability-adjusted life-year; NO_2, nitrogen dioxide; UI, uncertainty interval.

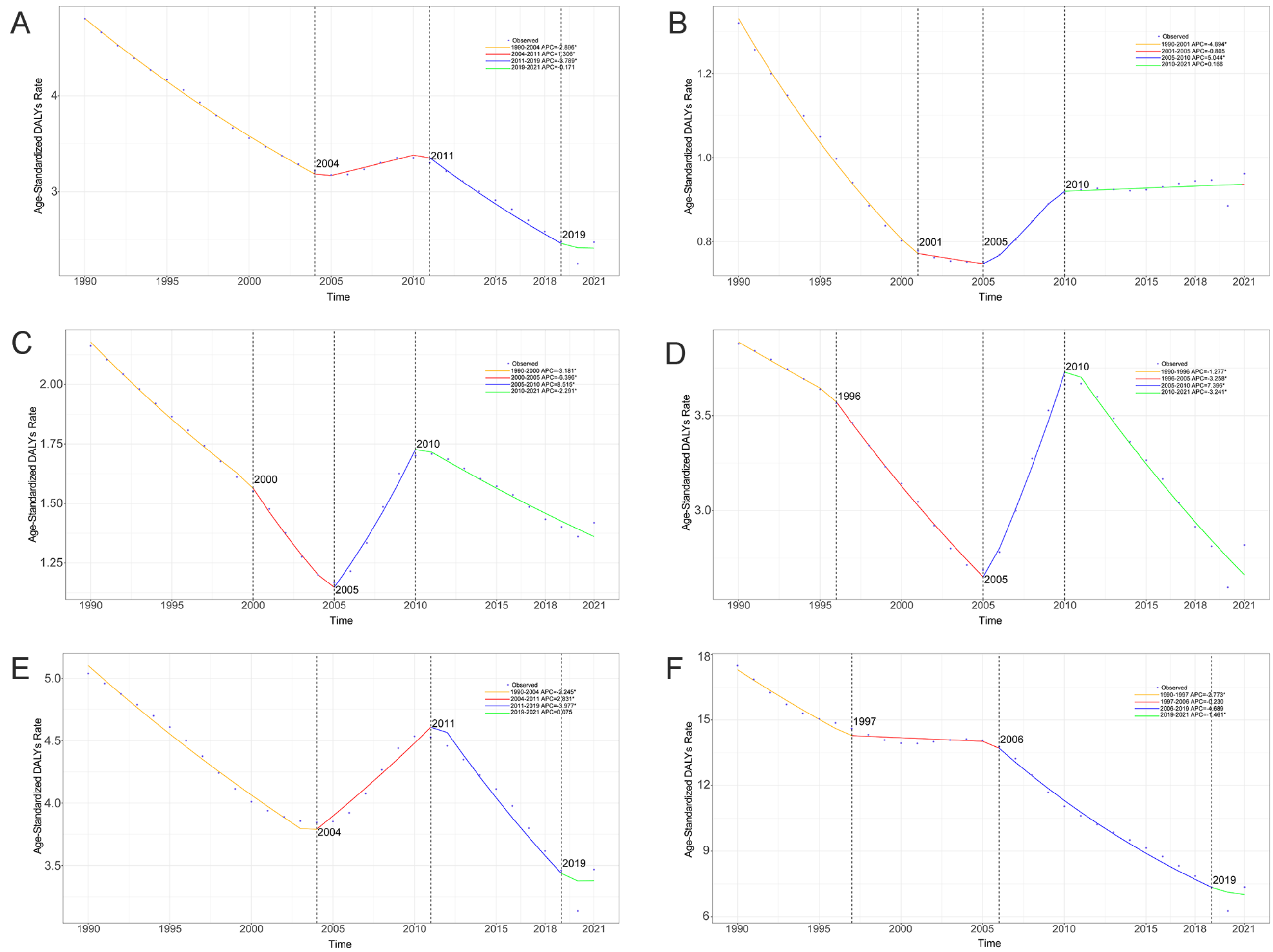

Figure 4 The trends of ASDR of asthma attributable to NO_2 pollution from 1990 to 2021 in global and five SDI categories regions. (A) APPC of ASDR in global; (B) APPC of ASDR in low SDI regions; (C) APPC of ASDR in low-middle SDI regions; (D) APPC of ASDR in middle SDI regions; (E) APPC of ASDR in high-middle SDI regions; (F) APPC of ASDR in high SDI regions. *Indicates that the APC is significantly different from zero at the alpha=0.05 level. AAPC, average annual percentage change; APC, annual percentage change; ASDR, age-standardised DALYs rate; DALYs, disability-adjusted life-years; NO_2, nitrogen dioxide.

a slight but statistically significant decline over the study period. The high SDI regions showed a consistent downward trend without the fluctuations seen in other regions, reflecting sustained improvements in reducing asthma burden, with an AAPC of −0.339% (95% CI −0.353% to −0.325%) (figure 4F).

The trend in ASDR for asthma burden attributable to NO_2 pollution across SDI by region or nation from 1990 to 2021

Figure 5A illustrates the relationship between observed and expected ASDR of asthma due to NO_2 pollution and SDI at the regional level from 1990 to 2021. A significant positive correlation (R=0.637, p<0.001) was found, suggesting that the burden increased as SDI values rose. Across the 21 regions with varying SDI levels, most regions showed an upward trend in ASDRs as SDI decreased between 1990 and 2021. The ASDR for asthma attributable to NO_2 pollution in high–income North America, Andean Latin America, Tropical Latin America and Caribbean, were much higher than the predicted value, while they were below or close to the expected value in other regions. Figure 5B shows the relationship between ASDRs and SDI across countries and territories in 2021. A positive correlation was observed at the national level, similar to the regional pattern (R=0.559, p<0.001), with ASDRs generally increasing alongside higher SDI values. Some countries, such as Lebanon, Peru and Qatar, exhibited significantly higher ASDRs than expected, while others, including Micronesia and Vanuatu, had much lower observed rates than predicted based on their SDI levels.

Prediction of asthma burden attributable to NO_2 pollution in China and the USA

Based on the comprehensive GBD data from 1990 to 2021, we further predicted the asthma burden attributable to NO_2 pollution in the next 14 years. We used the BAPC model to project that ASDR for asthma attributed to NO_2 pollution would significantly decrease globally for both sexes over the period 2021–2035 (figure 6A). The shaded areas in the figure indicate that the mortality could fluctuate dramatically as the corresponding rates

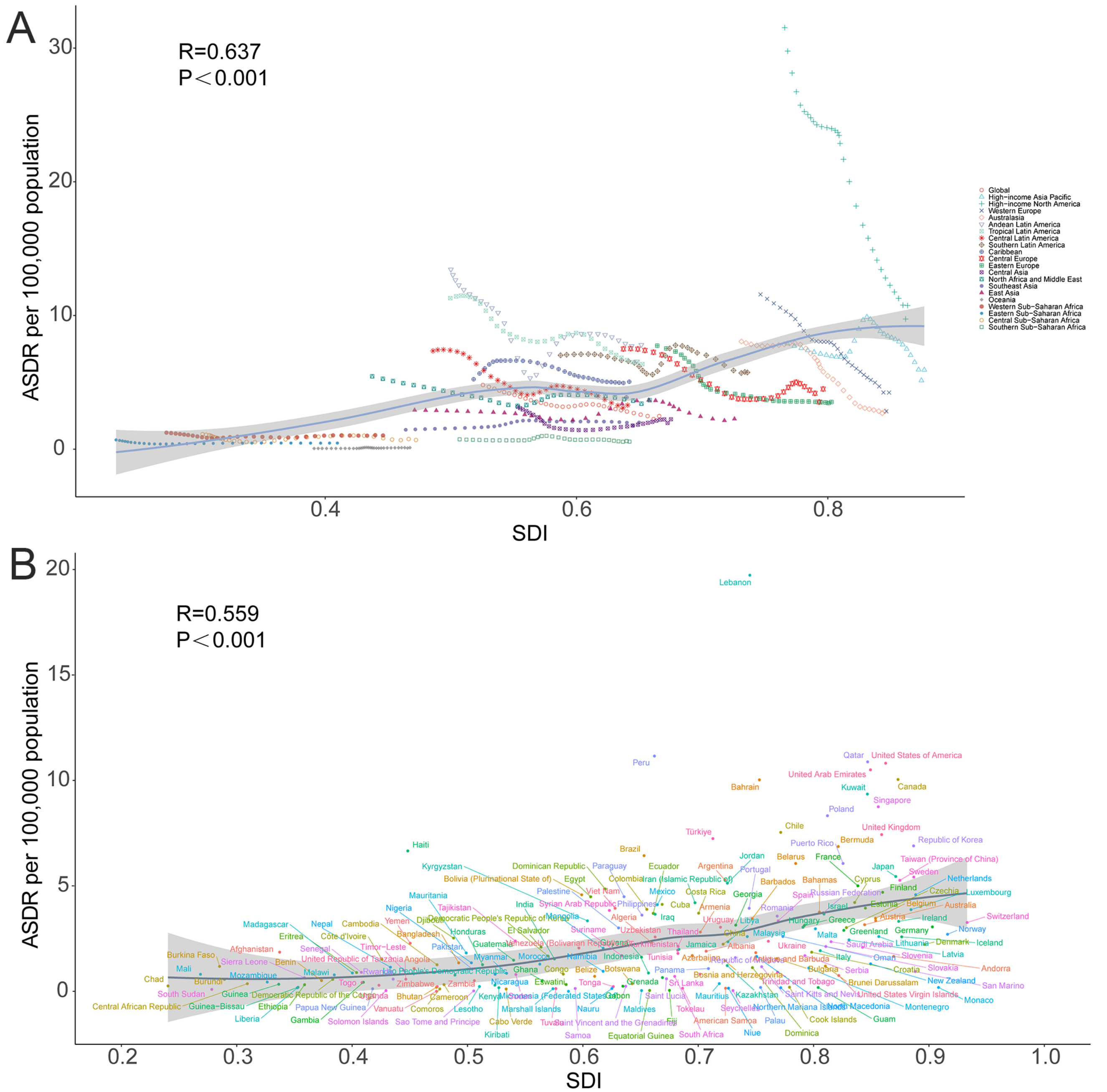

Figure 5 The correlation between ASDR of asthma attributable to NO_2 pollution and SDI at the global and 21 GBD regions level (A) at the national level (B). The solid line shows the expected value between the entire SDI and ASDR. Shaded areas represent 95% uncertainty intervals. ASDR, age-standardised DALYs rate; DALYs, disability-adjusted life-years; EAPC, estimated annual percentage change; GBD, Global Burden of Disease Study; NO_2, nitrogen dioxide; SDI, sociodemographic index.

rise or fall by 1% per year. According to the projections, the ASDR for asthma attributed to NO_2 pollution in the USA and China are projected to show a similar and continuous decreasing trend from 2021 to 2035, as shown in figure 6B,C.

DISCUSSION

Asthma is a complex and multifactorial disease influenced by a variety of genetic predisposition, allergens and environmental exposures.[14 15] Among these, exposure to indoor and outdoor allergens such as dust mites, pet dander and pollen is widely recognised as a primary trigger that can exacerbate asthma symptoms.[16 17] In addition to allergens, environmental pollutants also play a significant role in the development and progression of asthma.[18–20] Recent studies have highlighted NO_2 as a critical factor in asthma exacerbation.[21] NO_2, primarily emitted from vehicle exhaust and industrial activities, has been proven to exacerbate airway inflammation and increase the risk of asthma attacks, especially in children and vulnerable

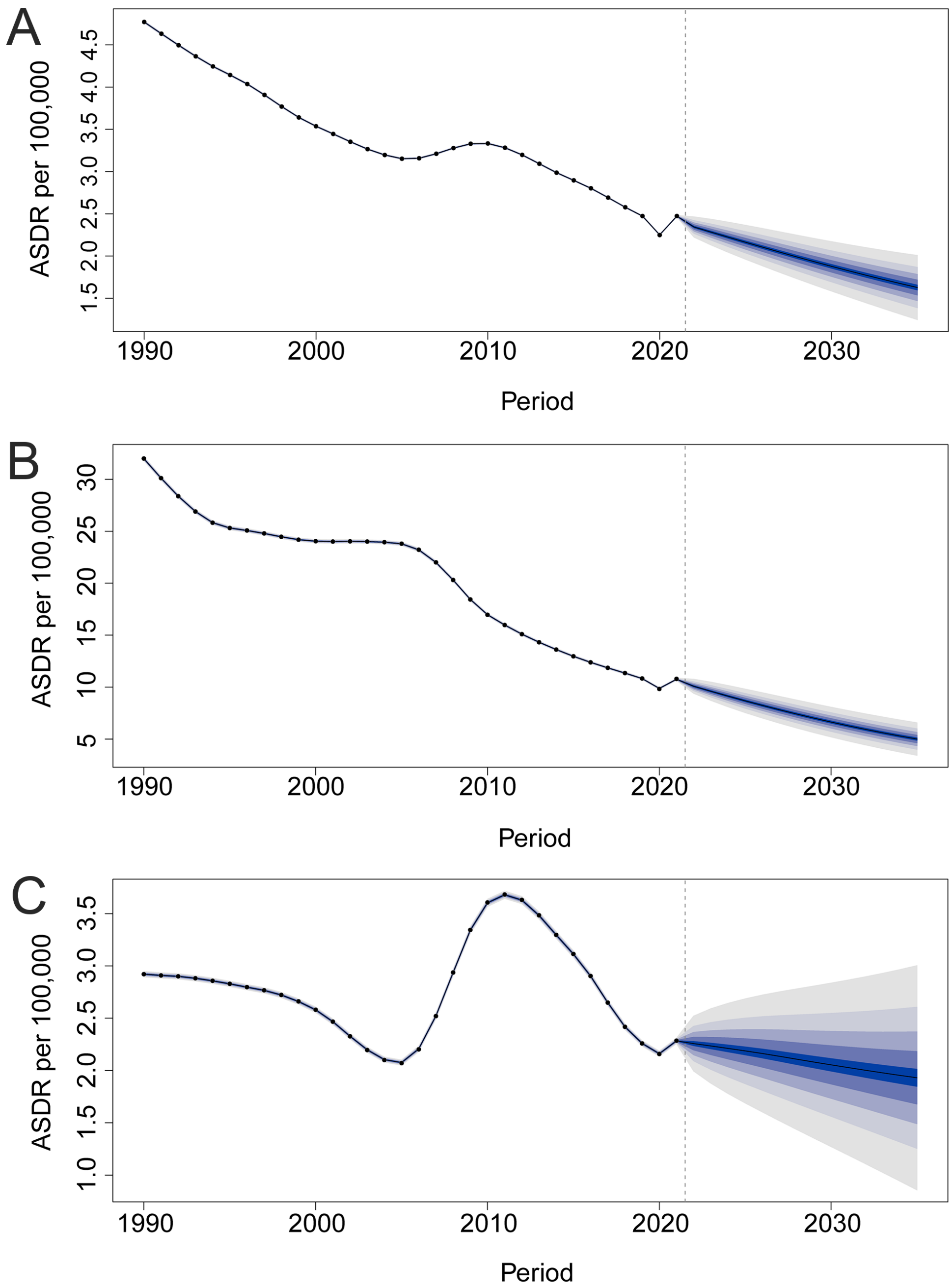

Figure 6 Changing trend and prediction ASDR of asthma burden attributable to NO_2 pollution from 1990 to 2035 in global (A), the USA (B) and China (C) using the BAPC model. Shading represented a 1% decrease and increase interval based on the rate of 2021. ASDR, age-standardised DALYs rate; BAPC, Bayesian age-period-cohort; DALYs, disability-adjusted life-years; NO_2, nitrogen dioxide.

populations.[22 23] This study used the latest GBD 2021 data to summarise the global epidemiological burden of asthma attributable to NO_2 pollution. To our knowledge, this is the first comprehensive evaluation of long-term trends in asthma burden due to NO_2 pollution from 1990 to 2021, encompassing global patterns, regional variations and socioeconomic associations at the country level. The asthma burden linked to NO_2 pollution significantly declined over the study period. The burden was strongly correlated with socioeconomic development, with higher SDI regions, such as high-income North America, experiencing a greater impact. The 5–9 age group bore the highest burden, and while males were more affected, the gender gap narrowed after age 15.

Several previous studies have investigated the relationship between NO_2 pollution and risk of asthma. A study by Solanki *et al* demonstrated that elevated levels of NO_2 were linked to higher paediatric asthma hospital admissions across various urban areas in the USA.[11] The research, which used data from EPA-monitored zip codes, identified a seasonal pattern between NO_2 concentrations and asthma exacerbations. Notably, the study found that even in regions where NO_2 levels were below the EPA standards, the pollutant still had a significant impact on asthma outcomes. Similarly, Hara *et al* explored the association between NO_2 exposure and asthma prevalence in Japanese adults, revealing that long-term exposure to NO_2 and PM2.5 significantly increased asthma prevalence in women but not in men, suggesting a potential sex-specific vulnerability to air pollution.[24] Furthermore, a prospective cohort study based on the UK Biobank data, involving over 400 000 participants, found that higher NO_2 exposure was associated with a significantly increased risk of developing adult-onset asthma, even after controlling for genetic predisposition and lifestyle factors.[25] However, most previous studies focused on specific regions or countries and primarily provided time-series estimates. In contrast, this study offers a comprehensive evaluation of the long-term global trends in asthma burden attributable to NO_2 pollution. Additionally, our analysis integrated a large body of studies and effect estimates, encompassing a broad range of NO_2 exposure levels.[26]

The exact mechanism of how NO_2 pollution contributes to asthma remains unclear. However, several studies have proposed potential pathways involving oxidative stress, airway inflammation and immune response modulation. For example, a study using an asthmatic mouse model found that exposure to NO_2 significantly increased levels of reactive oxygen species and malondialdehyde, which were accompanied by decreased glutathione levels.[27] Furthermore, the study observed an imbalance in the Th1/Th2 immune response, with NO_2 exposure promoting the differentiation of naive T cells into Th2 cells, leading to increased production of cytokines such as IL-4 and IL-13. These cytokines are known to drive airway hyper-responsiveness and mucus production, key features of asthma pathogenesis. Another study emphasised that coexposure to high humidity and NO_2 disrupted the Th1/Th2 immune balance, leading to increased allergic airway inflammation and heightened asthma susceptibility.[28] Collectively, these findings suggest that oxidative stress and immune dysregulation are critical mechanisms by which NO_2 exposure worsens asthma symptoms, particularly in individuals with pre-existing allergic airway conditions.

The variation in asthma burden attributable to NO_2 pollution across different regions reflects the complex interplay of environmental, socioeconomic and policy factors. In high-income regions like North America, the high asthma burden despite significant reductions in ASDR suggests that while stricter air quality regulations and healthcare improvements have been effective, other factors such as persistent high levels of urbanisation and traffic-related pollution continue to pose challenges. The relationship between socioeconomic development and asthma burden attributable to NO_2 pollution shows a generally upward trend with increasing SDI. However, a slowing of this trend, or plateau, is observed at mid-level SDI. This may be explained by the transitional phase of countries in this range, where rising urbanisation and industrial activity contribute to increasing NO_2 emissions, while initial improvements in healthcare systems and partial implementation of air quality policies begin to mitigate the associated health impacts. These counteracting forces could temporarily stabilise the asthma burden despite continued socioeconomic development. In contrast, regions such as Oceania and Southeast Asia, which have seen increases in ASDR, face a different set of challenges. Rapid urbanisation and industrial growth in these regions have led to rising NO_2 levels, and insufficient regulatory measures may have contributed to the increasing asthma burden.[29] These findings emphasise the need for comprehensive strategies that not only focus on reducing emissions but also improve healthcare access and public awareness regarding asthma management. The disparities observed between different regions highlight the importance of context-specific public health policies that address both environmental and healthcare infrastructure issues to effectively mitigate the impact of NO_2 on the asthma burden globally.

The burden of asthma attributable to NO_2 pollution varies significantly across different age groups. Our findings indicate that the asthma burden is highest in the 5–9 age group, followed by the under 5 age group, while it is lowest in the 15–49 age group. This trend suggests that younger children are particularly vulnerable to NO_2 exposure, which may be due to their developing respiratory systems and higher breathing rates relative to their body size, leading to increased exposure to airborne pollutants.[30 31] Additionally, children are often exposed to higher levels of indoor and outdoor allergens and environmental tobacco smoke, which can exacerbate the effects of NO_2 on their respiratory health.[32] Therefore, interventions aimed at reducing NO_2 exposure in environments where children live and play, such as schools and residential areas, are crucial for mitigating the asthma burden in this age group. In terms of gender differences, the study revealed that in childhood (under 14 years), males have a higher asthma burden compared with females. This could be due to anatomical and physiological differences in boys, such as narrower airways relative to lung size and a higher prevalence of atopy.[33] However, in the 15–49 age group, the asthma burden becomes nearly equal between males and females. This shift may be attributed to the hormonal changes and lifestyle factors that occur during and after adolescence, which could influence the susceptibility to asthma and its triggers. These findings underscore the importance of considering both age and gender when designing public health strategies for asthma prevention and management, as different demographic groups may require tailored approaches to effectively address their specific risk factors.

From 1990 to 2021, the global asthma burden has shown complex spatiotemporal variations. In many low-income and middle-income countries and regions, the burden of asthma has been gradually increasing with the acceleration of industrialisation and urbanisation, especially in areas with severe air pollution, such as Southeast Asia and some African countries. Although some high-income countries, such as North America and Europe, have implemented stringent air quality control measures leading to a decrease in concentrations of key pollutants like NO_2, the reduction in asthma burden has not been significant.[34–36] This suggests that even with improvements in air quality, asthma incidence is still influenced by other factors such as allergen exposure and lifestyle changes. Future strategies should include targeted interventions, such as urban planning to reduce vehicular emissions through improved public transportation and low-emission zones. Public awareness campaigns can educate communities on the risks of NO_2 pollution and promote behavioural changes, such as reduced car use. Additionally, healthcare systems should prioritise vulnerable populations, especially children, by ensuring access to preventive care, early diagnosis and effective asthma management. Furthermore, with the intensification of global climate change, the spatial and temporal distribution patterns of air pollution may change, potentially impacting the asthma burden profoundly.[37 38] Hence, further research is needed to predict the potential impact of climate change on asthma burden and to develop corresponding mitigation strategies.

Despite the comprehensive analysis of the global asthma burden attributable to NO_2 pollution using the latest GBD data, several limitations must be acknowledged. First, the primary data for NO_2 exposure were sparse in less developed countries, particularly in sub-Saharan Africa and other low-SDI regions. In these areas, the estimates relied heavily on mathematical modelling and extrapolation from nearby regions, leading to wide UIs and potential inaccuracies in exposure assessment. Second, NO_2 exposure data were primarily derived from land-use regression models, satellite-based measurements and chemical transport models, which may overestimate concentrations in rural areas due to their sensitivity to urban-centric inputs, such as road networks and land-use variables. This limitation may introduce biases, particularly in regions lacking comprehensive ground-level monitoring data. Third, this study lacks sufficient data to calculate the population-attributable risk (PAR) for asthma due to NO_2. The absence of detailed exposure–response relationships and integrated population-level data limits the ability to quantify NO_2's exact contribution to asthma development. Additionally, this study is based on secondary data from the GBD 2021 and lacks the ability to directly account for other important risk factors for asthma, such as indoor air pollution, genetic predisposition and lifestyle factors. The absence of these factors could lead to potential confounding, particularly in regions where NO_2 is not the sole contributor to the asthma burden. Finally, the study focused solely on NO_2 pollution, without evaluating the combined effects of other common air pollutants, such as PM2.5, PM10 and ozone, which often co-occur with NO_2 and may jointly contribute to the asthma burden. This limitation restricts the ability to discern the specific impact of NO_2 from other pollutants, which is crucial for targeted policy and intervention measures.

CONCLUSIONS

This study systematically assessed the global burden of asthma attributable to NO_2 pollution from 1990 to 2021, revealing complex regional patterns influenced by economic development and pollution control measures. The findings highlight the need for tailored interventions to address NO_2-related asthma burden, especially in rapidly urbanising areas with insufficient air quality management. Strengthening public health policies, enhancing air quality standards and improving asthma care are critical steps to mitigate the impact of NO_2 pollution. Future research should focus on identifying effective strategies for reducing exposure and preventing asthma exacerbations in vulnerable populations.

Contributors JL: formal analysis, data curation, writing-original draft preparation, funding acquisition. CZ: data curation, visualisation. EQ: writing-original draft preparation. JS: supervision, writing-reviewing and editing. LL: data curation, writing-original draft preparation. GP: conceptualisation, supervision, funding acquisition, writing-reviewing and editing. GP acted as a guarantor.

Funding The study was supported by the Medical Science and Technology Project of Zhejiang Province (2023RC289, 2022RC272) and Shaoxing People's Hospital Cultivation Fund Project (2024PY04).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. The datasets generated and/or analysed during the current study are available in the (GBD Results Tool of the GHDx) repository, (ghdx.healthdata.org/gbd-resultstool).

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REFERENCES

1 Yorgancıoğlu A, Reddel HK, GINA Board of Directors and GINA Science Committee. Global initiative for asthma: 30 years of promoting evidence-based asthma care. *Allergy* 2023;78:1737–9.
2 Safiri S, Carson-Chahhoud K, Karamzad N, *et al*. Prevalence, Deaths, and Disability-Adjusted Life-Years Due to Asthma and Its Attributable

Risk Factors in 204 Countries and Territories, 1990-2019. *Chest* 2022;161:318–29.
3 Goodwin RD, Zhou C, Silverman KD, *et al*. Cannabis use and the prevalence of current asthma among adolescents and adults in the United States. *Prev Med* 2024;179:107827.
4 Kankaanranta H, Viinanen A, Ilmarinen P, *et al*. Comorbidity Burden in Severe and Nonsevere Asthma: A Nationwide Observational Study (FINASTHMA). *J Allergy Clin Immunol Pract* 2024;12:135–45.
5 Wang J, Cortes-Ramirez J, Gan T, *et al*. Effects of climate and environmental factors on childhood and adolescent asthma: A systematic review based on spatial and temporal analysis evidence. Sci Total Environ 2024;951:175863.
6 Tian F, Zhong X, Ye Y, *et al*. Mutual Associations of Exposure to Ambient Air Pollutants in the First 1000 Days of Life With Asthma/Wheezing in Children: Prospective Cohort Study in Guangzhou, China. *JMIR Public Health Surveill* 2024;10:e52456.
7 Buteau S, Doucet M, Tétreault L-F, *et al*. A population-based birth cohort study of the association between childhood-onset asthma and exposure to industrial air pollutant emissions. *Environ Int* 2018;121:23–30.
8 Wang W, Gulliver J, Beevers S, *et al*. Short-Term Nitrogen Dioxide Exposure and Emergency Hospital Admissions for Asthma in Children: A Case-Crossover Analysis in England. *J Asthma Allergy* 2024;17:349–59.
9 Kelly C, Kenny P, O'Dwyer M, *et al*. Ambient air pollutant concentrations and asthma-related hospital admissions during COVID-19 transport restrictions. *Public Health (Fairfax)* 2022;211:66–71.
10 Singh A, Morley GL, Coignet C, *et al*. Impacts of ambient air quality on acute asthma hospital admissions during the COVID-19 pandemic in Oxford City, UK: a time-series study. *BMJ Open* 2024;14:e070704.
11 Solanki N, Bruckman D, Wang X, *et al*. Nitrogen dioxide, an EPA parameter, may forecast the incidence of asthma exacerbations across urban areas: An observational study. *Pediatr Pulmonol* 2023;58:262–70.
12 Larkin A, Geddes JA, Martin RV, *et al*. Global Land Use Regression Model for Nitrogen Dioxide Air Pollution. *Environ Sci Technol* 2017;51:6957–64.
13 Lamsal LN, Martin RV, van Donkelaar A, *et al*. Ground-level nitrogen dioxide concentrations inferred from the satellite-borne Ozone Monitoring Instrument. *J Geophys Res* 2008;113.
14 Chen W, Puttock EJ, Schatz M, *et al*. Risk Factors for Acute Asthma Exacerbations in Adults With Mild Asthma. *J Allergy Clin Immunol Pract* 2024;12:2705–16.
15 eBioMedicine. Asthma: a complex disease from causes to phenotype. *EBioMedicine* 2024;100:105022.
16 Agache I, Canelo-Aybar C, Annesi-Maesano I, *et al*. The impact of indoor pollution on asthma-related outcomes: A systematic review for the EAACI guidelines on environmental science for allergic diseases and asthma. *Allergy* 2024;79:1761–88.
17 Mahdavinia M, Fyolek JP, Jiang J, *et al*. Gut microbiome is associated with asthma and race in children with food allergy. *J Allergy Clin Immunol* 2023;152:1541–9.
18 Becerra BJ, Arias D, Becerra MB. Sex-Specific Association between Environmental Tobacco Smoke Exposure and Asthma Severity among Adults with Current Asthma. *Int J Environ Res Public Health* 2022;19:5036.
19 Keirsbulck M, Savouré M, Lequy E, *et al*. Long-term exposure to ambient air pollution and asthma symptom score in the CONSTANCES cohort. *Thorax* 2023;78:9–15.
20 Bi J, D'Souza RR, Moss S, *et al*. Acute Effects of Ambient Air Pollution on Asthma Emergency Department Visits in Ten U.S. States. *Environ Health Perspect* 2023;131:47003.
21 Zheng X-Y, Orellano P, Lin H-L, *et al*. Short-term exposure to ozone, nitrogen dioxide, and sulphur dioxide and emergency department visits and hospital admissions due to asthma: A systematic review and meta-analysis. *Environ Int* 2021;150:106435.
22 Gillespie-Bennett J, Pierse N, Wickens K, *et al*. The respiratory health effects of nitrogen dioxide in children with asthma. *Eur Respir J* 2011;38:303–9.
23 Carthy P, Ó Domhnaill A, O'Mahony M, *et al*. Local NO2 concentrations and asthma among over-50s in Ireland: A microdata analysis. *Int J Epidemiol* 2021;49:1899–908.
24 Hara A, Sato T, Kress S, *et al*. Sex-specific associations between air pollutants and asthma prevalence in Japanese adults: a population-based study. *Int J Environ Health Res* 2024;1–9.
25 Zhu Y, Pan Z, Jing D, *et al*. Association of air pollution, genetic risk, and lifestyle with incident adult-onset asthma: A prospective cohort study. *Ecotoxicol Environ Saf* 2023;257:114922.
26 GBD 2021 Risk Factors Collaborators. Global burden and strength of evidence for 88 risk factors in 204 countries and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet* 2024;403:2162–203.
27 Lu C, Wang F, Liu Q, *et al*. Effect of NO_2 exposure on airway inflammation and oxidative stress in asthmatic mice. *J Hazard Mater* 2023;457:131787.
28 Lu C, Liu Q, Qiao Z, *et al*. High humidity and NO2 co-exposure exacerbates allergic asthma by increasing oxidative stress, inflammatory and TRP protein expressions in lung tissue. *Environ Pollut* 2024;353:124127.
29 Zhang Y, Hu M, Xiang B, *et al*. Urban-rural disparities in the association of nitrogen dioxide exposure with cardiovascular disease risk in China: effect size and economic burden. *Int J Equity Health* 2024;23:22.
30 Saxena K. Association Between Maternal Prenatal Exposure to Household Air Pollution and Child Respiratory Health: A Systematic Review and Meta-analysis. *Yale J Biol Med* 2024;97:29–40.
31 Chao M-R, Cooke MS, Kuo C-Y, *et al*. Children are particularly vulnerable to environmental tobacco smoke exposure: Evidence from biomarkers of tobacco-specific nitrosamines, and oxidative stress. *Environ Int* 2018;120:238–45.
32 Galvao ES, Reis Junior NC, Goulart EV, *et al*. Refining Children's exposure assessment to NO2, SO2, and O3: Incorporating indoor-to-outdoor concentration ratios and individual daily routine. *Chemosphere* 2024;364:143155.
33 Pascoe CD, Seow CY, Hackett TL, *et al*. Heterogeneity of airway wall dimensions in humans: a critical determinant of lung function in asthmatics and nonasthmatics. *Am J Physiol Lung Cell Mol Physiol* 2017;312:L425–31.
34 Clappier A, Thunis P, Beekmann M, *et al*. Impact of SOx, NOx and NH3 emission reductions on PM2.5 concentrations across Europe: Hints for future measure development. *Environ Int* 2021;156:106699.
35 Paramesh H. Air Pollution and Allergic Airway Diseases: Social Determinantsand Sustainability in the Control and Prevention. *Indian J Pediatr* 2018;85:284–94.
36 De Marco A, Proietti C, Anav A, *et al*. Impacts of air pollution on human and ecosystem health, and implications for the National Emission Ceilings Directive: Insights from Italy. *Environ Int* 2019;125:320–33.
37 Lavigne E, Donelle J, Hatzopoulou M, *et al*. Spatiotemporal Variations in Ambient Ultrafine Particles and the Incidence of Childhood Asthma. *Am J Respir Crit Care Med* 2019;199:1487–95.
38 Kinney PL. Interactions of Climate Change, Air Pollution, and Human Health. *Curr Environ Health Rep* 2018;5:179–86.