# Global, national, and urban burdens of paediatric asthma incidence attributable to ambient $NO_2$ pollution: estimates from global datasets

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## Summary

**Background** Paediatric asthma incidence is associated with exposure to traffic-related air pollution (TRAP), but the TRAP-attributable burden remains poorly quantified. Nitrogen dioxide ($NO_2$) is a major component and common proxy of TRAP. In this study, we estimated the annual global number of new paediatric asthma cases attributable to $NO_2$ exposure at a resolution sufficient to resolve intra-urban exposure gradients.

**Methods** We obtained 2015 country-specific and age-group-specific asthma incidence rates from the Institute for Health Metrics and Evaluation for 194 countries and 2015 population counts at a spatial resolution of 250×250 m from the Global Human Settlement population grid. We used 2010–12 annual average surface $NO_2$ concentrations derived from land-use regression at a resolution of 100×100 m, and we derived concentration-response functions from relative risk estimates reported in a multinational meta-analysis. We then estimated the $NO_2$-attributable burden of asthma incidence in children aged 1–18 years in 194 countries and 125 major cities at a resolution of 250×250 m.

**Findings** Globally, we estimated that 4·0 million (95% uncertainty interval [UI] 1·8–5·2) new paediatric asthma cases could be attributable to $NO_2$ pollution annually; 64% of these occur in urban centres. This burden accounts for 13% (6–16) of global incidence. Regionally, the greatest burdens of new asthma cases associated with $NO_2$ exposure per 100 000 children were estimated for Andean Latin America (340 cases per year, 95% UI 150–440), high-income North America (310, 140–400), and high-income Asia Pacific (300, 140–370). Within cities, the greatest burdens of new asthma cases associated with $NO_2$ exposure per 100 000 children were estimated for Lima, Peru (690 cases per year, 95% UI 330–870); Shanghai, China (650, 340–770); and Bogota, Colombia (580, 270–730). Among 125 major cities, the percentage of new asthma cases attributable to $NO_2$ pollution ranged from 5·6% (95% UI 2·4–7·4) in Orlu, Nigeria, to 48% (25–57) in Shanghai, China. This contribution exceeded 20% of new asthma cases in 92 cities. We estimated that about 92% of paediatric asthma incidence attributable to $NO_2$ exposure occurred in areas with annual average $NO_2$ concentrations lower than the WHO guideline of 21 parts per billion.

**Interpretation** Efforts to reduce $NO_2$ exposure could help prevent a substantial portion of new paediatric asthma cases in both developed and developing countries, and especially in urban areas. Traffic emissions should be a target for exposure-mitigation strategies. The adequacy of the WHO guideline for ambient $NO_2$ concentrations might need to be revisited.

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## Introduction

Global paediatric asthma prevalence has increased strikingly since the 1950s, and asthma is now the most commonly reported non-communicable disease among children worldwide.[1] Over the past decade, several epidemiological studies done in North America, Latin America, Europe, and east Asia have reported associations between traffic-related air pollution (TRAP) exposure and new-onset asthma in children, whereas such associations are less clear in adults.[2–6] Corroborating evidence from toxicological and gene-environment studies have suggested that TRAP causes oxidative injury to the airways, leading to inflammation and remodelling that, in a genetically predisposed individual, could result in asthma development.[7,8] Although the putative agent (or agents) within the TRAP mixture has yet to be identified,[9] epidemiological studies have most often relied on nitrogen dioxide ($NO_2$) as a proxy, because $NO_2$ measurements are readily available in many countries, and the variability of TRAP mixture appears to be well characterised by $NO_2$.[10,11] Results from four meta-analyses of TRAP exposure and paediatric asthma incidence all indicated consistent associations with $NO_2$, but results were mixed for associations with fine particulate matter ($PM_{2.5}$; appendix).[2–5] Reviews[12,13] done by the US Environmental Protection Agency and Health Canada, published in 2016, also concluded that the overall evidence indicates that a causal relationship probably exists

See Online for appendix

## Research in context

### Evidence before this study

We searched MEDLINE, PubMed, and Google Scholar to identify meta-analyses of epidemiological studies on traffic-related air pollution (TRAP) exposure and paediatric asthma incidence, using a combination of the search terms "traffic-related air pollution", "asthma incidence" or "asthma development", "meta-analysis", and "child*". We limited the search to studies that pooled results from multiple countries, reported a numerical relative risk (RR) accompanied by an estimate of precision, were written in English, and were published up to March 1, 2018. Nitrogen dioxide ($NO_2$) is a major component and commonly used proxy of the complex TRAP mixture. The most up-to-date and comprehensive multinational meta-analysis reported an RR of 1·26 (95% uncertainty interval 1·10–1·37) per 10 parts per billion (ppb) of TRAP-related $NO_2$. The Global Burden of Disease studies have not included air pollution as a risk factor for asthma incidence or prevalence, and the only previous study to have estimated the global burden of paediatric asthma incidence attributable to ambient air pollution relied on exposure datasets with resolutions too coarse to resolve the intra-urban $NO_2$ variability driven primarily by TRAP. A more recent study done at a resolution of 100 × 100 m for a major city in the UK estimated that 18–24% of all annual paediatric asthma incidence might be attributable to ambient $NO_2$, suggesting that the global burden of asthma associated with $NO_2$ exposure might be substantial.

### Added value of this study

To our knowledge, this study provides the first global estimate of the annual burden of paediatric asthma incidence attributable to ambient $NO_2$ pollution at a resolution sufficient to resolve intra-urban and near-roadway exposure gradients (250 × 250 m). We provide estimates for 194 countries and 125 major cities.

### Implications of all the available evidence

Our findings suggest that a substantial portion of paediatric asthma incidence could be avoided by reducing $NO_2$ pollution in both developed and developing countries, especially in urban areas. We estimate that about 97% of children lived and about 92% of new asthma cases attributable to $NO_2$ occurred in areas with annual average $NO_2$ concentrations lower than the WHO guideline of 21 ppb, suggesting that the adequacy of this guideline might need to be revisited.

between long-term $NO_2$ exposure and paediatric asthma development. $NO_2$ is a secondary pollutant formed mainly from fossil fuel combustion; traffic emissions can contribute up to 80% of ambient $NO_2$ in cities.[11,14]

Despite the accumulating epidemiological evidence, the burden of paediatric asthma incidence attributable to TRAP exposure remains poorly quantified and has not been included in previous global burden of disease studies.[15,16] In a study published in 2018,[6] Anenberg and colleagues estimated that global asthma incidence attributable to anthropogenic $NO_2$ and $PM_{2·5}$ might cause about 1·7 million disability-adjusted life-years (DALYs, ie, years of healthy life lost) among children in 2015, with about 97% of this burden due to $PM_{2·5}$. However, this assessment relied on satellite-derived $NO_2$ concentrations with a spatial resolution of approximately 10×10 km, which likely underestimated the effects of $NO_2$ for several reasons. First, the mid-afternoon satellite overpass time captures $NO_2$ concentration at a minimum in its diurnal cycle. Second, given that $NO_2$ concentrations decline to urban background levels at a distance greater than 300–500 m from major roadways and that intra-urban variation might be more strongly associated with exposure and asthma development than urban–rural variation, the spatial resolution of the satellite data was too coarse.[3,17] An assessment[18] done with a spatial resolution of 100×100 m in a major city in the UK estimated that 18–24% of all annual paediatric asthma incidence might be attributable to ambient $NO_2$. Because TRAP emissions are ubiquitous, the global burden is likely to be substantial, especially within densely populated urban areas.

In this study, we combined global datasets of $NO_2$ concentrations, population, and asthma incidence with relative risks drawn from a multinational epidemiological meta-analysis[5] to estimate the annual number of new paediatric asthma cases attributable to ambient $NO_2$ at a spatial resolution of 250×250 m. We focused on $NO_2$ because it is a widely used proxy of TRAP and because the evidence for association with paediatric asthma incidence is most robust for TRAP-derived $NO_2$.

## Methods

### Population and demographics

We used the 2015 Global Human Settlement population grid (GHS-POP) from the European Commission's Joint Research Centre, which provides population counts for 1975, 1990, 2000, and 2015 at a spatial resolution of 250×250 m, the finest resolution available with global coverage.[19] GHS-POP disaggregates residential population estimates from the Center for International Earth Science Information Network's Gridded Population of the World, version 4 (GPWv4), by use of the distribution and density of built-up areas derived from satellite imaging. To estimate the paediatric population, we calculated age group fractions (1–4, 5–9, 10–14, and 15–18 years) by use of the gridded GPWv4 and the Basic Demographic Characteristics (version 4.10) for 2010, the latest year available.[20] These outputs were then regridded from their original 30 arc-second resolution to 250×250 m and applied to the GHS-POP population estimates. Figure 1A shows national estimates of paediatric population size.

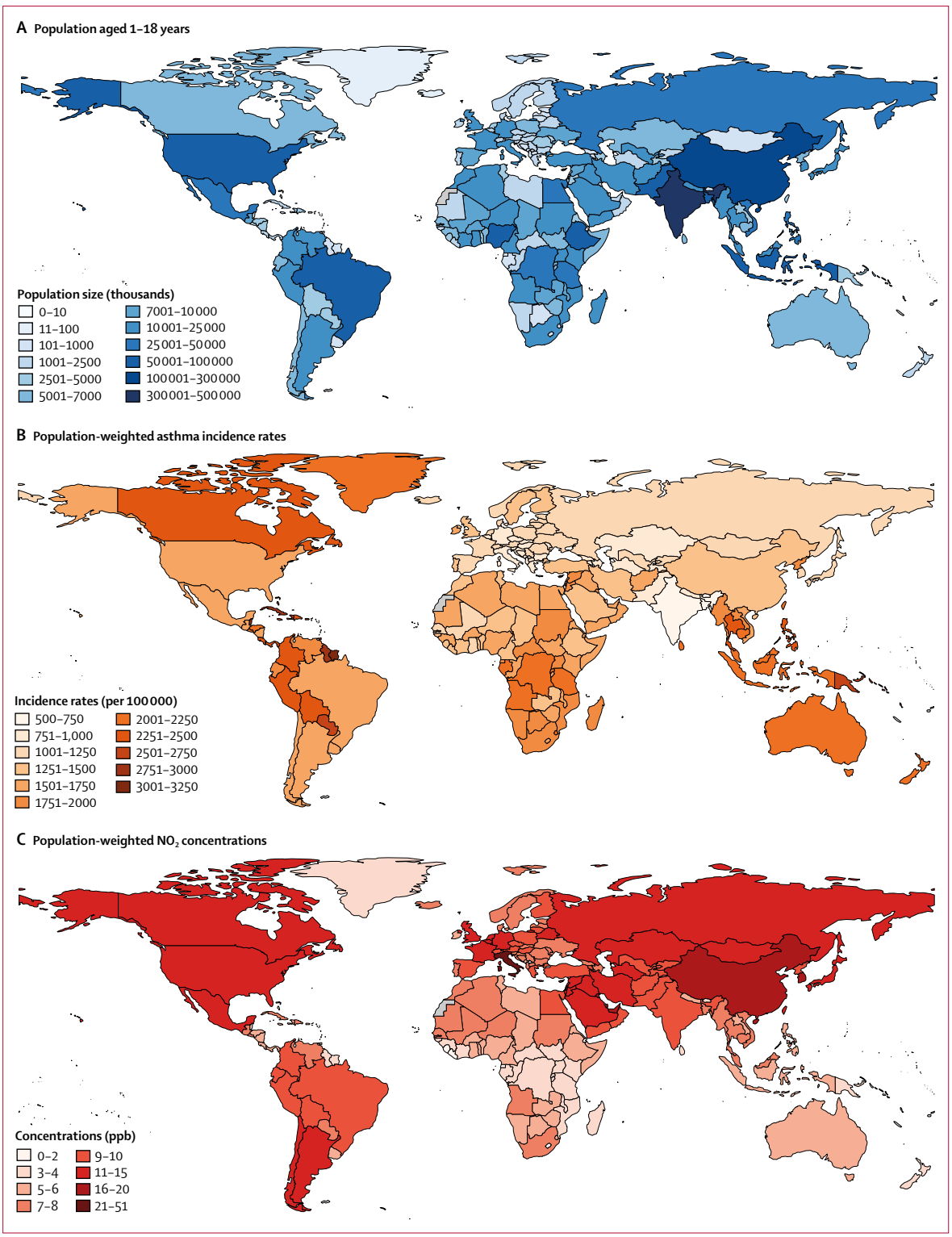


***Figure 1:*** **National estimates of population aged 1–18 years (A), population-weighted annual asthma incidence rates (B), and population-weighted annual average nitrogen dioxide ($NO_2$) concentrations (C)**

(B) Population-weighted averages were calculated from the country-specific and age-group-specific rates. (C) Concentrations are weighted by the size of the population aged 1–18 years of each country. ppb=parts per billion.

### Baseline asthma incidence

We obtained 2015 country-specific and age-group-specific asthma incidence rates from the Institute for Health Metrics and Evaluation (IHME) for 194 countries.[21] We found that most national asthma incidence rates did not change by more than 5% between 2010–12 and 2015 and, therefore, we chose 2015 to match the GHS-POP dataset. The definition of asthma was a reported diagnosis by a physician, with wheezing in the preceding 12 months. Figure 1B shows national asthma incidence rates standardised across the population aged 1–18 years. Additional details on the IHME incidence rates and methods for approximating DALYs are in the appendix.

### Concentration-response function

Anenberg and colleagues[6] did a literature review to identify meta-analyses of epidemiological studies on air pollution and asthma, four of which reported paediatric asthma incidence attributable to TRAP-related $NO_2$ (appendix). These meta-analyses pooled results from individual studies in different countries to derive relative risk (RR) estimates that could be generally representative of the global population. We used the same search criteria as Anenberg and colleagues[6] (appendix) and found no additional meta-analyses published more recently. In this study, we derived concentration response functions (CRFs) from RRs reported by Khreis and colleagues,[5] one of the meta-analyses identified in the search. By comparison with the other three meta-analyses, Khreis and colleagues reviewed the largest number of studies, which included all but one of those considered in the other meta-analyses: 20 studies from Europe, 11 from North America, five from Japan, three from China, one from South Korea, and one from Taiwan, totalling 41 studies; although there was variation in the RRs reported in these studies, no regional heterogeneity was apparent. The meta-analysis[5] reported an overall random-effects RR of 1·26 per 10 parts per billion (ppb) TRAP-related $NO_2$ (95% uncertainty interval [UI] 1·10–1·37). This UI encompassed the central RR estimates reported in the other three meta-analyses (appendix).

Available evidence is insufficient to establish whether a low-concentration threshold exists, below which there is no risk of paediatric asthma development, and whether the association is linear or non-linear. In this study, we assumed a log-linear relationship between $NO_2$ concentration and outcome, as Khreis and colleagues did.[5] We applied a counterfactual concentration of 2 ppb, the 5th percentile of the minimum exposure concentrations reported in the individual studies considered by Khreis and colleagues.[5] This approach assumes that long-term exposure to $NO_2$ less than 2 ppb confers no excess risk of incident asthma in children. As a sensitivity test, we also assumed counterfactual concentrations of 0 ppb and 5 ppb, the 25th percentile of the minimum exposure concentrations reported (appendix).

### Ambient $NO_2$ concentrations

We used a dataset of surface $NO_2$ concentrations developed by Larkin and colleagues,[22] which is, to date, the only global dataset able to resolve near-roadway concentrations at a spatial resolution of 100×100 m, for 2010–12 annual average concentrations. Larkin and colleagues used land-use regression modelling, an empirical method that combines ground-based air pollution measurements (from 5220 air monitors in 58 countries) with satellite-derived pollutant estimates and other geospatial variables to predict surface concentrations. The strongest predictors of these were major roads within 100 m and satellite-derived $NO_2$ concentrations. The land-use regression model captured 54% of global $NO_2$ variation with a mean absolute error of 3·7 ppb. On a continental level, this model varied between capturing 31% (Africa) to 63% (South America) of regional variation, with mean absolute errors ranging from 2·3 ppb (Africa) to 4·4 ppb (North America). The model also generated within-city spatial patterns and concentrations similar to other land-use regression models created for specific cities. Concentrations ranged between 0 ppb and 72 ppb (we estimated that about 0·5% of the global population lived in areas with 0 ppb). Urban–rural and intra-urban concentration gradients for three major cities are shown in the appendix. By comparison, the surface $NO_2$ concentration dataset used by Anenberg and colleagues[6] had a spatial resolution of 0·1°×0·1° (roughly 10×10 km), with values ranging between 0 ppb and 17·5 ppb. This dataset was derived from column retrievals from the Ozone Monitoring Instrument on board the US National Aeronautics and Space Administration's Aura satellite.[23]

We regridded and reprojected the output from Larkin and colleagues[22] to match the resolution and projection of the population dataset at 250×250 m, by use of the Geospatial Data Abstraction Library. Although some very fine-scale features were lost at this coarser scale, intra-city gradients such as those occurring near major roadways could still be captured at 250 m (appendix). Figure 1C shows national population-weighted $NO_2$ concentrations.

### Health impact function

Following the example of Anenberg and colleagues,[6] we applied methods typically used to assess premature mortality attributable to air pollution to estimate the number of new paediatric asthma cases attributable to $NO_2$ pollution annually,[15,24] by use of $NO_2$ data (2010–12 annual average) and population data (2015) that were as recent and as close in time to each other as possible, and spatially resolved below 250 m. The health impact function is:

$$\text{Burden} = Inc_{c,a} \times \sum_{i,j} Pop_{i,j,a} \times \left(1 - e^{-\beta x_{i,j}}\right)$$

where *Inc* is the asthma incidence for country *c* and age group *a* (1–4, 5–9, 10–14, and 15–18 years), *Pop* is the gridded population for age group *a*, β is the concentration-response factor (from the meta-analysis of epidemiological studies), and *X* is the gridded annual average $NO_2$ concentration. We applied

$$Pop_{i,j,a} \times \left(1 - e^{-\beta X_{i,j}}\right)$$

in each 250×250 m grid cell (*i,j*) globally before summing by national or urban extents. We then multiplied these aggregated sums by the relevant national asthma incidence rates, and provided results for 21 regions, 194 countries, and 125 major cities.

### Region, country, and city aggregation

We grouped countries into 21 regions or seven super-regions, according to IHME specifications based on epidemiological similarity and geographical closeness (appendix). Results were aggregated by country by use of the GPWv4 National Identifier Grid.[25] Defining city boundaries is challenging because no universal definition exists.[26] We used a globally consistent definition of urbanisation from the Global Human Settlement 1×1 km grid (GHS-SMOD), for 2015. Urban centres were defined as any contiguous cells with 50 000 or more people and a population density of 1500 or more inhabitants per km² or a density of built-up higher than 50% per grid cell.[27] By combining GHS-SMOD with GHS-POP, we selected the 125 most populous urban centres (population size >3·5 million people). Given that these urban centres do not necessarily match administrative boundaries and sometimes group together multiple neighbouring cities (appendix), we reported city-level results in units of cases per 100 000 children and percentage of total incidence.

### Uncertainties in input variables of the health impact function

Although each input variable is uncertain, our results are accompanied by UIs derived from those of the RR, given that this error is well constrained. We also did a sensitivity analysis to compare the influence of uncertainties in the RR, $NO_2$ concentrations, and asthma incidence rates (uncertainties in the GHS-POP population dataset were not available; appendix).

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. PA and SCA had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Globally, we estimated that ambient $NO_2$ might be associated with 4·0 million (95% UI 1·8–5·2) new paediatric asthma cases annually, accounting for 13% (95% UI 5·8–16) of global incidence (table). The mean burden of new cases associated with ambient $NO_2$ translates to approximately 730 000 DALYs per year (appendix). We estimated that about 97% of children lived and about 92% of $NO_2$-attributable paediatric asthma incidence occurred in areas with annual average $NO_2$ concentrations lower than the WHO guideline of 21 ppb.

Regionally, the largest burden of new asthma cases associated with $NO_2$ exposure per 100 000 children per year was estimated for Andean Latin America, followed by high-income North America and high-income Asia Pacific (table; appendix). The largest percentage of regional paediatric asthma incidence attributable to $NO_2$ pollution was estimated for high-income Asia Pacific, followed by east Asia and high-income North America, southern Latin America, and western Europe (table). Eastern sub-Saharan Africa was estimated to have the

| | New asthma cases due to $NO_2$ exposure per year, thousands (95% UI) | New asthma cases due to $NO_2$ exposure per year, per 100 000 children (95% UI) | New asthma cases due to $NO_2$ exposure per year, % of total incidence (95% UI) |
|---|---|---|---|
| High income | | | |
| Australasia | 12 (5·2–15) | 170 (77–230) | 8·7% (3·8–11) |
| High-income Asia Pacific | 97 (46–120) | 300 (140–370) | 25% (12–32) |
| High-income North America | 270 (120–340) | 310 (140–400) | 19% (8·5–24) |
| Southern Latin America | 56 (26–72) | 290 (130–370) | 18% (8·4–23) |
| Western Europe | 150 (70–200) | 190 (85–240) | 17% (7·8–22) |
| Latin America and Caribbean | | | |
| Andean Latin America | 73 (33–94) | 340 (150–440) | 15% (6·7–19) |
| Caribbean | 39 (17–51) | 280 (120–360) | 10% (4·4–13) |
| Central Latin America | 240 (110–310) | 260 (120–330) | 15% (6·7–19) |
| Tropical Latin America | 150 (66–190) | 230 (100–290) | 13% (5·8–17) |
| Sub-Saharan Africa | | | |
| Central sub-Saharan Africa | 61 (27–79) | 110 (47–140) | 5·1% (2·3–6·7) |
| Eastern sub-Saharan Africa | 150 (63–190) | 76 (33–100) | 4·4% (1·9–5·9) |
| Southern sub-Saharan Africa | 46 (20–60) | 160 (69–200) | 8·6% (3·8–11) |
| Western sub-Saharan Africa | 210 (92–280) | 110 (49–150) | 7·6% (3·3–9·9) |
| North Africa and Middle East | 570 (260–730) | 270 (120–350) | 17% (7·6–21) |
| South Asia | 520 (230–680) | 82 (37–110) | 14% (6·3–18) |
| Southeast Asia, east Asia, and Oceania | | | |
| East Asia | 800 (370–1000) | 260 (120–340) | 19% (8·9–25) |
| Oceania | 3·1 (1·4–4·1) | 82 (36–110) | 3·1% (1·4–4·1) |
| Southeast Asia | 440 (200–570) | 200 (89–260) | 9·4% (4·2–12) |
| Central Europe, eastern Europe, and central Asia | | | |
| Central Asia | 46 (21–60) | 160 (70–200) | 16% (7·0–20) |
| Central Europe | 29 (13–38) | 130 (60–170) | 14% (6·1–18) |
| Eastern Europe | 68 (31–88) | 180 (80–230) | 17% (7·6–21) |
| Global | 4000 (1800–5200) | 170 (77–220) | 13% (5·8–16) |

95% uncertainty intervals (UI) reflect uncertainties in the relative risk estimates of childhood asthma incidence attributable to traffic-related $NO_2$ pollution. Countries are grouped into regions according to the Institute for Health Metrics and Evaluation specification (appendix). Numbers are rounded to two significant figures.

***Table:*** **Annual number and percentage of new asthma cases attributable to ambient nitrogen dioxide ($NO_2$) exposure for children aged 1–18 years**

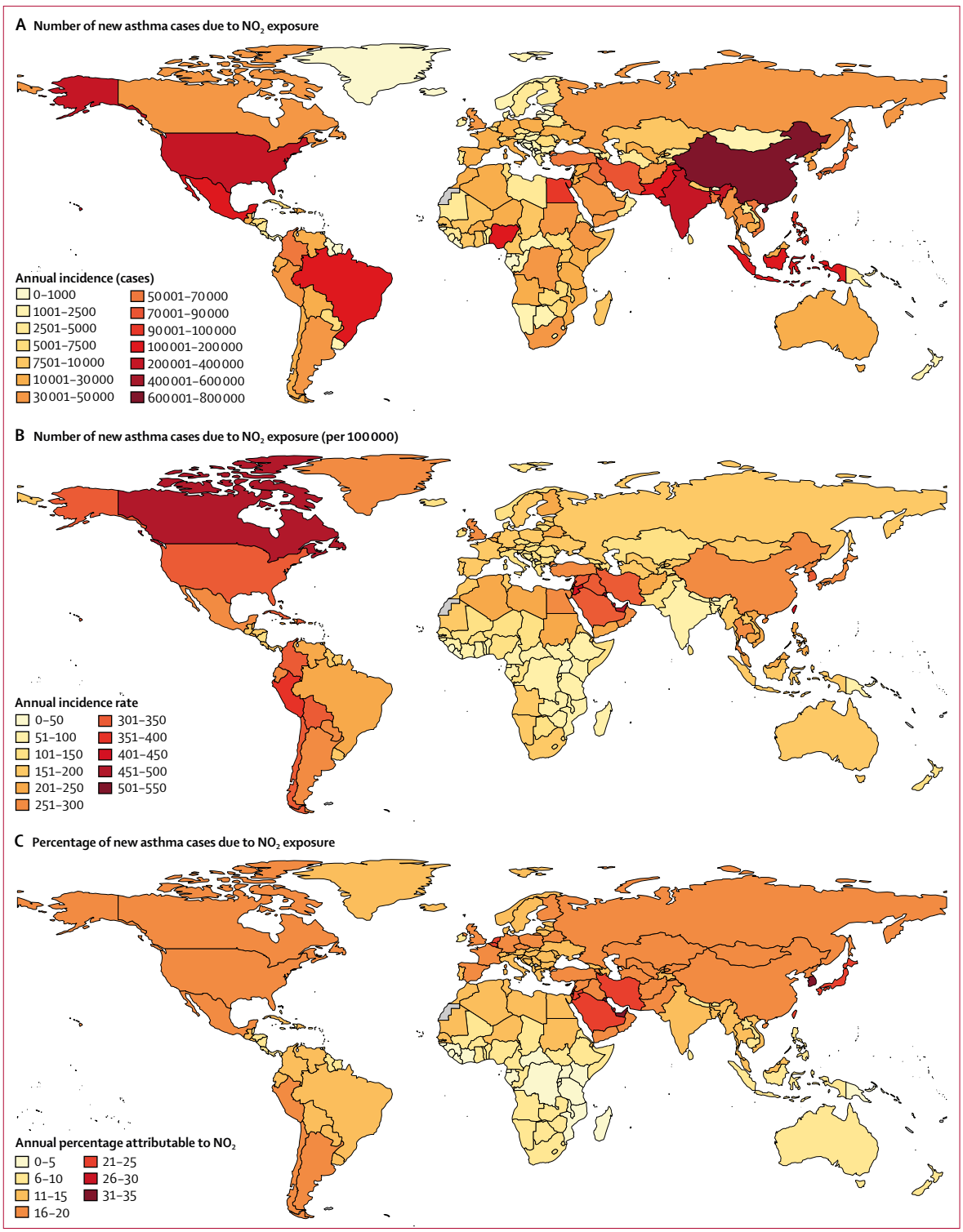


***Figure 2:*** **National annual estimates of number of new asthma cases (A), number of new asthma cases per 100 000 children (B), and percentage of new asthma cases attributable to ambient nitrogen dioxide ($NO_2$) exposure for children aged 1–18 years**

The values shown are derived using the central mean relative risk estimate and assuming a counterfactual $NO_2$ concentration of 2 parts per billion.

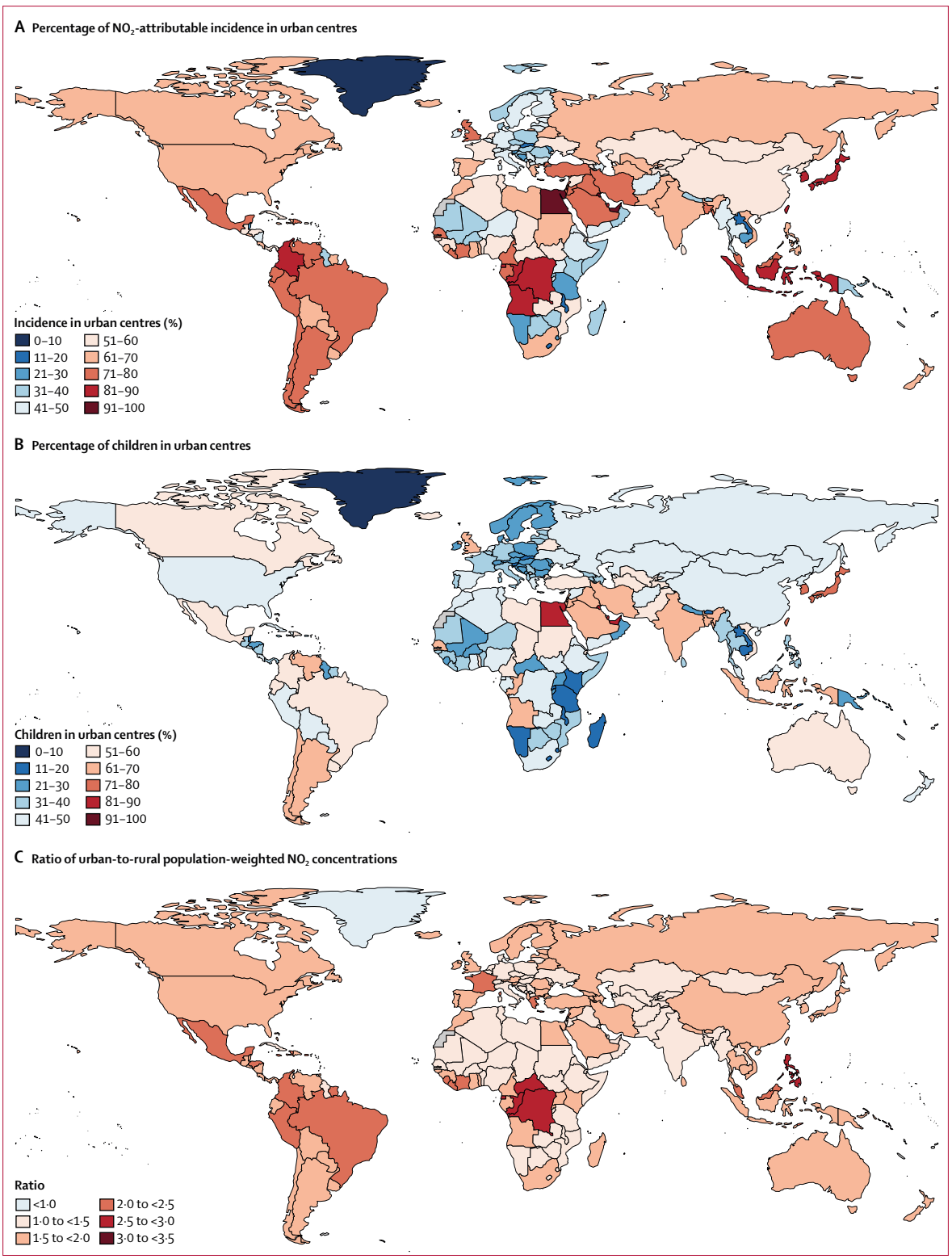


***Figure 3:*** **National annual estimates of percentage of nitrogen dioxide ($NO_2$)-attributable paediatric asthma incidence occurring in urban centres (A), percentage of children living in urban centres (B), and ratio of population-weighted $NO_2$ concentration in urban centres relative to non-urban areas (C)**
Urban centres are defined as any contiguous cells with 50 000 or more people and a population density of 1500 or more inhabitants per km² or a density of built-up greater than 50% per grid cell, following the Global Human Settlement classification.

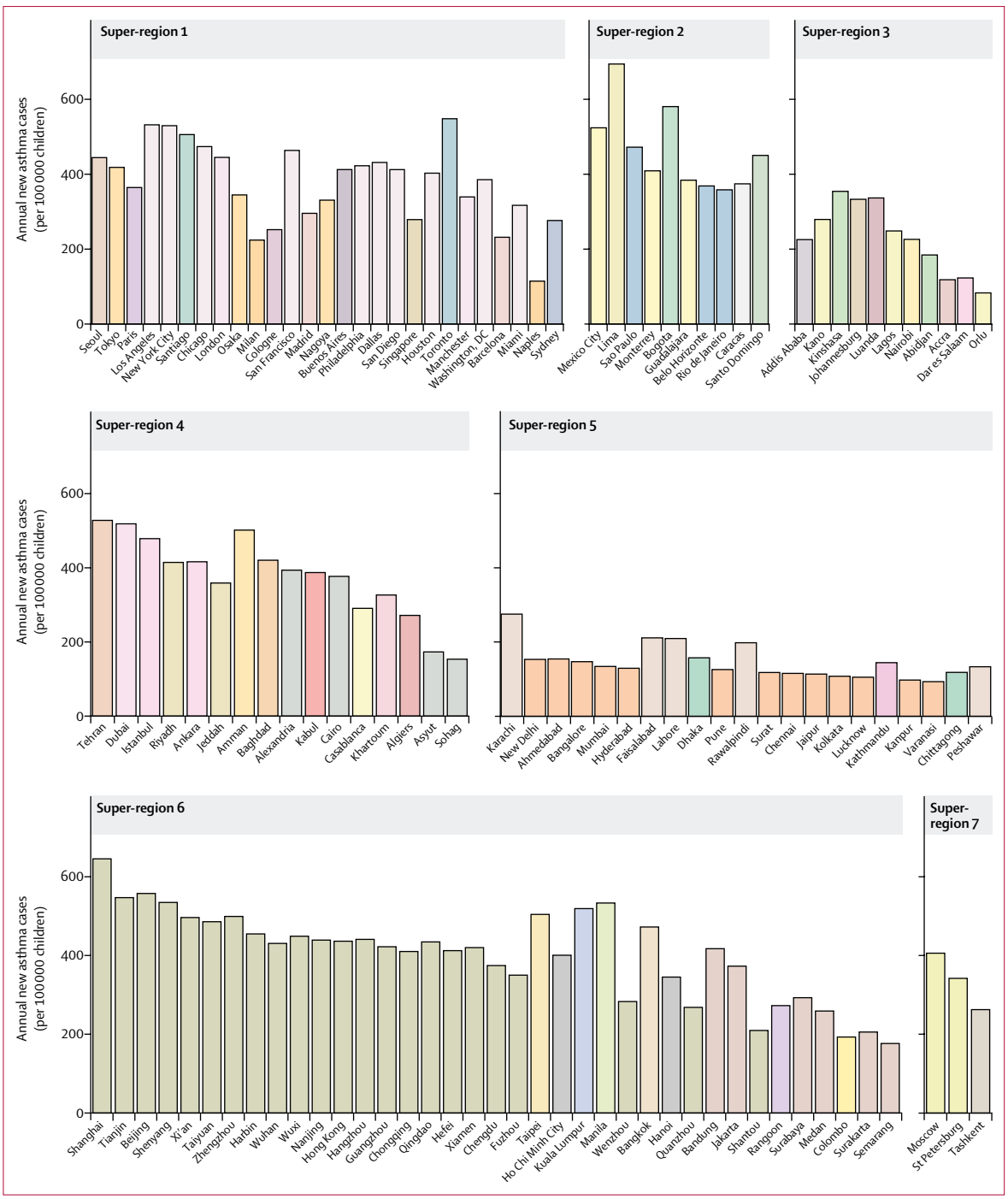


***Figure 4:*** **Annual number of new asthma cases per 100 000 children attributable to ambient nitrogen dioxide ($NO_2$) exposure for children aged 1–18 years**
Number of new paediatric asthma cases attributable to $NO_2$ exposure in 125 major cities, grouped into seven super-regions: high income (1); Latin America and Caribbean (2); sub-Saharan Africa (3); north Africa and Middle East (4); south Asia (5); southeast Asia, east Asia, and Oceania (6); and central Europe, eastern Europe, and central Asia (7). Within a super-region, cities were ranked in decreasing order of paediatric population-weighted $NO_2$ concentrations and coloured by country. The values shown were derived with use of the central mean relative risk estimate and assuming a counterfactual $NO_2$ concentration of 2 parts per billion. In some cases, an urban centre identified in the Global Human Settlement 1×1 km grid spans multiple cities (see appendix for full urban cluster names).

lowest incidence of new asthma cases attributable to $NO_2$ exposure per 100 000 children, whereas Oceania had the lowest percentage of incidence attributable to $NO_2$ (table).

The largest national burdens of new asthma cases attributable to $NO_2$ exposure were estimated for China (760 000 new cases per year, 95% UI 350 000–970 000),

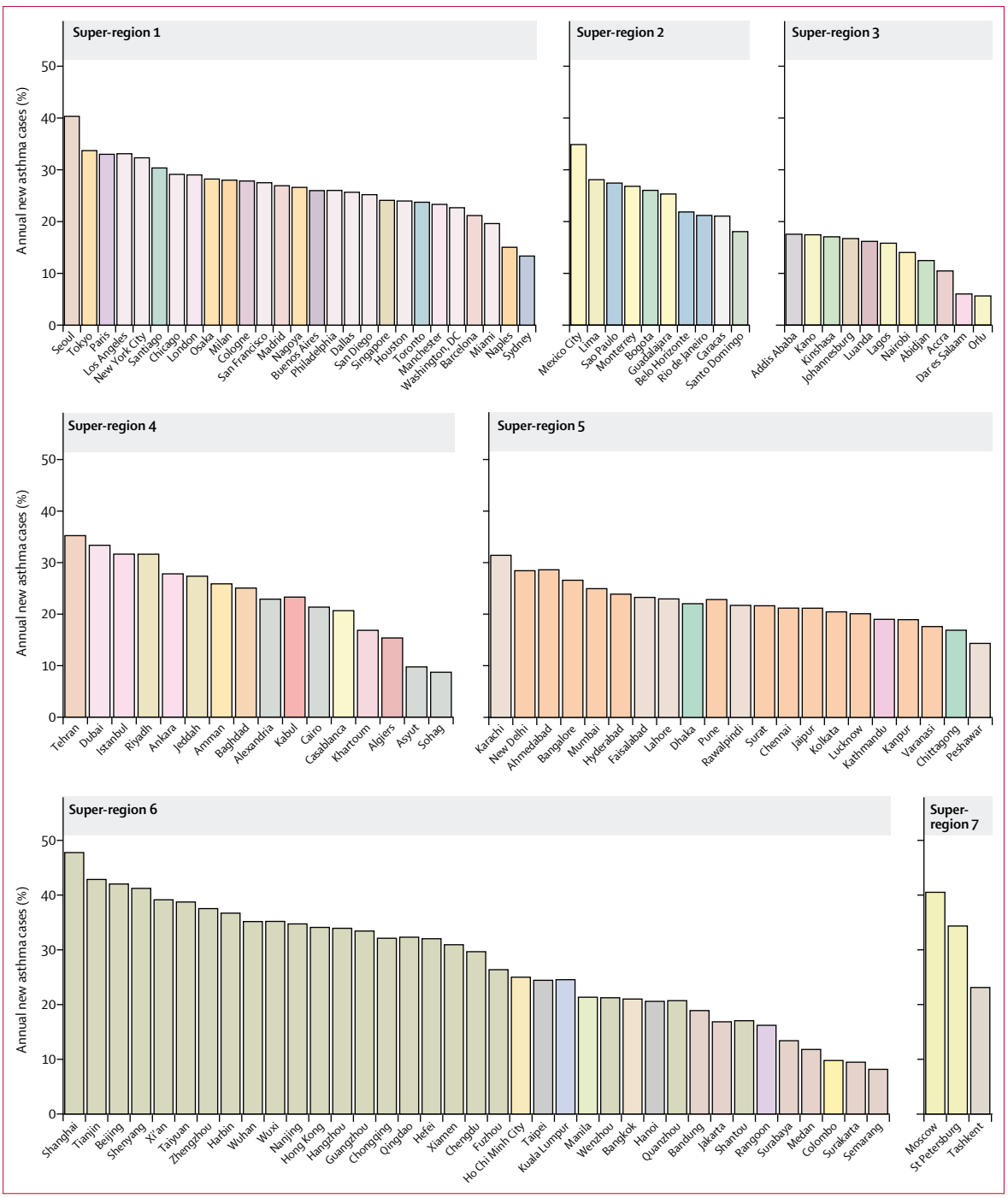


***Figure 5*: Annual percentage of new asthma cases attributable to ambient nitrogen dioxide ($NO_2$) exposure for children aged 1–18 years**
Percentage of new paediatric asthma cases attributable to $NO_2$ exposure in 125 major cities, grouped into seven super-regions: high income (1); Latin America and Caribbean (2); sub-Saharan Africa (3); north Africa and Middle East (4); south Asia (5); southeast Asia, east Asia, and Oceania (6); and central Europe, eastern Europe, and central Asia (7). Within a super-region, cities were ranked in decreasing order of paediatric population-weighted $NO_2$ concentrations and coloured by country. The values shown were derived with use of the central mean relative risk estimate and assuming a counterfactual $NO_2$ concentration of 2 parts per billion. In some cases, an urban centre identified in the Global Human Settlement 1×1 km grid spans multiple cities (see appendix for full urban cluster names).

India (350 000, 160 000–450 000), the USA (240 000, 110 000–300 000), Indonesia (160 000, 72 000–210 000), and Brazil (140 000, 63 000–180 000; figure 2A, appendix). Of all countries, China had the second largest paediatric population and third highest population-weighted $NO_2$ concentrations (figure 1). India, despite having the lowest

paediatric asthma incidence rate, had the largest paediatric population. Although the USA, Indonesia, and Brazil had similar paediatric population sizes, the USA had the highest population-weighted $NO_2$ concentrations and Indonesia had the highest asthma incidence rate among these three countries. The largest national burden per 100 000 children per year was estimated for Kuwait (550 cases per year, 95% UI 260–690), followed by the United Arab Emirates (460, 220–580), Canada (450, 210–580), Taiwan (420, 190–540), and Qatar (410, 200–520; figure 2B) due to high asthma incidence rates, high population-weighted urban $NO_2$ concentrations, or both. Of 194 countries assessed, Canada had the 34th highest paediatric asthma incidence rate—the highest among high-income nations. Regarding the percentage of asthma incidence attributable to $NO_2$ exposure, we estimated values exceeding 15% for 48 countries (figure 2C). The highest percentages of asthma incidence attributable to $NO_2$ were estimated for South Korea (31%, 95% UI 15–38), United Arab Emirates (30%, 14–38), Kuwait (30%, 14–38), and Qatar (30%, 14–37).

We estimated that 64% of paediatric asthma incidence attributable to $NO_2$ occurred in urban centres globally. This percentage increased to 90% if surrounding sub-urban areas were also considered (GHS-SMOD's so-called low-density clusters). On a national level, the percentage of paediatric asthma incidence attributable to $NO_2$ occurring in urban centres exceeded 50% in 108 countries (figure 3, appendix), reflecting the distribution of children living in urban areas and the prevalence of high $NO_2$ concentrations found in urban centres. Generally, national asthma incidence rates were highest in the youngest age group (1–4 years) and decreased with increasing age. This effect dwarfed the age group variations in population size, resulting in the largest asthma burdens attributable to $NO_2$ being estimated for children aged 1–4 years, both in total and per 100 000 children, in all but one country (Moldova; appendix). Regarding the influence of uncertainties in the input variables, we found that asthma incidence rates had the least influence, given that their UIs were small. UIs resulting from those of RRs and from $NO_2$ concentrations were generally within the same order of magnitude (appendix).

Of the 125 major cities we investigated, the largest burdens of paediatric asthma incidence attributable to $NO_2$ exposure per 100 000 children were estimated for Lima, Peru (690 cases per year, 95% UI 330–870); Shanghai, China (650, 340–770); Bogota, Colombia (580, 270–730); Beijing, China (560, 280–680); and Toronto, Canada (550, 250–700; figure 4, appendix). The large burdens estimated for Chinese cities were primarily driven by high population-weighted $NO_2$ concentrations (28–33 ppb). By contrast, Lima, Bogota, and Toronto had medium $NO_2$ concentrations (14–17 ppb), but had among the highest national paediatric asthma incidence rates, especially for children aged 1–4 years, in the 54 countries where the 125 cities are located. The lowest population-standardised burdens were found in Orlu, Nigeria (83 cases per year, 95% UI 36–110), and in four cities in India (Varanasi, 88 [40–110]; Kanpur, 92 [42–120]; Lucknow, 99 [45–130]; and Kolkata, 100 [47–130]; figure 4, appendix). India had the lowest asthma incidence rate among all countries, whereas Orlu had the lowest population-weighted $NO_2$ concentration (5 ppb). The percentage of new asthma cases attributable to $NO_2$ pollution by city ranged from 5·6% (95% UI 2·4–7·4) in Orlu, Nigeria, to 48% (25–57) in Shanghai, China, and primarily reflected the variations in $NO_2$ exposures within each region (figure 5). These percentages exceeded 20% in 92 cities and exceeded 30% in 32 cities (figure 5, appendix). The ten largest contributions were estimated for eight cities in China (Shanghai, Tianjin, Beijing, Shenyang, Xi'an, Taiyuan, Zhengzhou, and Harbin), for Moscow (Russia), and for Seoul (South Korea; figure 5, appendix). All these cities had high urban $NO_2$ concentrations. The meta-analysis from which the RRs were drawn included three epidemiological studies done in China.

## Discussion

This study provides the first global estimate of the burden of paediatric asthma incidence attributable to ambient $NO_2$ at a spatial resolution fine enough to resolve intra-urban and near-roadway exposure gradients, for 194 countries and 125 major cities. We estimated that, each year, 4·0 million (95% UI 1·8–5·2) new cases of paediatric asthma might be attributable to $NO_2$ pollution, accounting for 13% (5·8–16) of global incidence; 48 of 194 countries had percentages greater than 15% of national incidence. The city-level percentages ranged between 6% and 48%, with 92 of 125 cities exceeding 20%. The 2015 Global Burden of Disease study[21] estimated that smoking and occupational asthmagens could account for 16·5% of the global asthma prevalence for all ages in 2015. Although the burden of premature mortality attributable to ambient $PM_{2·5}$ pollution is generally greater in low-income and middle-income countries because of high exposures,[15] the effects of $NO_2$ pollution on paediatric asthma incidence appear to be less differentiated by level of development. Many high-income countries have high $NO_2$ exposures, especially those in North America, western Europe, and Asia Pacific. In Canada, this problem is also exacerbated by high paediatric asthma incidence rates (appendix).

Because transportation can contribute up to 80% of ambient $NO_2$ in cities and is an important driver of increasing greenhouse gas emissions globally,[14,28] we also explored whether there were associations between carbon dioxide ($CO_2$) emissions and $NO_2$ exposure, to highlight potential co-benefits of exposure-mitigation policies. We found that, in general, countries and cities with higher $CO_2$ emissions tended to have higher paediatric $NO_2$ exposures and larger burdens of asthma incidence attributable to ambient $NO_2$ (appendix).

Anenberg and colleagues[6] have estimated the global burden of asthma incidence attributable to anthropogenic $NO_2$ for children aged 0–17 years, relying on satellite-derived $NO_2$ concentrations, from the Ozone Monitoring Instrument, at a resolution of roughly 10×10 km. The authors suggested that they likely underestimated actual exposures because the satellite's mid-afternoon overpass time coincides with the minimum concentration in diurnal $NO_2$ variation and because near-roadway concentrations were not resolved. Indeed, with use of the same RR drawn from Khreis and colleagues,[5] but with different population data, their estimated global burden of 1·3 million new asthma cases per year attributable to $NO_2$ is about 3·1 times smaller than our estimate assuming a counterfactual concentration of 2 ppb (and about 1·7 times smaller than our estimate assuming a counterfactual concentration of 5 ppb). In another study,[18] published in 2018, Khreis and colleagues quantified the annual paediatric asthma incidence attributable to air pollution in Bradford, UK, by use of concentration estimates at 100×100 m resolution and assuming no low concentration threshold. By use of ambient $NO_2$ concentrations modelled by land-use regression, Khreis and colleagues estimated that 24% of annual paediatric asthma cases might be attributable to $NO_2$ exposure in 2009 (with an annual mean $NO_2$ concentration of 12 ppb). This matches our equivalent estimate (assuming a counterfactual of 0 ppb) of 28% for the Leeds–Bradford metropolitan area, which had annual mean $NO_2$ concentrations of 13 ppb during 2010–12. Estimates assuming a counterfactual concentration of 2 ppb were 23%, whereas those assuming 5 ppb were 17% (data not shown).

Several important limitations and uncertainties exist in our approach. First, the epidemiological evidence considered by Khreis and colleagues[5] and the ground-based $NO_2$ monitoring data used in the global land-use regression model for $NO_2$ developed by Larkin and colleagues[22] are mainly available only for North America, Europe, and east Asia. These limitations in the global representation of the outcome measure and of the exposure characterisation upon which we relied consequently apply to our estimates. Additionally, because most ground-based $NO_2$ monitors are in urban areas, the global land-use regression model might overestimate concentrations in rural areas. However, this is unlikely to add appreciable bias because rural populations are sparse. Available epidemiological studies have also been done within a range (about 1–50 ppb) that approximately spans global exposures (0–72 ppb).

A second limitation is that $NO_2$ concentrations used in this study represent the 2010–12 annual average, whereas the population and asthma incidence rates are 2015 estimates. Duncan and colleagues[29] found that between 2005 and 2014, there have been substantial trends in urban $NO_2$ concentrations worldwide, with general decreases in US and European cities and increases in Asia, although complex spatial heterogeneity exists. Future assessments could apply these trends to the $NO_2$ land-use regression dataset to estimate effects in other years.

Third, we relied on national paediatric asthma incidence rates in our analysis, but subnational variations most likely exist, especially between urban and rural populations. Additionally, although the IHME incidence rates were derived from prevalence data covering 121 countries and all 21 regions,[21] the definition of asthma based on physician diagnosis might underestimate the effects of vehicular emissions on asthma in low-income and middle-income countries because of low health-care access or the neglect of subclinical symptoms that might not manifest in a diagnosis. Fourth, uncertainties remain in the shape of the CRF of paediatric asthma incidence and $NO_2$ exposure. In this study, we assumed a log-linear relationship and a low-concentration threshold of 2 ppb. We also assumed a causal relationship between $NO_2$ exposure and asthma incidence and used a CRF derived from single-pollutant epidemiological models (because multipollutant models were not available). The evidence so far suggests that associations with asthma incidence are more robust for $NO_2$ than for other air pollutants and that $NO_2$ is better than $PM_{2·5}$ for representing near-roadway variability of the TRAP mixture.[30,31] However, it is possible that $NO_2$ is a proxy for other putative agents in the TRAP mixture, that the reported associations are sensitive to control for co-pollutants, or both. All these uncertainties mean that our $NO_2$-attributable asthma estimates might be overestimated or underestimated.

Our analysis and characterisation of uncertainties can consequently be improved by future studies aiming to resolve the limitations described. The availability of global $NO_2$ concentration and population datasets that are up to date and have even finer temporal and spatial resolutions than those of the datasets used in this study will be particularly valuable. In this study, we did not isolate traffic-specific contributions to ambient $NO_2$ concentrations, but this approach is more consistent with existing epidemiological studies, the majority of which also relied on $NO_2$ exposures derived from land-use regression without isolating the contribution of traffic emissions.[5] Isolating the role of TRAP can help to constrain estimates of the portion of total asthma incidence that could be avoided by targeting this emission source. Additionally, it would be useful for future epidemiological studies to identify the putative agents within the TRAP mixture and target understudied populations, especially in Africa and central and southeast Asia.

Despite substantial decreases in $NO_2$ concentrations over the past decade in large areas of the USA and western Europe,[29] our findings suggest that existing levels of ambient $NO_2$ pollution are a substantial risk factor for paediatric asthma incidence in both developed and developing countries, especially in urban areas. In fact, our findings suggest that the adequacy of the WHO

guideline for annual average $NO_2$ concentrations might need to be revisited. We also found that countries and cities with higher $CO_2$ emissions from fossil fuel combustion tend to have higher $NO_2$ exposures, providing further support that alignment of policy initiatives to mitigate air pollution and climate change can have multiple public health benefits.[32,33] Traffic emissions should be a target for exposure-mitigation strategies.

#### Contributors

SCA and MB conceived the project idea. SCA and PA designed the analysis methods. PH and MB contributed to the development of the land-use regression $NO_2$ dataset used in this analysis. PA did the analysis and had primary responsibility for writing the manuscript, to which all authors contributed.

#### Declaration of interests

SCA provided research consulting services on separate projects for the International Council on Clean Transportation and the Health Effects Institute within the 36 months during and before the work reported in this article. PA, MB, and PH declare no competing interests.

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