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Global and national assessment of the incidence of asthma in children and adolescents from major sources of ambient NO_2

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Abstract

Pediatric asthma incidence has been associated with exposure to nitrogen dioxide (NO_2) in ambient air. NO_2 is predominantly emitted through fossil fuel use in land transportation, power generation and the burning of solid biofuels in households. We simulated NO_2 with a global atmospheric chemistry model, combined with a land use regression model, to estimate NO_2 exposure in all countries worldwide. The global asthma incidence among children and adolescents attributable to NO_2 was estimated by deriving an exposure-response function from a meta-analysis which included epidemiological studies from multiple countries, baseline incidence rates from the Global Burden of Disease and gridded population data. The sectoral contribution to pediatric asthma from NO_2 exposure (NO_2-related asthma incidence: NINC) was estimated for different source categories to provide guidance to mitigation policies. We estimate 3.52 (2.1–6.0) million NINC per year globally, being about 14% of the total asthma incidence cases among children and adolescents. We find that emissions from land transportation are the leading contributor to NINC globally (∼44%), followed by the domestic burning of solid fuels (∼10.3%) and power generation from fossil fuels (∼8.7%). Biogenic emissions which are not anthropogenically induced may contribute ∼14% to the total NINC. Our results show large regional differences in source contributions, as the domestic burning of solid fuels is a main contributor to NINC in India and Nepal (∼25%), while emissions from shipping are the leading source in Scandinavian countries (∼40%), for example. While only 5% of all children and adolescents live in areas where NO_2 exceeds the WHO annual guideline of 21.25 ppb (40 μg m^{-3}) for NO_2, about 90% of the NINC is found in regions that meet the WHO guideline, related to the uneven distribution of children and adolescents in the population. This suggests the need for stricter policies to reduce NO_2 exposure, and revisiting the current WHO guideline to reduce the health risks of children and adolescents.

1. Introduction

Chronic respiratory diseases are among the leading contributors to morbidity worldwide (Soriano *et al* 2017, Stanaway *et al* 2018, Murray *et al* 2020). Asthma is a common respiratory condition leading to about 0.5 (95% confidence interval (CI) : 0.33–0.65) million premature deaths per year, associated with the loss of 22 (18–28) million disability adjusted life years in 2017 among all age groups (Soriano *et al* 2017, Stanaway *et al* 2018). Although the premature mortality from asthma decreased by 17.5% from 1990 to 2017, asthma affected about 330 million people in 2016) and according to the Global Burden of Disease

(GBD) its prevalence increased by 30% in the same time period (Soriano *et al* 2017, Stanaway *et al* 2018). In low- and middle-income countries, where access to medical facilities and asthma medication is often limited, the increase is expected to continue in future (Foreman *et al* 2018, Global Asthma Network 2018).

Long term exposure to ambient air pollution not only exacerbates pre-existing asthma (Friedman *et al* 2001, Shima *et al* 2002, O'Connor *et al* 2008, Guarnieri and Balmes 2014, Brandt *et al* 2015), but is also a major driver of new asthma cases (Gauderman *et al* 2004, Jerrett *et al* 2008, Gehring *et al* 2013, Nishimura *et al* 2013, Guarnieri and Balmes 2014, Wijga *et al* 2014, Gehring *et al* 2020). Some studies indicate that air pollution increases the risk of the development of asthma during adulthood (Jacquemin *et al* 2009, Modig *et al* 2009), while infants (<5 years) are generally at greatest risk considering the immaturity of their lungs (USEPA 2008, 2016, Guarnieri and Balmes 2014). The human respiratory system develops fully in the first 18–20 years, and during this period there is a higher intrinsic risk for the development of asthma (USEPA 2016, Gehring *et al* 2020). The asthma incidence rate is about twice as high in young people ($\leqslant$19 years) than among adults (>19 years) (Soriano *et al* 2017, Stanaway *et al* 2018).

The GBD has not yet included the impact of air pollutants on asthma. Recent studies demonstrate associations between both long-term and short-term ambient NO_2 exposure and asthma incidence in children, supported by experimental studies that characterize a probable adverse effect of NO_2 on the respiratory system (Gauderman *et al* 2004, Gehring *et al* 2013, Kudo *et al* 2013, USEPA 2016, Global Asthma Network 2018, Stevens *et al* 2019). The biological pathway of NO_2 exposure leading to airway inflammation, airflow obstruction and new asthma development is also well established (Fukuto *et al* 2012, Kim *et al* 2013, USEPA 2016, Stevens *et al* 2019). After assessing the evidence from recent cohort studies on exposure to NO_2, the 2016 integrated science assessment report by the United States Environmental Protection Agency (US EPA) changed the formulation of causal determination from long-term exposure to NO_2 on respiratory effects from 'sufficient to infer a likely causal relationship' in the 2008 Integrated Science Assessment report to a 'causal relationship' (USEPA 2008, p 201, 2016). The World Health Organization (WHO) sets the annual guideline for NO_2 at 40 μg m^{-3} ($\sim$21.25 ppb at 25 °C temperature and 1 atmosphere pressure). However, this was proposed in the early 2000s when a robust basis for an annual average guideline for NO_2 through direct health effects was still lacking (WHO 2006).

Since the conversion between NO and NO_2 is rapid, typically they are considered as the tracer family NO_x (Seinfeld and Pandis 2016). NO_x is predominantly emitted as NO by anthropogenic activities involving the burning of fossil fuels (about 10% is directly emitted as NO_2), but it rapidly reacts with tropospheric ozone (O_3) to form NO_2. Previous health impact studies used satellite retrievals and land use regression (LUR) models to estimate the exposure to NO_2, and assumed the incident cases of asthma to be linked to transportation related emissions (Anenberg *et al* 2018, Achakulwisut *et al* 2019). While studies have shown that transportation is a major source of NO_x, other emission sectors like biomass burning, agricultural waste burning, agricultural soils, power generation, industries, shipping and domestic solid fuel use also emit significant amounts of NO_x (Gerstle *et al* 1965, Jaegle *et al* 2005, Tian *et al* 2013, Boersma *et al* 2015, Janssens-Maenhout *et al* 2015, USEPA 2016, Ding *et al* 2017, Degraeuwe *et al* 2019). Here, we combine the outputs from an atmospheric chemistry model and an LUR model to estimate the burden of incident cases of asthma among children and adolescents from the exposure to ambient NO_2 and attribute it to different source categories. Our study adds to previous work (Anenberg *et al* 2018, Achakulwisut *et al* 2019, Khreis *et al* 2019) by using an atmospheric chemistry model to distinguish the contributions by the above-mentioned NO_2 sources, to guide policies aimed at regulating NO_2 exposure.

2. Methods

2.1. Model setup and emission inventory

We used the ECHAM5/MESSy atmospheric chemistry (EMAC)–general circulation model at a T106 horizontal spectral resolution (1.12° × 1.12° latitude × longitude), with 31 vertical hybrid terrain-following and pressure levels up to 10 hPa in the lower stratosphere (Sander *et al* 2005, Kerkweg *et al* 2006, Jöckel *et al* 2010, De Meij *et al* 2012, Pozzer *et al* 2012, Lelieveld *et al* 2015, Joeckel *et al* 2016). The core atmospheric model is the 5th generation European Centre Hamburg (ECHAM5) general circulation model. EMAC includes sub-models that represent tropospheric and stratospheric processes and their interaction with oceans, land and human influences. We used the Modular Earth Submodel System (MESSy, v.2.54, (Joeckel *et al* 2010)) to link submodels that describe emissions, atmospheric chemistry, aerosol and deposition processes. The gas phase and heterogeneous chemistry was simulated through the Module Efficiently Calculating the Chemistry of the Atmosphere (MECCA) submodel (Sander *et al* 2011, 2019), which accounts for the photochemical oxidation of natural and anthropogenic emissions, also accounting for the volatile organic compounds. The evolution of organic aerosol compounds is simulated with the ORACLE submodel (Tsimpidi *et al* 2014, 2018), which effectively accounts for primary and secondary combustion products from biofuel, fossil fuel, biomass burning

and their chemical oxidation during any atmospheric transport. Further, EMAC was nudged to simulate actual meteorological conditions, applying European Reanalysis Interim (ERA Interim) data for a period of 2 years (2014–2015), using 2014 as model spin-up.

We applied monthly varying sector-specific anthropogenic emissions to the model from the Community Emissions Data System (CEDS (Hoesly *et al* 2018)) at 0.5° × 0.5° resolution for the primary emitted species like sulfur dioxide (SO_2), oxides of nitrogen (NO_x), carbon monoxide (CO), black carbon (BC), organic carbon (OC), ammonia (NH_3) and speciated non-methane volatile organic compounds. We improved the model emissions over India using region-specific and updated emission inventories (Venkataraman *et al* 2020). Biomass burning emissions were obtained from the Global Fire Assimilation System (GFAS, Kaiser *et al* 2012). The emissions data were then pre-processed by distributing them in six emission heights; please see Pozzer *et al* (2009) for further details on distribution of emission from different sources to the six emission heights. Ambient NO_2 exposure was first estimated for all sources and then all source categories were removed one by one to obtain the contribution of nine sectors to ambient NO_2 exposure (Lelieveld *et al* 2015, 2019a).

The sectors considered are (a) land transportation (TRA) which includes emissions from road transportation and railways, (b) industries (IND) with emissions from iron and steel, paper and pulp, chemical, food, solvent and other manufacturing, oil refineries and fuel production, (c) domestic energy use (DOM) by the burning of fuels in households for cooking, lighting, domestic gas heating, diesel generators and biofuel use, (d) power generation (PGN) by thermal, oil and gas based power plants, (e) agricultural soils (AGS) that cause emissions from manure and fertilizer application and cultivation practices, (f) agricultural waste and residue burning (AWB), (g) emissions from ships and other water navigation (SHP), (h) biomass burning (BMB) which includes tropical, savanna, middle and high latitude forest fires, deforestation, savanna and shrub fires and (i) biogenic emissions from soils and plants (BGN).

2.2. Estimating the burden of incident cases of asthma

A recent study performed an extensive review of epidemiological studies that reported impacts of long-term exposure to NO_2 on NINC in children and adolescents (Anenberg *et al* 2018). Among five meta-analyses (Gasana *et al* 2012, Takenoue *et al* 2012, Anderson *et al* 2013, Bowatte *et al* 2015, Khreis *et al* 2017) identified by the study, Khreis *et al* (2017) is the most recent and included the largest number of epidemiological studies. The exposure-response function (ERF) from Khreis *et al* (2017) was also used by recent studies to estimate the total NINC in children (Achakulwisut *et al* 2019, Khreis *et al* 2019). Khreis *et al* (2017) included 41 epidemiological studies performed mostly in East Asia, Europe and North America and reported an relative risk (RR) of 1.26 (95% confidence interval (CI) 1.10–1.37) per 10 ppb increase in ambient NO_2. The information from (Khreis *et al* 2017) was utilized here to build an ERF for impacts of NO_2 on NINC using the following relationship:

$$\mathrm{RR} = \exp^{\beta \Delta x}, \quad \Delta x = \max[0, (\mathrm{NO_2} - \mathrm{LCC})]. \qquad (1)$$

β was first estimated by taking ln-RR of 1.12 (95% Uncertainty Interval: 1.08, 1.16) for a 10 ppb increase in NO_2. The β obtained was then used to obtain the RR for exposure to NO_2 using a low-concentration cut-off (LCC: 0.8 ppb). The LCC was selected based on the lowest concentration at which health impact was recorded (Khreis *et al* 2017, 2019). We performed sensitivity studies with lower (0 ppb) and higher LCCs' (1 and 2 ppb). We evaluated the ERFs obtained from Khreis *et al* (2017) against those from the other four meta-analyses (Gasana *et al* 2012, Takenoue *et al* 2012, Anderson *et al* 2013, Bowatte *et al* 2015) and found that the estimates of NINCs from the ERFs drawn from all the five studies overlap within their uncertainty bounds (see: figures S1 and S12(b) (available online at stacks.iop.org/ERL/16/035020/mmedia)).

The burden of NINC among children and adolescents for 2015 was estimated using equation (2). A similar relation was applied in our earlier studies (Lelieveld *et al* 2019b, Chowdhury *et al* 2020) to estimate excess mortality

$$\mathrm{NINC} = \left(\frac{\mathrm{RR}-1}{\mathrm{RR}}\right) \times p \times \mathrm{BINC}, \qquad (2)$$

where p is the exposed population with age $\leqslant$19 years for 2015. The age profile of the population for 2015 was obtained from the GBD and was merged with population data at ~1 km spatial resolution obtained from Global Human Settlement Layers (Florczyk *et al* 2019), resampled at 5 × 5 km spatial resolution. Age-specific baseline incidence rates (BINC) for the age classes <5, 5–9, 10–14 and 15–19 for asthma were obtained for each country from the GBD (https://vizhub.healthdata.org/gbd-compare/) . All estimates of NINC in this study are accompanied by 95% CIs. The 95% CI ranges were estimated by combining the uncertainty of the BINCs obtained from GBD and the uncertainty in the RR curves estimated by 10 000 random samples over the log-normal distribution of baseline incidence rates and RR. 95% CI was obtained from the resulting 10 000 estimates of NINC for each grid. Subsequently, the results were integrated and are presented at country level.

3. Results and discussions

3.1. Modeled NO_2 exposure and bias-correction

The EMAC model simulated global, gridded NO_2 at 15 min time intervals has been averaged, and the output stored at monthly time periods. The spatial distribution of NO_2^{EMAC} is depicted in figure S2(a). The NO_2^{EMAC} was then evaluated against annual averaged *in-situ* observation data for 2015 (NO_2^{OBS}), which were collected from ∼5000 sites around the world. The density of measurement locations is highest over Europe, East Asia and North America. NO_2^{EMAC} was found to have a low-bias compared to ground-based observations NO_2^{OBS} across the globe (figure S2(b)). The global population weighted NO_2^{EMAC} was estimated at 4.3 ppb. The low-bias in NO_2^{EMAC} may be due to: (a) its simulation at coarse horizontal resolution (1.12° × 1.12°) which averages out local gradients, this is especially relevant for urban areas and other locations with dense traffic, where mixing ratios are expected to be relatively high (below we will discuss the importance of traffic); (b), The lifetime of NO_x ($NO + NO_2$) is short, typically of the order of a few hours to a day, hence spatial-temporal gradients between sources and locations downwind can be steep, which are not captured well at the applied horizontal and time resolution. However, the EMAC tropospheric column densities of NO_2 compared well with those from the ozone monitoring instrument (Boersma *et al* 2018), indicating that sources and sinks are overall well represented. Please see supplementary information sections S1, figure S3 for more details on the comparison.

The bias towards low values was most notable over densely populated regions, whereas in background locations EMAC performs rather well (figures S4(a) and (b), detailed description on identification of background sites across the globe is provided in supplementary information sections S2). To amend the low-bias in densely populated areas, we utilized a publicly available LUR model (Larkin *et al* 2017) with which a high-resolution NO_2 dataset was derived, henceforth referred to as NO_2^{LUR}. NO_2^{LUR} was established for 2011 at 100 m resolution globally, by using information from 5220 monitoring sites located in 58 countries globally and predictor variables like active fires, population density, proximity to major and minor roads, tree cover, impervious surface area, normalized difference vegetation index, water body and satellite retrieved NO_2. NO_2^{LUR} was able to predict 54% of global variability, with a mean absolute error of 3.7 ppb (see Larkin *et al* (2017) for further details on formulation of NO_2^{LUR}). The LUR model was shown to perform better compared to NO_2^{EMAC} over the densely populated and urban areas, and was able to capture the spatial variability over such locations. However, it was found to overestimate NO_2 compared to observations over the background locations (figure S5), with a mean bias (MB) of −44% for NO_2^{OBS} compared to NO_2^{LUR}. Also note the high values of NO_2^{LUR} over the regions with sparse availability of predictor variables and low monitoring station density (e.g. Saudi Arabia, Saharan Africa, Midwest USA, central Australia; see figure S5(a)). Sparse availability of predictor variables also impacted the efficiency of NO_2^{LUR} in biomass burning dominated regions of Central Africa (figure S5a).

To optimize the contributions of both NO_2^{EMAC} and NO_2^{LUR}, we combined the two data sets with information from the global human settlement layers settlement model (GHS-SMOD). The GHS-SMOD classifies each 1 km grid by population clusters into eight broad settlement classes: urban center, dense urban cluster, semi-dense urban cluster, suburban/peri-urban, rural cluster, low density rural, very low-density rural and water grid cells (see Florczyk *et al* (2019), Melchiorri *et al* (2018) for more details on GHSL-SMOD classifications). Merging of the data was performed by first resampling the NO_2^{LUR} at 1 × 1 km resolution and then implementing NO_2^{EMAC} over the background grids while using NO_2^{LUR} over the other grids. The grid cells with the GHSL-SMOD classifications low-density rural and very low-density rural were considered as background (more details on background grid classification in supplementary material section S2). A sensitivity study was performed by also including rural cluster grid cells into the background grid. Subsequently, the merged NO_2 exposure data were weighted by population (of children and adolescents ⩽19 years) to obtain NO_2^{F} (NO_2^{EMAC} fused ('F') with NO_2^{LUR}) at 5 × 5 km resolution. Figures S6 and S7 depicts the algorithm for obtaining NO_2^{F} by combining NO_2^{LUR} and NO_2^{EMAC} by summarizing globally and also zooming in over a city.

The global population weighted NO_2^{LUR} was estimated at 9.8 ppb. Since 26% of the global child and adolescent population were estimated to reside in background grid locations (who were assigned NO_2^{EMAC} for exposure), the global population weighted NO_2^{F} was estimated to be lower at 8.1 ppb. The percentages of the population in all countries residing in background grid locations are depicted in figure S8(a). A large proportion of the child and adolescent population in Africa (31%) resides in background locations. In India, China, USA and Western Europe* 26%, 27%, 30% and 27% of the total child and adolescent population reside in background locations. We estimated the global population weighted NO_2^{F} exposure over background grid cells to be 2.9 ppb, compared to 6.3 ppb estimated with NO_2^{LUR}. The population weighted NO_2^{F} exposure at country-level is depicted in figure 1(a). We find that South Korea, Kuwait and Qatar have the

* Countries considered in Western Europe: The Netherlands, Belgium, Germany, France, Austria, Portugal, Spain, Switzerland, Luxembourg, Italy, Republic of Ireland and the United Kingdom.

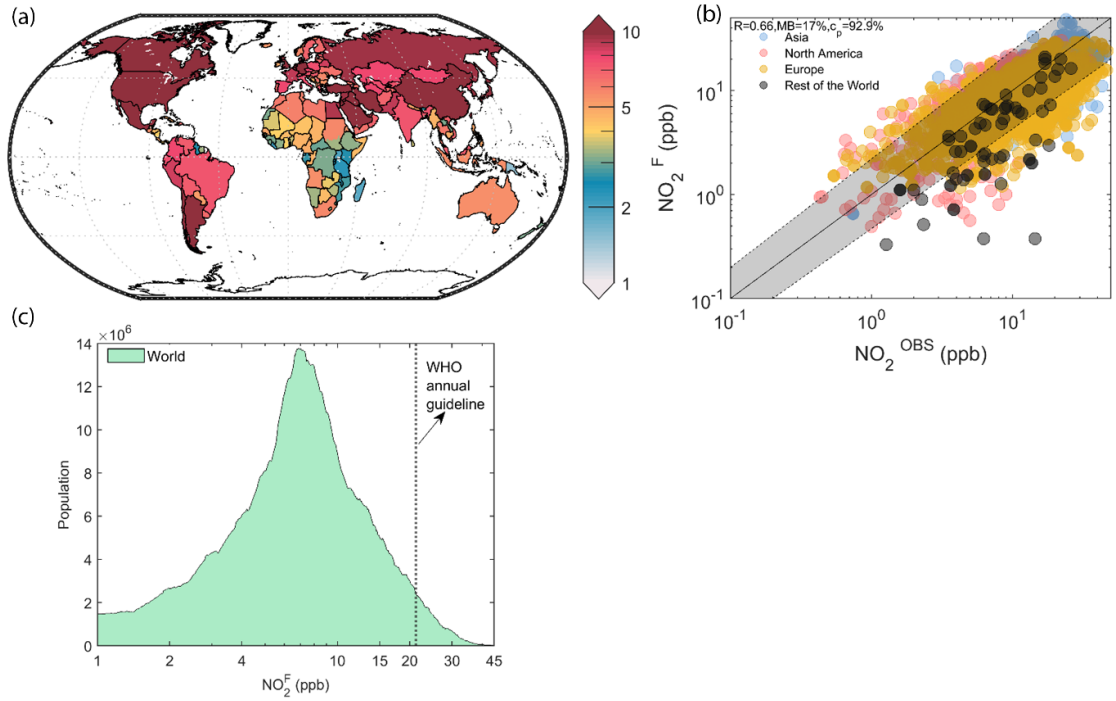

Figure 1. (a) Bias-corrected spatial distribution of exposure to annual mean NO_2. (b) Comparison of NO_2^F with NO_2^{OBS} at all observational sites. The area between the 1:2 and 2:1 lines is shaded gray. R is the correlation coefficient, MB the mean bias between NO_2^{OBS} and NO_2^F, and c_p the percentage of measurement data that fall within the gray shaded region. (c) Global distribution of the pediatric population exposed to NO_2.

highest population weighted NO_2^F exposure at 18.6, 17.4 and 17.2 ppb, respectively. Population weighted NO_2^F exposure for China, the USA and India were estimated to be 12.5, 10.5 and 7.8 ppb, respectively. Figure 1(b) depicts the comparison between NO_2^{OBS} and NO_2^F across the world. The correlation coefficient for comparison between NO_2^{OBS} and NO_2^F ($R = 0.66$) is higher compared to comparison with NO_2^{LUR} ($R = 0.63$) and NO_2^{EMAC} ($R = 0.43$).

A histogram of the pediatric population-NO_2 exposure curve was generated using the global gridded NO_2^F (figure 1(c)). The distribution was built by summing up the child and adolescent population in 500 logarithmically spaced bins from <1 ppb to 47 ppb and was found to have a distinct peak at 8 ppb. This feature is dominated by high exposure to NO_2^F among children and adolescents in India and China. The child and adolescent population-NO_2 exposure distribution of the five major countries are depicted in figure S9(a). We estimate that globally about 5% of all children and adolescents reside in areas where NO_2^F exceeds the WHO annual guideline level. These percentages are higher in South Korea (37%), Qatar (22%), Japan (16%), Egypt (12%) and China (10%) (figure S9(b)), while only ∼2% of the children and adolescents in India and Western Europe live in areas where exposure exceeds the WHO guideline. We performed a sensitivity analysis by considering the GHSL-SMOD threshold to classify background grid cells by combining the rural cluster with the low density rural and very low-density rural grid cells as background locations and then merging NO_2^{EMAC} and NO_2^{LUR} to obtain NO_2^{FR}. About 36% of the global child and adolescent population lives in these (rural cluster, low density rural, very low-density rural) settlement grids (figure S8(b)). Global population weighted NO_2^{FR} was estimated to be 7.8 ppb. Population weighted NO_2^F was higher than NO_2^{FR} for all countries, and figure S8(c) depicts the percentage difference between population weighted NO_2^F and NO_2^{FR}.

3.2. Burden of asthma incidence

Globally, we attribute 3.52 (2.16–6.05) million yr^{-1} NINC among children and adolescents to the long-term exposure to NO_2, among which 56.5%, 18.1%, 16.4% and 10.8% occur among population of ages <5 years, 5–9 years, 10–14 years and 15–19 years, respectively. This amounts to ∼13% of the total incidence. The NINC is highest in China, followed by India, Brazil, the USA and Indonesia, in that order, (figure 2, table 1). The numbers for the top nine countries (ranked according to NINC) plus Western Europe are listed in table 1. The supplementary data present this information for all countries worldwide considered in this study. The total burden of NINC depends on the size of the exposed child and adolescent population, BINC and NO_2^F. For example, India has the highest number of exposed children and adolescents (520 million), being 1.75 times that in China; however, the lower BINC in India (425 per 100 000 children and adolescent) compared to China (917 per 100 000) and significantly lower population weighted NO_2^F (38% lower) in India result in 47%

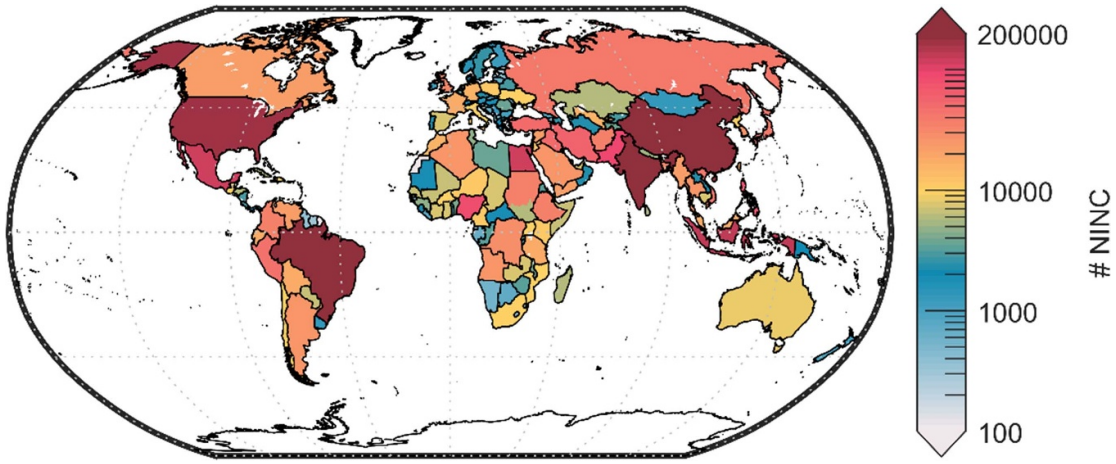

Figure 2. Incident cases of asthma among children and adolescents (NINC) attributed to exposure to ambient NO_2^F .

Table 1. Incident asthma cases attributed to ambient NO_2 exposure in children, and the percentage contribution of major source categories in the countries with highest incidence plus Western Europe. Data of incident cases of asthma from exposure to NO_2^F by country are listed in SI DATA1.

		Contribution from the major sectors (%)								
Countries	NINC (95% CI) in million	TRA	IND	DOM	PGN	AGS	AWB	SHP	BMB	BGN
China	0.57 (0.33–0.96)	41.5	22.9	7.1	20.7	1.3	0.1	0.4	0.1	5.8
India	0.3 (0.17–0.52)	26.1	2.2	25.6	2.6	24.6	0.8	0.5	0.5	17
Brazil	0.2 (0.12–0.33)	53.4	7.5	2.3	4.6	3.3	0.2	6.8	5.3	16.6
United States of America	0.2 (0.12–0.3)	58.8	6.1	15.8	6.1	0	0	4.6	0.9	7.6
Indonesia	0.15 (0.09–0.24)	65.7	3.3	3	10.8	2.9	0	2	6.2	6.2
Mexico	0.13 (0.08–0.22)	73.4	3.3	3.6	2.7	1.8	0.1	1.9	2.1	11
Egypt	0.13 (0.08–0.22)	58.7	2.1	6.4	5.3	11.3	0.1	5.7	0	10.4
Pakistan	0.1 (0.06–0.17)	36.5	0.9	18.4	0.7	27.5	1.4	0.1	0	14.5
Nigeria	0.09 (0.06–0.18)	33	2.8	23.8	1.1	3.5	0.8	1.7	10	23.4
Western Europe	0.11 (0.06–0.17)	56.8	4	9	5.2	2	0	15.5	0.1	7.4

lower NINC. To adjust for the exposed population, the rate of NINC (per 100 000 children and adolescents) was calculated. The annual rate of NINC is highest in the Middle East, e.g. in the United Arab Emirates (UAE), Kuwait and Qatar [612 (412–1101), 564(367–992) and 446 (304–859) per 100 000 children and adolescent, respectively]. The spatial distribution is depicted in figure S10(a). In Brazil, the USA, China and India, the annual rate of NINC is estimated at 313 (187–513), 235 (144–359), 193 (113–324), and 57 (33–100) per 100 000, respectively. We estimate that in Kuwait 32% of all pediatric NINC may be attributed to NO_2 exposure. The estimates for China, Brazil, India, United States of America and Western Europe are 22%, 14%, 13.8%, 19% and 18%, respectively (figure S10(b)). Using NO_2^{FR}, we attribute 3.33(2.06–5.78) million NINC to long-term NO_2 exposure. Using NO_2^{LUR}, 4.07 (2.5–7.01) million NINC (15.5% higher compared to NO_2^F) was estimated, which is close to the result (4 million) obtained by a recent study that used the LUR model (Achakulwisut *et al* 2019). Figure S11 depicts the percentage differences between NINC estimated using NO_2^{LUR} and NO_2^F and NO_2^{FR}. Large differences (up to 55% in the sub-Saharan countries) were found between NINC calculated with NO^{LUR} and NO_2^F in the countries with a large fraction of background grids (see figure S8). For China, India, Brazil and the USA the difference was estimated at 3.8%, 12%, 12% and 13.5% respectively.

3.3. Source sector attribution

The impacts of the nine aforementioned source categories was determined by omitting them one by one from the total NO_x emissions in the global model results, following an earlier study (Lelieveld *et al* 2015). The relative difference between incident cases of asthma estimated by the simulation with total NO_x and the simulation without emissions from a sector determines the contribution by the sector. The source contribution in the nine countries with highest NINC burden and Western Europe are depicted in figure 3 and listed in table 1. Land transportation (TRA) is the single largest contributor to NINC globally, accounting for 44%, followed by BGN, DOM, PGN, IND, AGS, SHP, BMB and AWB with 14.1%, 10.3%, 8.7%, 7%, 6.6%, 4%, 5% and 0.4%, respectively. The source contributions for all countries are presented in the supplementary data.

TRA is the largest contributor to NINC in most countries in East Asia, Central Asia, Europe, North and South America (figure 4), associated with

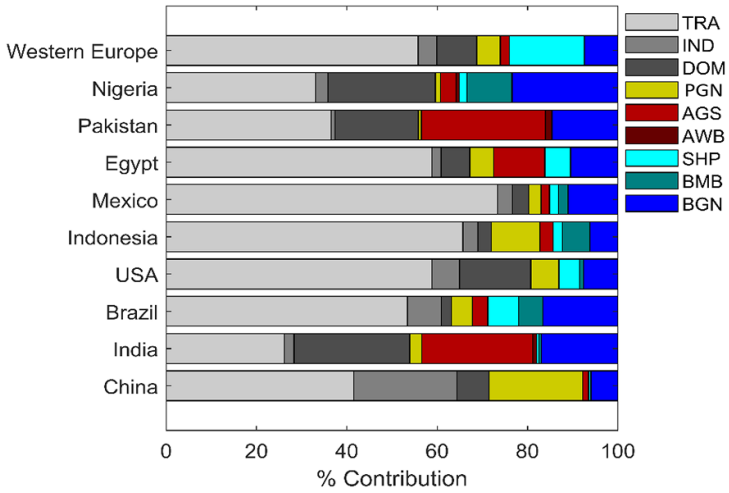

Figure 3. Contribution of the main sources of NO_2^F to NINC in the nine countries plus Western Europe with the highest asthma incidence from NO_2^F exposure.

1.56(0.95–3) million yr^{-1} NINCs. In Mexico and the USA, TRA contributes up to 73% and 59%, respectively. In Iran, Iraq, Saudi Arabia, Qatar and Kuwait, TRA is estimated to contribute to 60%–70% of the total NINC. We found it to be associated with 42%, 57% and 54% of NINC in China, Western Europe and Brazil, respectively. Its contribution is found to be lower in India (26%) and Nepal (29%) where the domestic use of solid fuels (DOM) is also a prevalent source of ambient NO_2 at the surface.

DOM is associated with 0.37 (0.22–0.63) million yr^{-1} NINCs globally, of which almost 21% occur in India (0.08 (0.04–1.33) million yr^{-1}). In Nepal, Pakistan and China, its contribution is 33.4%, 18.4% and 8%, respectively. DOM is also a major contributor to NINCs in Central African countries such as Rwanda (32%), Burundi (27%), Ethiopia (25%), Uganda (25%) and Nigeria (24%). In Argentina, its contribution to NINC is 42%. In high-income countries such as the USA (15%), Japan (11.4%) and Australia (3%) the DOM contribution is comparatively lower (figure 4). DOM contributes to 9% of NINC in Western Europe.

Power generation from fossil fuels (PGN) is a major source of NO_2 as well (Tian *et al* 2013). It is associated with 0.3 (0.18–0.51) million yr^{-1} NINCs globally. In Russia, the Philippines and China it is a major contributor to NINC with 25%, 23% and 21%, respectively. Its role is considerably less in the USA (6.3%), Western Europe (5%), Brazil (4.6%) and India (2.6%). Emissions from fuel combustion in industries and industrial processes (IND) contribute comparatively less. With a global fraction of ∼7%, it is associated with 0.24 (0.15–0.41) million yr^{-1} NINCs. It is relatively important in Japan (12%), South Korea (16%) and China (17.8%) while in most western high-income countries its contribution is comparatively low (4–8%).

The application of manure and fertilizers to soils for agriculture (AGS) is the next largest contributor at 6.6% accounting for 0.23 (0.14–0.4) NINCs. Use of nitrogen-based fertilizers has increased over time and is largely driven by intensive farming practices. In South Asia (e.g. India, Pakistan, Nepal, Bhutan and Bangladesh) where intensive farming is predominant, AGS contributes ∼20% to the total NINC. In Europe and North America, the contribution is small (up to 5%). Agricultural waste and residue burning is a minor contributor to NINC with 0.01 (0.006–0.02) million yr^{-1}.

NO_x from ship emissions (SHP) is expected to result in NINCs in coastal locations, major harbors and countries with coastlines adjacent to the major shipping routes. Globally, SHP is associated with 0.14 (0.09–0.23) million yr^{-1} NINCs. In Scandinavian countries it is a relatively large contributor to NINC, e.g. in Denmark (69%), Sweden (48%), Norway (44%) and Finland (20%). It also contributes significantly in island states, e.g. Iceland (65%), the UK (17%), Ireland (37%), Australia (16%) and New Zealand (14%).

Biomass burning, forest and grassland fires (BMB) account for 5% or 0.18 (0.11–0.31) million yr^{-1} NINCs globally. It plays a major role in sub-Saharan and particularly central African countries (figure 4) where it can contribute more than 60%. It contributes ∼15% in Southeast Asia (e.g. Cambodia, Laos, Indonesia). BMB is also important (6%–10%) in South America and Australia. BGN from natural vegetation and soil is associated with 0.49 (0.31–0.87) million NINCs. It was found to be a major contributor to NINCs in sub-Saharan, central and south African countries (12%–20%). In China, USA, Brazil and India it contributes about 6%, 7.5%, 16.7% and 16.9% respectively.

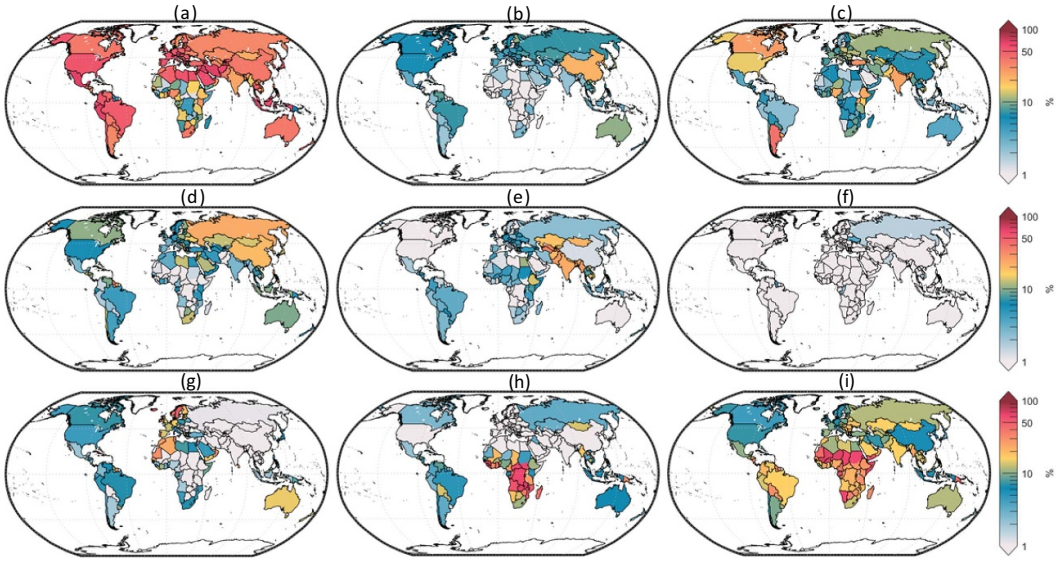

Figure 4. Global maps of the major source contributions (a) TRA, (b) IND, (c) DOM, (d) PGN, (e) AGS, (f) AWB, (g) SHP, (h) BMB, (i) BGN to incident cases of asthma (NINC) caused by the exposure to ambient NO_2^F.

3.4. Uncertainties and assumptions

All estimates of NINC in this study are accompanied by 95% CIs. The 95% CI ranges were estimated by combining the uncertainty of the BINCs and the uncertainty in the RR curves by distributing the RR and BINCs lognormally across the 95% CIs to obtain 10 000 estimates of NINC for each grid cell, from which the overall 95% CIs were estimated (see Chowdhury *et al* (2020) for details). Several other limitations may affect the results presented in this study. Firstly, the model was simulated to estimate NO_2 exposure at 1.12° × 1.12° horizontal resolution, which may be responsible for averaging out the local scale gradients in NO_2 exposure (USEPA 2016, Larkin *et al* 2017, Achakulwisut *et al* 2019). Nevertheless, this was alleviated by merging the model simulations (of 2015) with fine resolution LUR model calculations of NO_2 (of 2011). However, the source attribution was performed at the coarse model resolution and applied to the merged NO_2^F data, assuming only the steep NO_2 concentration gradients in the vicinity of sources, e.g. in urban centers, and not the emission strengths of the sources, which are not well represented.

Secondly, the main results of this study were obtained by using an LCC of 0.8 ppb, following the lowest concentration at which causality was noted in a recent analysis (Khreis *et al* 2017). We performed sensitivity calculations by considering no threshold (i.e. LCC = 0 ppb), and threshold levels of 1 ppb and 2 ppb (based on Achakulwisut *et al* (2019)) (figure S12(a)). The estimates of NINC were 12% higher and 3% and 16% lower when LCC was changed to 0, 1 and 2 ppb respectively (figure S12(a)). We estimated 3.93 (2.41–6.75) million, 3.42 (2.09–5.87) million and 2.95 (1.8–5.06) million incident cases of asthma from exposure to NO_2 per year among children and adolescents using 0, 1 and 2 ppb as LCC, respectively, which corresponds to 14.5%, 12% and 10.9% of the total global incidence of asthma, respectively.

Thirdly, the Khreis *et al* (2017) meta-analysis included epidemiological studies from East Asia, Europe and North America, therefore missing out on epidemiological evidence from the rest of the world. Also, an ERF derived from a single-pollutant epidemiological model was used to assume a causal relationship between NO_2 exposure and asthma incidence (because multipollutant models that adjust for other co-pollutants are currently not available). Nonetheless, the evidence is suggestive of more robust associations asthma incidence with NO_2 exposure, than for other air pollutants like $PM_{2.5}$ (Anderson *et al* 2013, USEPA 2016). However, it may be possible that the reported associations are sensitive to control for co-pollutants which may potentially change the estimates presented in this study. A sensitivity study was performed by estimating the NINC based on ERF curves from other available meta-analyses (figure S1). It was found that all the estimates of NINCs overlap within the uncertainty bounds (figure S12(b)).

A recent study by Holst *et al* (2020) that inspected association of multiple pollutants on onset of asthma found that only $PM_{2.5}$ remained significantly associated with asthma after controlling for other pollutants (NO_2, PM_{10}) among children of parents with asthma and mothers who smoked during pregnancy. However, after adjusting for parental asthma, parental income and parental education, a significant association was obtained for NO_2 and new incidence of asthma among children. Another recent study (Gehring *et al* 2020) found stronger association of long-term exposure to NO_2 and incidence of asthma

among children and adolescents compared to exposure to $PM_{2.5}$. Nonetheless, we estimated the incident cases of of asthma from long-term exposure to $PM_{2.5}$ (PINC) simulated by the EMAC model as a sensitivity study to our estimates of NINC (supplementary information section S3). Globally, we estimated PINC to be ∼2 times higher than NINC, which is consistent with a previous study (Annenberg *et al* 2018). However we emphasize that, unlike for long-term exposure to NO_2, there is no consensus among studies that associate exposure to long-term exposure to $PM_{2.5}$ with incidence of asthma (Gasana *et al* 2012, Anderson *et al* 2013, Guarnieri and Balmes 2014, USEPA 2016). We reiterate that our estimates of NINC and PINC are not additive considering significant overlap between them due to the use of single-pollutant epidemiological models in this study in absence of models that control for co-pollutants. We refer to supplementary information section S3 for further discussion.

4. Summary and conclusions

We estimate that 3.52 (1.2–7.2) million yr^{-1} new incident cases of asthma in children and adolescents are attributable to exposure to ambient NO_2. Our result is slightly lower than that of a recent study (Achakulwisut *et al* 2019), which used exposure obtained from an LUR model only, but is three times that from a prior study (Anenberg *et al* 2018). We combined results from a global LUR model for NO_2 with atmospheric chemistry model simulations to obtain the NO_2 exposure metric. We estimate that globally 5% of all children and adolescents live in areas where NO_2 exposure exceeds the WHO annual guideline of 21.25 ppb (the WHO guideline of 40 $\mu g\,m^{-3}$ was converted to ppb at standard temperature and pressure). However, ∼90% of the total NINC burden occurs in locations where the WHO annual guideline is met. This calls for revisiting the WHO annual guideline (WHO 2006) for NO_2. It was formulated in 2006 when a robust basis for the guideline from epidemiological studies was not yet available (WHO 2006, USEPA 2008). If the areas where the WHO guideline for NO_2 is currently exceeded would actually meet the guideline, ∼2% [0.07 (0.04–0.11) million yr^{-1}] of the NINC could be averted. Note that we do not account for the effect of NO_2 in causing exacerbations of symptoms in children and adolescents with pre-existing asthma, and hence we provide a lower limit of the full effect.

To help direct policy decision making, we provide the first estimates of source sector specific contributions of NO_2-induced NINC, whereas previous work attributed the exposure generally to traffic related sources (Anenberg *et al* 2018, Achakulwisut *et al* 2019). Nevertheless, our results corroborate the suggestion that land transportation (TRA) is the leading contributor to NINC, with a global average of 44%. In the USA and Mexico, the TRA contributions are very high, 58.8% and 73.4%, respectively. In Western Europe the contributions vary between 50% and 65%. In India and Nepal, where the burning of solid fuels in households is ubiquitous (Lelieveld *et al* 2015, Chowdhury *et al* 2019), this source sector is prevalent (∼25%). In China the industrial sector and power generation from fossil fuels together contribute ∼35% to NINC. In central Africa, biomass burning is the single largest contributor to NINC (>70%). Our results suggest that targeted air quality control measures and tightening of the WHO guideline for ambient NO_2 are needed to substantially reduce the burden of new asthma incident cases in children and adolescents.

Data availability statement

Data on incidence of asthma from exposure to NO_2 produced by this study are disseminated by country through SI Data1. Spatial raster of NO_2^F and data of incidence of asthma from exposure to NO_2 by provinces will be made available upon reasonable request to the authors.

The data that support the findings of this study are available upon reasonable request from the authors.

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Conflict of interest

The authors declare no competing interests.

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