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Estimates of the Global Burden of Ambient $PM_{2.5}$, Ozone, and NO_2 on Asthma Incidence and Emergency Room Visits

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Background: Asthma is the most prevalent chronic respiratory disease worldwide, affecting 358 million people in 2015. Ambient air pollution exacerbates asthma among populations around the world and may also contribute to new-onset asthma.

Objectives: We aimed to estimate the number of asthma emergency room visits and new onset asthma cases globally attributable to fine particulate matter ($PM_{2.5}$), ozone, and nitrogen dioxide (NO_2) concentrations.

Methods: We used epidemiological health impact functions combined with data describing population, baseline asthma incidence and prevalence, and pollutant concentrations. We constructed a new dataset of national and regional emergency room visit rates among people with asthma using published survey data.

Results: We estimated that 9–23 million and 5–10 million annual asthma emergency room visits globally in 2015 could be attributable to ozone and $PM_{2.5}$, respectively, representing 8–20% and 4–9% of the annual number of global visits, respectively. The range reflects the application of central risk estimates from different epidemiological meta-analyses. Anthropogenic emissions were responsible for ~37% and 73% of ozone and $PM_{2.5}$ impacts, respectively. Remaining impacts were attributable to naturally occurring ozone precursor emissions (e.g., from vegetation, lightning) and $PM_{2.5}$ (e.g., dust, sea salt), though several of these sources are also influenced by humans. The largest impacts were estimated in China and India.

Conclusions: These findings estimate the magnitude of the global asthma burden that could be avoided by reducing ambient air pollution. We also identified key uncertainties and data limitations to be addressed to enable refined estimation. https://doi.org/10.1289/EHP3766

Introduction

Approximately 358 million people worldwide were estimated to have had asthma in 2015 (GBD 2015 Chronic Respiratory Disease Collaborators 2017), including about 14% of the world's children (Global Asthma Network 2014). Asthma prevalence is considered the fourth leading cause of years lived with disability (YLDs) for children ages 5–14 globally, and the 16th leading cause of YLDs for all ages (GBD 2015 Chronic Respiratory Disease Collaborators 2017). Asthma is among the top causes of YLDs among children ages 5–14 across all sociodemographic index categories, affecting both high- and low-income populations. Economic costs are substantial and include both direct [e.g., inpatient care, emergency room visits (ERVs), physician visits, diagnostic tests, and medication] and indirect costs (e.g., school and work days lost; Bahadori et al. 2009). Epidemiological and clinical experimental studies have shown over decades that exposure to air pollution is a key risk factor for asthma exacerbation and may also contribute to new-onset asthma (Guarnieri and Balmes 2014; Toskala and Kennedy 2015).

Ambient fine particulate matter ($PM_{2.5}$) exposure, currently considered the leading environmental risk factor globally, is estimated to be associated with 4.2 million premature deaths and 103 million Disability Adjusted Life Years (DALYs, YLDs plus Years of Life Lost) in 2015 (Cohen et al. 2017). Updated for 2016, the $PM_{2.5}$ disease burden estimate includes 4.1 million deaths and 106 million DALYs (GBD 2016 Risk Factors Collaborators 2017). This global burden attributable to $PM_{2.5}$ accounts for 27% of all DALYs from chronic obstructive pulmonary disease (COPD; an additional 6% are attributable to ambient ozone); 20% of those from ischemic heart disease; 16% of those from stroke; 17% of those from tracheal, bronchus, and lung cancer; and 31% from child acute lower respiratory infections (GBD 2016 Risk Factors Collaborators 2017). The Global Burden of Disease Study 2016 estimated that smoking and occupational asthmagens were each responsible for 10% of DALYs from asthma in 2016 (GBD 2015 Chronic Respiratory Disease Collaborators 2017).

The contribution of air pollution to asthma exacerbation and new asthma incidence remains unquantified and has not been included in global burden of disease studies (Cohen et al. 2017;

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GBD 2016 Risk Factors Collaborators 2017; WHO 2016, 2017a). Estimates of air pollution's impact on asthma in individual countries or sets of cities suggest that the global burden could be substantial (Fann et al. 2012; Perez et al. 2013). Nitrogen dioxide (NO_2) has not yet been included in global burden of disease assessments but is associated with asthma exacerbation and incidence (Orellano et al. 2017; Zhang et al. 2016; Zheng et al. 2015) and has been considered a key pollutant in country- and city-level air pollution impact estimates (Walton et al. 2015). Here we quantitatively estimate asthma ERVs and, as a secondary analysis, new asthma cases that may be attributable to ambient ozone, $PM_{2.5}$, and NO_2 globally. We use epidemiologically derived health-impact functions combined with datasets on population, baseline asthma incidence and prevalence rates, and pollutant concentrations. As these first estimates of the global asthma burden from ambient air pollution are subject to many important assumptions and uncertainties, we anticipate that future studies will further advance the input data and methods piloted here.

Methods

The analytical process is similar to that typically used to estimate air pollution-related premature deaths (Anenberg et al. 2010), but uses data that are specific to asthma. We first combined national asthma incidence and prevalence rates and a newly constructed dataset of asthma ERV rates from survey data in 54 countries and Hong Kong (Table 1 and Figures S1 and S2) with globally gridded population counts to estimate the baseline number of new asthma cases and asthma ERVs at $0.1^\circ \times 0.1^\circ$ resolution. We then estimated the pollution-attributable fraction of asthma ERVs and new asthma cases using globally gridded pollution concentrations, derived from satellite remote sensing and chemical transport modeling ($0.1^\circ \times 0.1^\circ$ resolution; Figure 1), with concentration–response factors drawn from several multinational meta-analyses of epidemiological studies (Table 2). These epidemiological studies examined associations between air pollutants and both asthma exacerbation and incident asthma in 27 countries spanning North America, Europe, Asia, and Latin America (Table S1). We used best practices in data reporting outlined by the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) (Stevens et al. 2016).

Concentration–Response Factors

Concentration–response factors for asthma exacerbation and incidence were taken from meta-analyses of epidemiological studies that combined multiple individual studies from different countries into pooled risk estimates. We first conducted a literature review to identify meta-analyses of epidemiological studies on air pollution and asthma, using MEDLINE, PubMed, and Google Scholar, supplemented with additional reviews of U.S. Environmental Protection Agency Integrated Science Assessments for $PM_{2.5}$ (U.S. EPA 2009) and ozone (U.S. EPA 2015a). We limited the search to meta-analyses pooling results from epidemiological studies across multiple countries to derive relative risk (RR) estimates that might be most generalizable to the global population. We included only studies that were written in English and reported a numerical concentration–response relationship accompanied by an estimate of precision. We excluded studies that only examined personal exposure rather than ambient concentrations (because the concentration estimates we use do not represent personal exposure) or that only included lung function tests.

Based on these criteria, we found 10 meta-analyses on short-term exposure to air pollution (including ozone, $PM_{2.5}$, and NO_2) and asthma exacerbation or prevalence and six meta-analyses on long-term exposure to air pollution (including $PM_{2.5}$ and NO_2) and asthma incidence. Our search did not identify any multinational meta-analyses reporting a significant relationship between ozone and asthma incidence, though some individual studies report increased risk (Anderson et al. 2013; McConnell et al. 2002). Although some studies examined relationships between asthma and PM_{10} concentrations, we focused on $PM_{2.5}$ because globally gridded concentration estimates are not available for PM_{10}.

Asthma exacerbation endpoints were either self-reported increase of symptoms (Karakatsani et al. 2012) or more commonly, asthma-related ERVs and/or hospital admissions. We identified three asthma exacerbation studies that addressed ozone, $PM_{2.5}$, and NO_2 for all ages, children, and adults (Orellano et al. 2017; Zhang et al. 2016; Zheng et al. 2015), and used these studies for the core results because they included the broadest range of populations, pollutants, and ages. We found six additional meta-analyses reporting relationships between asthma ERVs and $PM_{2.5}$ and NO_2 for children only (Fan et al. 2016; Favarato et al. 2014; Gehring et al. 2015; Lim et al. 2016; Mölter et al. 2015; Weinmayr et al. 2010). We excluded two studies that had the narrowest age ranges (Gehring et al. 2015; Mölter et al. 2015). We also excluded one study that relied on self-reported asthma symptoms rather than official hospital records or medical diagnoses. In total, we used seven of the 10 meta-analyses found in our literature review for asthma exacerbation. From each of these studies, we extracted the concentration–response functions that we judged to be most broadly representative of exposures among the general population (e.g., all year versus warm or cold season only, pooled all individual studies rather than only statistically significant studies, included both men and women, etc.), without regard for the magnitude or significance of the risk estimates. We used RRs for combined ERVs and hospital admissions to take advantage of the largest number of underlying studies in the meta-analyses and the largest number of meta-analyses, as only a subset of studies and meta-analyses reported RRs specifically for ERVs (e.g., Orellano et al. 2017 reported RRs only for ERVs and hospital admissions together). Ideally, a broad category of asthma exacerbations would most comprehensively account for the effect of air pollution on worsening asthma symptoms, as only a portion of exacerbations end in ERVs or hospital admissions (e.g., Pollart et al. 2011). We judged that using the combined ERV and hospital admission RRs would capture more of the exacerbation effect of pollution, in comparison with using only ERV or hospital admission RRs.

For asthma incidence, we identified two meta-analyses of long-term epidemiological studies that included $PM_{2.5}$ and NO_2 and asthma development among all ages (Anderson et al. 2013; Jacquemin et al. 2015). Neither study reported significant associations for $PM_{2.5}$, but one reported a significant association for NO_2 (Anderson et al. 2013). We also found three meta-analyses examining traffic-related $PM_{2.5}$ and NO_2 associations with asthma development among children (Bowatte et al. 2015; Gasana et al. 2012; Khreis et al. 2017), and one on NO_2 from any source and children (Takenoue et al. 2012). For children, two of the four analyses (Bowatte et al. 2015; Khreis et al. 2017) examining $PM_{2.5}$ (both traffic-related studies) and all five analyses examining NO_2 (Anderson et al. 2013; Bowatte et al. 2015; Gasana et al. 2012; Khreis et al. 2017; Takenoue et al. 2012) reported significant associations with pediatric asthma development. To estimate $PM_{2.5}$ and NO_2-attributable asthma incidence, we applied RR estimates for all ages from Anderson et al. (2013) and Jacquemin et al. (2015). We also estimated $PM_{2.5}$ and NO_2-attributable pediatric asthma incidence using RR estimates from Anderson et al. (2013) and from the most recent of the

Table 1. Fraction of asthma group visiting the emergency room per year in each country, with data source.

Country	Study	Study Survey[a]	Fraction visiting emergency room[b]
Algeria	Nafti et al. 2009	AIR	0.379
Argentina	Neffen et al. 2010	AIR	0.417
Australia	Thompson et al. 2013	AIM	0.150
Austria	Price et al. 2014	REALISE	0.239
Belgium	Price et al. 2014	REALISE	0.239
Brazil	Neffen et al. 2010	AIR	0.417
Bulgaria	Rabe et al. 2004	AIR	0.207
Canada	Sastre et al. 2016	AIR	0.280
Chile	Neffen et al. 2010	AIR	0.417
China	Weighted[c]		0.329
	Rabe et al. 2004	AIR	0.190
	Zainudin et al. 2005	AIR	0.315
	Thompson et al. 2013	AIM	0.40
	Su et al. 2013	AIR	0.339
Colombia	Neffen et al. 2010	AIR	0.417
Costa Rica	Neffen et al. 2010	AIR	0.417
Croatia	Rabe et al. 2004	AIR	0.207
Czech Republic	Rabe et al. 2004	AIR	0.207
Ecuador	Neffen et al. 2010	AIR	0.417
Ethiopia	Zemedkun et al. 2014	ACT	0.312
Finland	Price et al. 2014	REALISE	0.239
France	Weighted		0.079
	Rabe et al. 2004	AIR	0.100
	Price et al. 2014	REALISE	0.239
Germany	Weighted		0.195
	Rabe et al. 2004	AIR	0.100
	Price et al. 2014	REALISE	0.239
	Sastre et al. 2016	AIM	0.180
Hungary	Rabe et al. 2004	AIR	0.207
India	Thompson et al. 2013	AIM	0.420
Italy	Weighted		0.143
	Rabe et al. 2004	AIR	0.100
	Price et al. 2014	REALISE	0.239
	Sastre et al. 2016	AIM	0.150
	Allegra et al. 2012	PRISMA	0.065
	Corrado et al. 2013	Survey of patients in 16 Italian pulmonary units	0.499
Japan	Rabe et al. 2004	AIR	0.130
Jordan	Khadadah et al. 2009	AIR	0.520
Kuwait	Khadadah et al. 2009	AIR	0.520
Latvia	Rabe et al.2004	AIR	0.207
Lebanon	Khadadah et al. 2009	AIR	0.520
Lithuania	Rabe et al. 2004	AIR	0.207
Malaysia	Weighted		0.246
	Rabe et al. 2004	AIR	0.190
	Zainudin et al. 2005	AIR	0.120
	Thompson et al. 2013	AIM	0.400
	Neffen et al. 2010	AIR	0.417
Morocco	Nafti et al. 2009	AIR	0.210
Netherlands	Weighted		0.195
	Rabe et al. 2004	AIR	0.100
	Price et al. 2014	REALISE	0.239
Nigeria	Desalu et al. 2013	GAPP	0.427
Norway	Price et al. 2014	REALISE	0.239
Oman	Khadadah et al. 2009	AIR	0.520
Peru	Neffen et al. 2010	AIR	0.417
Philippines	Weighted		0.211
	Rabe et al. 2004	AIR	0.19
	Zainudin et al. 2005	AIR	0.252
Poland	Rabe et al. 2004	AIR	0.207
Romania	Rabe et al. 2004	AIR	0.207
Russia	Rabe et al. 2004	AIR	0.207
Singapore	Weighted		0.164
	Rabe et al. 2004	AIR	0.190
	Zainudin et al. 2005	AIR	0.114
	Thompson et al. 2013	AIM	0.170

[a]Note: ACT, International Asthma Control Test; AIM, Asthma Insights and Management Survey; AIR, Asthma Insights and Reality Survey; GAPP, Global Asthma Physician and Patient survey; PRISMA, Prospective Study on Asthma Control; Realise, Recognise Asthma and Link to Symptoms and Experience Survey.
[b]The studies reported the rate of ERVs and hospital admissions among study participants, which we used as nationwide rates, assuming the survey sample was nationally representative.
[c]For countries where more than one asthma ERV rate were available from the included surveys, we weighted the rates based on study sample size and used this rate for the total countrywide rate.

Table 1. (*Continued.*)

Country	Study	Study Survey[a]	Fraction visiting emergency room[b]
Slovak Republic	Rabe et al. 2004	AIR	0.207
Slovenia	Rabe et al. 2004	AIR	0.207
South Korea	Weighted		0.148
	Zainudin et al. 2005	AIR	0.058
	Rabe et al. 2004	AIR	0.190
	Thompson et al. 2013	AIM	0.160
Spain	Weighted		0.235
	Rabe et al. 2004	AIR	0.100
	Price et al. 2014	REALISE	0.239
	Sastre et al. 2016	AIM	0.360
Sweden	Weighted		0.184
	Rabe et al. 2004	AIR	0.100
	Price et al. 2014	REALISE	0.239
Thailand	Weighted		0.350
	Thompson et al. 2013	AIM	0.350
	Boonsawat et al. 2015	AIM	0.350
Tunisia	Nafti et al. 2009	AIR	0.254
Turkey	Turktas et al. 2010	AIR	0.233
Ukraine	Rabe et al. 2004	AIR	0.207
United Arab Emirates	Weighted		0.400
	Khadadah et al. 2009	AIR	0.520
	Mahboub et al. 2010	AIR	0.280
United Kingdom	Weighted		0.175
	Rabe et al. 2004	AIR	0.100
	Price et al. 2014	REALISE	0.239
	Sastre et al. 2016	AIM	0.090
United States	Rabe et al. 2004	AIR	0.230
Uruguay	Neffen et al. 2010	AIR	0.417
Venezuela	Neffen et al. 2010	AIR	0.417
Vietnam	Weighted		0.206
	Rabe et al. 2004	AIR	0.190
	Zainudin et al. 2005	AIR	0.225
Hong Kong	Weighted		0.168
	Thompson et al. 2013	AIM	0.150
	Zainudin et al. 2005	AIR	0.164
	Rabe et al. 2004	AIR	0.190

meta-analyses focusing explicitly on traffic-related pollution, Khreis et al. (2017). All RR estimates considered are listed in Table 2. In total, we used three of the six meta-analyses found in our literature review for asthma incidence. One of these meta-analyses reported ranges of 8 to 34 $\mu g/m^3$ $PM_{2.5}$ and 0 to 61.7 ppb NO_2 (Jacquemin et al. 2015). Concentration ranges in the other two meta-analyses were unreported but are unlikely to be substantially wider because all three meta-analyses were limited to epidemiological studies conducted in the United States and Europe (Anderson et al. 2013; Khreis et al. 2017). Several meta-analyses indicated that most underlying epidemiological studies focused on within-city variation in exposure levels, and studies comparing exposures between communities did not show significant associations with asthma incidence (Anderson et al. 2012, 2013). To more closely capture asthma incidence from the increment of exposure over background levels within each community, we focused on the health burden due to anthropogenic contributions. This method could still overestimate asthma incidence from air pollution because background concentrations within communities are also influenced by regional anthropogenic emissions.

Central RR estimates for asthma ERVs among all ages ranged from 1.01–1.03 per 10 $\mu g/m^3$ increase in $PM_{2.5}$, 1.02–1.05 per 10 ppb increase in ozone, and 1.02–1.03 per 10 ppb increase in NO_2 (Table 2). For pediatric incident asthma, central RR estimates ranged from 1.34–1.93 per 10 $\mu g/m^3$ $PM_{2.5}$ and 1.10–1.28 per 10 ppb NO_2. These relationships were all based on single-pollutant models that did not control for other pollutants; thus, there may be overlap between asthma effect estimates for ozone, $PM_{2.5}$, and NO_2. As these meta-analyses used different methods, captured different sets of studies (with some overlap), and often examined different models and subgroups, we applied RR estimates from multiple studies separately. Of the 87 studies included by Zheng et al. (2015), 12 studies were overlapping with Zhang et al. (2016) and nine studies were overlapping with Orellano et al. (2017). Zheng et al. (2015) and Zhang et al. (2016) had only two studies in common. Concentrations ranges included in the underlying epidemiological studies were reported by two of the three meta-analyses, and ranged from 6.1 to 45.3 $\mu g/m^3$ $PM_{2.5}$, 2 to 98.3 ppb ozone, and 5.4 to 92.7 ppb NO_2 (Zhang et al. 2016; Zheng et al. 2015). The third meta-analysis is likely to also include wide concentration ranges because the underlying epidemiological studies were conducted in 12 different countries spanning relatively clean locations (e.g., Australia, Canada) to relatively polluted locations (e.g., China; Orellano et al. 2017).

Health Impact Functions

We used the "attributable fraction" approach to estimate asthma ERVs and new asthma cases attributable to each pollutant (e.g., Miettinen 1974), following other air pollution health impact assessments (e.g., Anenberg et al. 2010; Cohen et al. 2017; Fann et al. 2012). It is unclear based on these meta-analyses whether the concentration–response functions between pollutant and asthma effect are linear or nonlinear. Several of the studies indicate that the results given describe linear relationships (Lim et al. 2016; Orellano et al. 2017; Zhang et al. 2016; Zheng et al. 2015), whereas the others did not specify the functional shape (Anderson et al. 2013; Fan et al. 2016; Jacquemin et al. 2015).

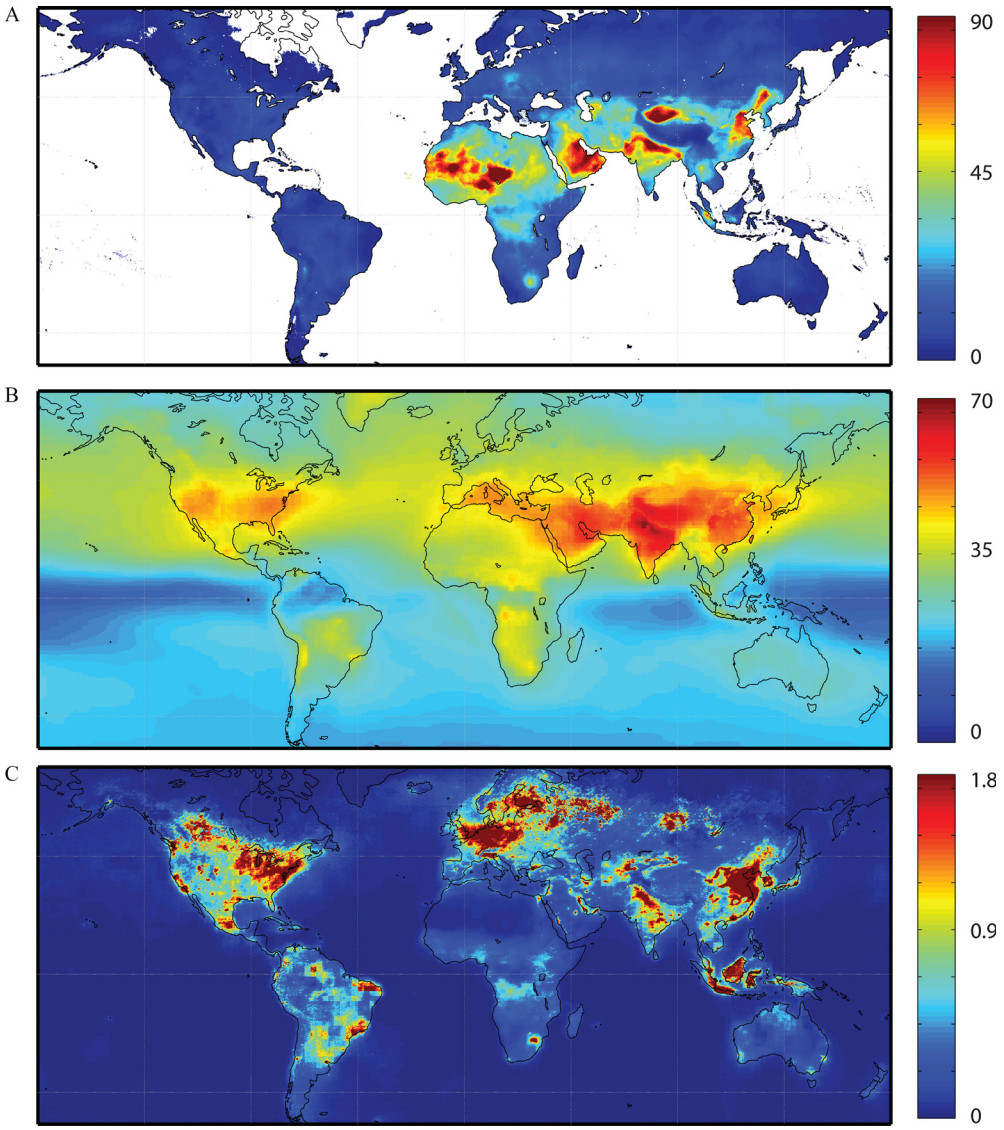

Figure 1. Pollutant concentrations used to estimate asthma impacts. (*A*) $PM_{2.5}$ concentrations (annual average, in $\mu g/m^3$) in 2015, described by van Donkelaar et al. (2016; max concentration = 179.8 $\mu g/m^3$). (*B*) Ozone concentrations in 2015 (annual average of 8hr daily maximum, in ppb), using multi-model average from TF HTAP ensemble (max concentration = 72.9 ppb). (*C*) NO_2 concentrations in 2015 (annual average, in ppb), using satellite-derived dataset from method described by Lamsal et al. (2008) and adjusted by modeled ratio of daily average to 1–2 P.M. (1300–1400 hours) concentration (max concentration = 17.5 ppb).

Linear functions would imply that the same change in risk per unit concentration change would occur in very polluted and very clean atmospheres. Other diseases caused by $PM_{2.5}$ appear to have nonlinear relationships that flatten out at high concentrations (Burnett et al. 2014; Cohen et al. 2017). Here, to account for potential flattening of the concentration–response relationship at very high concentrations, we applied log-linear relationships for $PM_{2.5}$, ozone, and NO_2. The log-linear and linear functions describe similar concentration–response relationships within the range of concentrations found in most developed countries ($\sim$5–50 $\mu g/m^3$ $PM_{2.5}$) and begin to diverge at higher concentrations found in many developing countries (>50 $\mu g/m^3$). We estimated 3–8% more asthma ERVs globally associated with ozone and $PM_{2.5}$ using a linear rather than log-linear function. Nevertheless, the lack of information about the shape of the concentration–response function or heterogeneity in risk estimates at different concentration levels is a limitation.

The health impact function for the change in asthma ERVs attributable to $PM_{2.5}$, ozone, or NO_2 (ΔERV) is:

$$\Delta ERV = Pop_a \times Prev_{c,a} \times ERV_c \times (1 - e^{-\beta X}), \quad (1)$$

where *Pop* is the gridded population for age group a, *Prev* is asthma prevalence for country *c* and age group *a*, *ERV* is the fraction of total number of individuals with asthma visiting the emergency room in the last year for country *c*, β is the concentration–response factor from the meta-analyses of epidemiological studies, and *X* is the gridded pollutant concentration in 2015.

The health impact function for asthma incidence attributable to $PM_{2.5}$ or NO_2 ($\Delta Asthma$) is:

$$\Delta Asthma = Pop_a \times Inc_{c,a} \times (1 - e^{-\beta X}), \quad (2)$$

where *Inc* is the asthma incidence rate for country *c* and age group *a*.

We applied these health impact functions in each $0.1^\circ \times 0.1^\circ$ grid cell globally, separately for each pollutant and concentration–response factor. For estimates of the asthma burden attributable to anthropogenic-only concentrations, we subtracted the gridded

Table 2. Relative risks (RRs), extracted from meta-analyses of epidemiological studies, which were used for estimating asthma impacts [95% confidence intervals (CI) in parentheses]. RRs are reported per 10 $\mu g/m^3$ for $PM_{2.5}$ and per 10 ppb for ozone and NO_2 (RRs reported per 10 $\mu g/m^3$ were converted to RRs per 10 ppb assuming ambient pressure of 1 atmosphere and temperature of 25°C).

Pollutant	Study	Concentration range	Relative Risk – all ages	Relative Risk – pediatric (<18 years)	Relative Risk – adult (18–64 years)	Relative Risk – elderly (65 years and older)	Used?
Short-term exposure and asthma exacerbation							
$PM_{2.5}$	Orellano et al. (2017)	NR	1.03 (1.01–1.05)	–	–	–	Core
	Zheng et al. (2015)	6–45 $\mu g/m^3$	1.02 (1.02–1.03)	1.03 (1.01–1.04)	1.03 (1.01–1.05)	1.02 (1.01–1.03)	Core
	Zhang et al. (2016)	21–46 $\mu g/m^3$	1.01 (1.00–1.03)	1.02 (1.02–1.03)	1.02 (1.01–1.03)	1.02 (1.01–1.03)	Core
	Fan et al. (2016)	8–115 $\mu g/m^3$	–	1.04 (1.02–1.05)	1.02 (1.01–1.03)	–	SA – Pediatric
	Lim et al. (2016)	7–65 $\mu g/m^3$	–	1.05 (1.03–1.07)	–	–	SA – Pediatric
Ozone	Orellano et al. (2017)	NR	1.03 (1.01–1.06)	–	–	–	Core
	Zheng et al. (2015)	2–89 ppb	1.02 (1.01–1.02)	1.02 (1.01–1.02)	1.03 (1.02–1.04)	1.02 (1.00–1.03)	Core
	Zhang et al. (2016)	17–100 ppb	1.05 (1.04–1.07)	1.06 (1.04–1.07)	1.05 (1.00–1.11)	1.05 (1.03–1.06)	Core
NO_2	Orellano et al. (2017)	NR	1.02 (1.01–1.04)	1.04 (1.00–1.08)	–	–	Core
	Zheng et al. (2015)	5–93 ppb	1.03 (1.03–1.04)	1.03 (1.03–1.04)	1.02 (1.01–1.03)	1.04 (1.03–1.05)	Core
	Zhang et al. (2016)	12–77 ppb	1.03 (1.02–1.05)	1.07 (1.05–1.09)	1.02 (0.98–1.07)	1.05 (1.03–1.07)	Core
	Favarato et al. (2014)	2–52 ppb	–	1.12 (1.00–1.22)	–	–	SA – Pediatric
	Weinmayr et al. (2010)	4–90 ppb	–	1.06 (1.00–1.12)	–	–	SA – Pediatric
Long-term exposure and asthma incidence							
$PM_{2.5}$	Anderson et al. (2013)	NR	1.16 (0.98–1.37)	1.34 (0.96–1.86)	–	–	Core
	Jacquemin et al. (2015)	8–34 $\mu g/m^3$	1.08 (0.77–1.51)	–	–	–	Core
	Khreis et al. (2017)	NR	–	1.34 (1.11–1.63)	–	–	Core
	Bowatte et al. (2015)	NR	–	1.93 (1.00–3.71)	–	–	No
	Gasana et al. (2012)	NR	–	1.40 (0.77, 2.56)	–	–	No
NO_2	Anderson et al. (2013)	NR	1.14 (1.04–1.26)	1.10 (1.02–1.20)	1.93 (1.28–2.96)	–	Core
	Jacquemin et al. (2015)	0–62 ppb	1.20 (0.98–1.43)	–	1.08 (0.96–1.21) Age <50	1.02 (0.94–1.12) Age ≥50	Core
	Khreis et al. (2017)	NR	–	1.26 (1.10–1.37)	–	–	Core
	Bowatte et al. (2015)	NR	–	1.18 (0.93–1.48)	–	–	No
	Gasana et al. (2012)	NR	–	1.28 (1.12–1.50)	–	–	No
	Takenoue et al. (2012)	NR	–	1.14 (1.03–1.25)	–	–	No

Note: –, no information was collected at that particular examination point; NR, Not Reported; SA, Sensitivity Analysis.

burden from natural concentrations from the gridded burden using total concentrations.

Uncertainty bounds for health impacts were calculated by applying the 2.5 percentile or 97.5 percentile of the RR estimate, following Anenberg et al. (2010). Each input to the health impact function is uncertain, including estimated concentrations, baseline disease rates, asthma ERV rates, the concentration–response factor, and the existence and magnitude of population-level low-concentration thresholds, below which air pollutants would not affect asthma. Uncertainty estimates are available for some of these variables ($PM_{2.5}$ concentrations, baseline disease rates, concentration–response factor), but not others (ozone and NO_2 concentrations, asthma ERV rates, low-concentration thresholds). For ozone and NO_2 concentrations, output from multiple modeling studies are available at global scales to quantify model variability in concentration estimates. However, this variability reflects differences between models and their parameterizations and not necessarily errors in their concentration estimates, which are more difficult to evaluate globally given the paucity of observational data outside the United States, Europe, and parts of Asia. For this pilot analysis, we simplify the treatment of uncertainty by incorporating only error in the concentration–response functions, as the air pollution–asthma RRs are a key novel aspect of this study and likely to contribute most to differences in results that were calculated separately for each RR. The choice of RR was also found to be the most influential source of uncertainty in estimating the global burden of air pollution on mortality (Ostro et al. 2018). Because our resulting confidence intervals reflect only the error in the concentration–response factor for each epidemiological meta-analysis, reported confidence intervals (CIs) should be interpreted within the context of the larger uncertainty surrounding the entire analysis, as has been cautioned elsewhere (Hubbell et al. 2005). In future work, it should be feasible to generate more comprehensive uncertainty intervals that incorporate error in $PM_{2.5}$ concentrations and baseline disease rates, though additional advances in estimating uncertainty around global ozone and NO_2 concentrations, asthma ERV rates, and other health impact function inputs will be needed to fully characterize uncertainties in the results.

$PM_{2.5}$, Ozone, and *NO_2* Concentrations

We used globally gridded annual average surface $PM_{2.5}$ concentration estimates (maximum concentration 179.8 $\mu g/m^3$) for 2015 at $0.1^\circ \times 0.1^\circ$ resolution developed using information from satellites, a chemical transport model, and *in situ* monitors (van Donkelaar et al. 2016). Aerosol optical depth from multiple satellite products was combined with a simulation using the GEOS-Chem chemical transport model, followed by geographic weighted regression to fuse the $PM_{2.5}$ estimates with *in situ* monitors. The resultant $PM_{2.5}$ estimates were highly consistent ($R^2 = 0.81$) with out-of-sample cross-validated $PM_{2.5}$ concentrations from *in situ* monitors. Although the asthma exacerbation studies examined short-term daily exposures, we used annual average concentrations, following previous studies applying longer-term average concentrations with RR estimates from acute ozone and $PM_{2.5}$ exposures (West et al. 2006; Anenberg et al. 2009; Fann et al. 2012). Using annual average concentrations has several advantages: computational efficiency and the ability to use datasets that assimilate satellite observations with chemical transport models. Because the concentration–response functions applied here are near-linear, using annual averages is not expected to introduce a substantial amount of error. This method is further supported by only 3–8% differences in estimated ozone and $PM_{2.5}$-attributable asthma ERVs when using a linear health impact function in comparison with the log-linear one used in the main results; using a linear model, the sum

of daily impact results estimated using daily concentrations would be equal to annual impacts estimated using annually averaged concentrations.

To estimate asthma ERVs attributable to just the anthropogenic portion of each pollutant, we subtracted the asthma burden from modeled natural background concentrations. Natural background concentrations were simulated using the GEOS-Chem chemical transport model with combustion emissions of all species (including from biomass burning) removed. We considered soil dust concentrations to be natural, although they can be subject to human influence, including from land-use changes, population density, and already-realized influence of anthropogenic climate change.

For ground-level ozone, which is not easily detected using satellites (Martin 2008), we used gridded multimodel mean concentrations for the year 2010 simulated by an ensemble of five chemical transport models organized for Phase 2 of the Task Force on Hemispheric Transboundary Air Pollution (TF HTAP) project (Galmarini et al. 2017): CHASER_re1 (Sudo et al. 2002), CHASER_t106 (Sudo et al. 2002), EMEP_rv48 (Simpson et al. 2012), GEOS-Chem adjoint (Henze et al. 2007), and HadGEM2-ES (Collins et al. 2011). Model configurations and details were described by Galmarini et al. (2017). Concentrations were regridded to a common $0.1^\circ \times 0.1^\circ$ grid and then averaged. We used annual average daily 8-h maximum ozone concentrations (maximum concentration = 72.9 ppb). Using an annual average is consistent with the RR estimates from the meta-analyses, which reported ozone RR estimates for the full year. One meta-analysis found that ozone RR estimates for asthma were similar between warm and cold seasons (Zheng et al. 2015). Because several of the meta-analyses did not distinguish which metric was used to derive the pooled risk estimates, we present results using the daily 8-h maximum because it is between the 24-h average and 1-h maximum in terms of magnitude. Standard deviations in simulated concentrations across the five TF HTAP models were generally greatest in areas with large biomass burning or biogenic influences, because the TF HTAP models only harmonized anthropogenic emissions and not natural emissions (Figure S3).

We used surface NO_2 concentrations (maximum concentration = 17.5 ppb) for 2015 from a dataset developed from satellite observations, following Lamsal et al. (2008). Column NO_2 observations from Ozone Monitoring Instrument (OMI) onboard the Aura satellite were gridded to $0.1^\circ \times 0.1^\circ$ resolution, and satellite-derived ground-level concentrations were estimated using vertical structure from the GMI-Replay chemical transport model. Concentrations are annual average at the Aura satellite sun-synchronous overpass time of ~1:45 P.M. (1345 hours) local time. These concentrations could underestimate actual exposures because midafternoon concentrations are typically at a low point of the diurnal NO_2 concentration cycle, resulting from a combination of fewer emissions between the morning and evening rush hours, high boundary layer heights, and photolysis of NO_2 to NO (Lamsal et al. 2008). We therefore multiplied the satellite-derived exposure estimates by the gridded ratio of 24-h average to 1–2 P.M. (1300–1400 hours) NO_2 concentrations simulated by the GMI-Replay model at $2^\circ \times 2.5^\circ$ resolution for the year 2010 (Figure S3). Resulting NO_2 concentrations used to estimate health impacts are annual average of the 24-h average concentration in each gridcell. Because our $0.1^\circ \times 0.1^\circ$ grid is too coarse to resolve near-roadway concentrations, these concentrations are still likely lower than the measured concentrations used in epidemiological studies focusing on traffic-related air pollution in particular. Because the use of satellite-derived NO_2 concentrations is relatively novel for global health impact assessment, we compared the annual average surface derived from Aura OMI with those derived from the Dutch OMI NO_2 (DOMINO) data product V2.0 (Boersma et al. 2011), finding only minor differences (Figure S3).

Demographics and Baseline Asthma Rates

We used global gridded population of the world from the Center for International Earth Science Information Network (CIESIN) Gridded Population of the World v4 for the year 2015, regridding the 30 arc-second resolution to $0.1^\circ \times 0.1^\circ$ (total population 7.34 billion). We obtained country- and age-specific incidence and prevalence rates for asthma (defined by ICD-10 code J45–J45.5, J45.8–J45.9, and ICD-9 code 493–493.4, 493.8–493.9) from the Institute for Health Metrics and Evaluation (IHME) for 2015 (GBD 2015 Chronic Respiratory Disease Collaborators 2017). The definition of asthma was a reported diagnosis by a physician, with wheezing in the past 12 months, though asthma can also have clinical subphenotypes (Anderson et al. 2013). National asthma incidence and prevalence rates were estimated using the DisMod MR 2.1 modeling tool (earlier version described by Barendregt et al. 2003) with input data from the following sources: WHO Study on Global Aging and Adult Health series, the WHO World Health Survey series, the Belgian Health Interview Survey, studies carried out as part of the International Study of Asthma and Allergies in Childhood (ISAAC) collaboration, claims data in the United States, and other sources for individual countries where available (GBD 2015 Chronic Respiratory Disease Collaborators 2017). In the absence of data from a particular geography (country or in limited cases, subnational administrative regions), information from the parent geography was used. The percentage of geographies with data on asthma rates (65%) was relatively high in comparison with many other diseases, including ischemic heart disease (51%) and COPD (32%). The top five countries for both asthma incidence and prevalence were India, China, Brazil, Indonesia, and the United States, driven largely by population size (GBD 2015 Chronic Respiratory Disease Collaborators 2017). We used the IHME datasets to calculate pediatric (under 18 y), adult (18–64 y), and elderly (65 y and older) populations. Country-specific baseline disease rates are uncertain, particularly in countries where rates were modeled rather than derived empirically (GBD 2015 Chronic Respiratory Disease Collaborators 2017), and estimated pollution-attributable asthma impacts would scale linearly with a change in the baseline disease rate.

We used asthma ERVs as a proxy for asthma exacerbation, though many cases of exacerbation may be self-treated with medication and may not manifest in an ERV. To estimate pollution-attributable asthma ERVs, we constructed a dataset of the rate of ERVs among asthmatics around the world. We conducted a literature review and identified 16 studies surveying health care utilization rates among asthmatics in 54 countries and Hong Kong (Table 1; Allegra et al. 2012; Boonsawat et al. 2015; Corrado et al. 2013; Desalu et al. 2013; Mahboub et al. 2010; Khadadah et al. 2009; Nafti et al. 2009; Neffen et al. 2010; Price et al. 2014; Rabe et al. 2004; Sastre et al. 2016; Su et al. 2013; Thompson et al. 2013; Turktas et al. 2010; Zainudin et al. 2005; Zemedkun et al. 2014). Surveys administered included the Asthma Insights and Reality Survey (AIR), Recognise Asthma and Link to Symptoms and Experience (REALISE), Insights and Management Survey (AIM), and International Asthma Control Test (ACT). The studies reported the rate of ERVs and hospital admissions among study participants, which we used to derive a nationwide rate. For countries where more than one estimate were available from the included studies, we weighted the rates based on study sample size and used this rate for the country-wide rate. We categorized the available country rates by World Health Organization (WHO) regions and World

Bank income categories (WHO 2017c, 2017b) to generate regional rates (average of available national rates weighted by sample size) and applied these to countries without data. In regions where only one estimate was available for the region, the available estimate was applied to all countries with missing data in that region. For low-income countries where no rates were available in the eastern Mediterranean (4 countries), Europe (3), Americas (1), and Southeast Asia (4), we applied the weighted rate from low-middle income countries in that region.

As the data set is not age-specific, we applied the ERV rate among people with asthma uniformly to each age group. The fraction of the total number of people with asthma visiting an emergency department in the last year ranged from 7.9% in France to 52% in Jordan, Kuwait, Lebanon, Oman, and United Arab Emirates, though approximately 60% of locations for which survey data were available had fractions in the 20–40% range (Figures S1 and S2). Estimated pollution-attributable asthma ERVs would scale linearly with a change in this fraction. We used this survey approach to maximize consistency across countries, but the approach is limited by only including approximately one-quarter of countries globally and by small survey sample size in each country. Future studies could explore the utility of combining this information with medical records of ERVs to create a more comprehensive dataset of global asthma-related ERVs. We were unable to develop fractions for a combined category of asthma ERVs and hospital admissions from these survey results; we therefore used ERV fractions with the RRs for combined ERVs and hospital admissions, judging that ERVs are likely to capture more asthma exacerbations in comparison with hospital admissions. The use of ERV fractions with RRs combining ERVs and hospital admissions may overestimate pollution-attributable asthma ERVs but likely underestimates pollution-attributable asthma exacerbations (because pollution-attributable hospital admissions are not calculated).

Results

Globally, we estimated that 9–23 million asthma ERVs among all ages in 2015 were attributable to ozone (Figure 2), 5–10 million were attributable to $PM_{2.5}$, and 0.4–0.5 million were attributable to NO_2 (0.4%; Figure S4), considering both anthropogenic and natural sources of pollution. Respectively, ozone, $PM_{2.5}$, and NO_2-attributable asthma ERVs represented 8–20%, 4–9%, and 0.4% of the 116 million global asthma ERVs in total (Figure 3 and Figure S5). The ranges reflect central RR estimates of three different epidemiological meta-analyses (Orellano et al. 2017; Zhang et al. 2016; Zheng et al. 2015). NO_2 impacts are likely underestimated because our methods do not fully capture near-roadway exposures, which can be $\sim$3 times larger than concentrations less than half a kilometer away (Karner et al. 2010), though there is also likely to be some overlap with the $PM_{2.5}$-attributable asthma ERV estimates. To evaluate the fraction of the burden associated with pollution sources that are more easily controllable, we also examined the influence of anthropogenic-only concentrations by subtracting "natural concentration" (simulated by setting anthropogenic emissions to zero in the chemical transport model) from total concentrations. Results using total concentrations were 2.7 times and 1.4 times higher than impacts of anthropogenic-only concentrations for ozone (3.4–8.3 million asthma ERVs, 3–7% of global total) and $PM_{2.5}$ (3.6–7.3 million asthma ERVs, 3–6%), respectively (Figure S6). The higher impact of total versus anthropogenic concentrations is largely due to sea salt and dust, though some airborne dust is attributable to human influences, such as land-use changes, population density, and potentially already-realized effects of anthropogenic climate change.

We tabulated gridded asthma ERVs by WHO regions. Nearly half (48%) of estimated ozone-attributable and over half (56%) of $PM_{2.5}$-attributable asthma ERVs were estimated in Southeast Asia (includes India), and western Pacific regions (includes China; Figure 2). Larger percentages were estimated in Africa and eastern Mediterranean regions when using total concentrations compared with anthropogenic-only concentrations, driven by high dust concentrations in these regions. Ozone and $PM_{2.5}$ were estimated to be responsible for 6–23% and 1–12%, respectively, of all asthma ERVs regionally, depending on the region and risk estimate applied (Figure 3). For Europe, we estimated that ozone and $PM_{2.5}$ were responsible for 7–18% and 2–4% of asthma ERVs, respectively. The percentage for $PM_{2.5}$ is lower than a previous estimate of 15% attributable to road traffic among children in European cities, which used distance from busy roads as a proxy for pollutant exposure (Perez et al. 2013).

Of all countries globally, India and China had the most estimated asthma ERVs attributable to total air pollution concentrations, respectively contributing 23% and 10% of global asthma ERVs estimated to be associated with ozone, 30% and 12% for $PM_{2.5}$, and 15% and 17% for NO_2 (Figure 4). Comparing $PM_{2.5}$-attributable with ozone-attributable asthma ERVs in each country, whether one of these pollutants dominates over the other in terms of impacts on asthma exacerbation is not clear (Figure 4 and Figure S7). However, in the Americas and in most European countries, ozone appears to exert more influence on asthma ERVs, for both total and anthropogenic concentrations, regardless of the RR estimate applied. In Africa, Southeast Asia, western Pacific regions, and eastern Mediterranean regions, we estimated substantial impacts for both $PM_{2.5}$ and ozone, and which pollutant dominates depends on the RR estimate applied.

We estimated the impacts of air pollution exposure on incident asthma as a secondary analysis, focusing only on pollutants and age groups for which epidemiological meta-analyses reported significant risk estimates: NO_2 exposure among all age groups (all ages, children, and adults), and $PM_{2.5}$ exposure among children (Table 2). Evidence of significant associations between NO_2 and asthma incidence appears relatively consistent across epidemiological meta-analyses (Anderson et al. 2013; Gasana et al. 2012; Khreis et al. 2017; Takenoue et al. 2012) with only one meta-analysis finding an insignificant association for children (Bowatte et al. 2015). However, the evidence for $PM_{2.5}$ is mixed, with two of the four studies in our literature review reporting significant associations with pediatric asthma incidence (Bowatte et al. 2015; Khreis et al. 2017) and two others reporting no significant associations (Anderson et al. 2013; Gasana et al. 2012). In contrast to asthma ERVs for which we estimated impacts of total concentrations as main results, our main results for air pollution-attributable asthma incidence used concentrations above "natural background" levels in each gridcell, because the epidemiological studies focused on within-city variation rather than between-city variation. Using central RR estimates from four epidemiological meta-analyses, we estimated that 400,000 (95% CI: 100,000 to 800,000) to 1.1 million (400,000 to 1.4 million) new pediatric asthma cases could occur globally each year due to anthropogenic NO_2 concentrations (Figure 5). Here, our satellite-derived NO_2 concentration estimates were too coarsely resolved to fully capture high near-roadway concentrations. Although the epidemiological evidence for associations with NO_2 is stronger, our estimates for $PM_{2.5}$-attributable asthma incidence are 1–2 orders of magnitude higher. Using RR estimates from two epidemiological meta-analyses (Anderson et al. 2013; Bowatte et al. 2015), we estimated that 16 million (95% CIs: 9 to 19 million and −5 to 20 million) new pediatric asthma cases could occur globally each year due to anthropogenic $PM_{2.5}$ concentrations, translating to

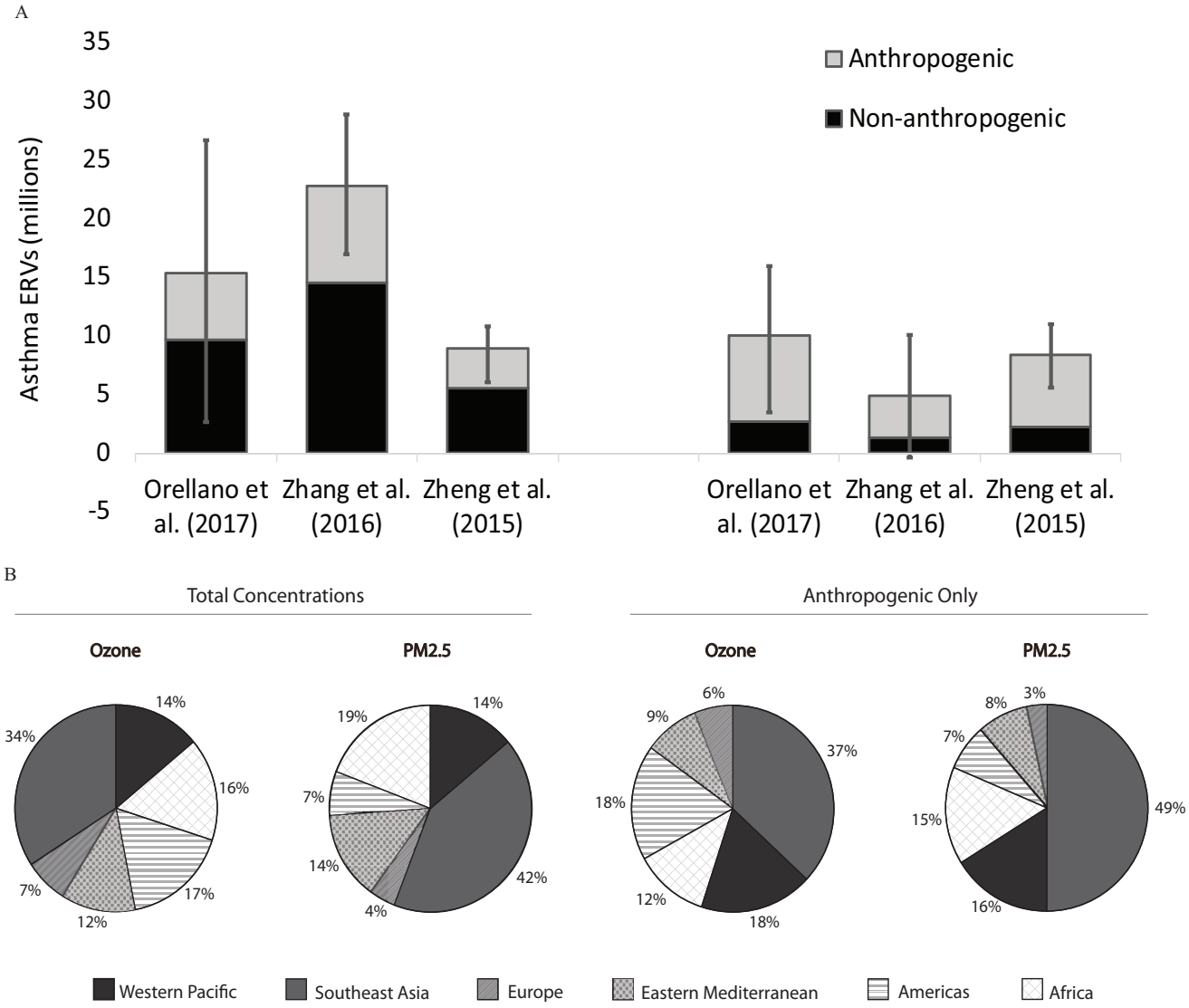

Figure 2. Global asthma ERVs associated with total ozone and $PM_{2.5}$ concentrations among all ages in 2015, using RR central estimates from three epidemiological meta-analyses. (*A*) Asthma ERVs (millions) attributable to ozone and $PM_{2.5}$ from anthropogenic and all sources. Confidence intervals (CI) (95%) reflect uncertainty in RR only. (*B*) Portion of pollution-attributable asthma ERVs occurring in each world region (results identical for all three RR estimates).

33% of global pediatric asthma incidence (Figure S8). The percentage of national pediatric asthma incidence that may be attributable to anthropogenic $PM_{2.5}$ was estimated to be 22% in the United States, 57% in India, 51% in China, and over 70% in Bangladesh (Figure S9). Approximately half of estimated NO_2- and $PM_{2.5}$- attributable new asthma cases were in the Southeast Asia and western Pacific regions (Figure 5). Estimated asthma incidence attributable to NO_2 and $PM_{2.5}$ translate to ~1.7 million DALYs among children (~97% of these attributable to $PM_{2.5}$), adding ~8% to the most recently estimated DALY burden from ambient air pollution among all ages (Cohen et al. 2017). Results are 1.2 and 1.6 times higher when using total concentrations for NO_2 and $PM_{2.5}$, respectively.

Discussion and Conclusions

We estimated that 9–23 million and 5–10 million annual asthma emergency room visits globally in 2015 could be attributable to total ozone and $PM_{2.5}$ concentrations, respectively, corresponding to 8–20% and 4–9%, respectively, of the annual number of global visits. The range reflects the application of central risk estimates from different epidemiological meta-analyses. We estimated that anthropogenic emissions are responsible for approximately 37% of ozone impacts and 73% of $PM_{2.5}$ impacts. The remaining impacts are attributed to naturally occurring ozone precursor emissions (e.g., from vegetation and lightning) and $PM_{2.5}$ (e.g., dust, sea salt), though several of these sources are also subject to human influence from land-use changes, anthropogenic climate changes, and other interactions between humans and the environment. India and China were estimated to contribute 23% and 10%, respectively, of all asthma ERVs attributable to ozone globally, and 30% and 12%, respectively, of those ERVs attributable to $PM_{2.5}$.

These results are subject to a number of important limitations and uncertainties, and estimated pollution-attributable asthma impacts could be overestimated or underestimated as a result. First, we assumed that reported associations between $PM_{2.5}$, ozone, and NO_2 and the asthma exacerbation and incidence outcomes included in our study are causal associations, following previous health impact analyses by the U.S. EPA (U.S. EPA

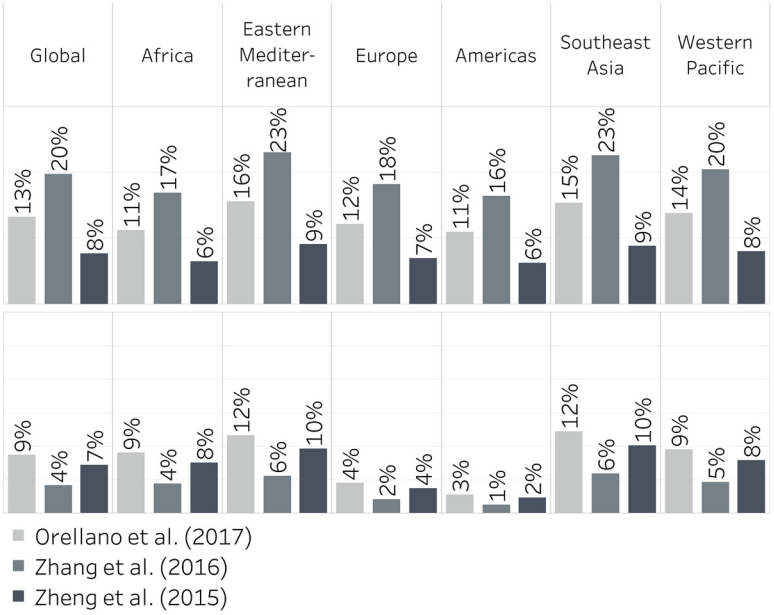

Figure 3. Percent of global and regional asthma ERVs for all ages in 2015 that are attributable to total ozone (top) and $PM_{2.5}$ (bottom) concentrations, using RR central estimates from three epidemiological meta-analyses.

2012, 2015b) and in the literature (e.g., Fann et al. 2012). Although the IHME Global Burden of Disease study considers only health effects of $PM_{2.5}$ and ozone in estimating the ambient air pollution burden of disease, we also considered NO_2, because of the strength and significance of its associations with asthma exacerbation and incidence, and because NO_2 may be a more precise marker of combustion-related pollution, because both $PM_{2.5}$ and ozone can be created by noncombustion sources (e.g., dust, biogenic precursors). As we used single pollutant epidemiological models that did not control for other pollutants, some overlap among ozone, $PM_{2.5}$, and NO_2 impacts is likely (thus causing our pollutant-specific results to together overestimate the burden from combined pollution components) (Winquist et al. 2014). Similar overlap among health impacts attributed to individual pollutants has been identified in previous assessments focusing on mortality effects, for which multipollutant models are available (WHO 2013). Without direct evaluation, the degree of underestimation or overestimation from the effects of pollution mixtures is unknown. Realistically, each of these pollutants may be an indicator of broader pollution mixtures. The magnitude of overlap in asthma ERVs attributable to individual pollutants is currently unquantifiable, though limited evidence suggests that effects of ozone on asthma ERVs could be independent from traffic-related pollution (Strickland et al. 2010). In addition, our reliance on single-pollutant models, though necessary given the lack of available multipollutant models, leads to uncertainty regarding the existence and magnitude of associations between each pollutant and asthma outcomes, because it is possible that reported associations are sensitive to control for copollutants.

Although we included uncertainty in the RR estimates to compare across epidemiological meta-analyses, we were unable to incorporate important uncertainties in other input variables to the health impact function, including asthma ERV rates and concentrations. The country-specific survey data we used to construct the dataset of asthma ERV rates were often limited to a small sample size, ranging from 100 to 5,063 (across multiple studies in Italy). It is not clear whether these population subsets are representative of the general population living with asthma, and given the small sample sizes, these asthma ERV rates are highly uncertain. Variation in asthma ERV rates around the world could be due to differences in asthma prevalence, health services and how they are used, and degree of asthma management, all of which vary worldwide and would realistically affect the number of estimated cases of asthma health end points attributable to air pollution. We also included only asthma ERVs among the asthma group, though the epidemiological studies did not distinguish between asthma ERVs among undiagnosed and diagnosed individuals. Although the percentage of asthma ERVs among people with undiagnosed wheezing is lower than that for individuals diagnosed with asthma, the prevalence of people with undiagnosed wheezing could be large (Gerald et al. 2009; Yeatts et al. 2003). However, some ERVs occurring among people with asthma may not actually be related to asthma, and if this number is substantial, our results could be overestimates.

We also transferred pooled risk estimates and asthma ERV rates to countries with no data, though the meta-analyses used represented a variety of countries on all populated continents except Africa, and ERV rates were from 55 locations on all populated continents. Although extrapolating beyond these countries is necessary in a global assessment, differences in health systems may exist that we were unable to account for (including acute-care delivery and diagnostic practices, population characteristics and behavior, and other factors), that would influence the representativeness of data from one country on another. These surveys may not be adequately nationally representative and could be biased by the age pattern of individuals in the study. Future studies could examine availability and consistency of coded emergency room records from different countries as another data source for this variable. The direction of influence of these uncertainties on estimated pollution-attributable asthma ERVs is unknown. Relying only on asthma ERVs will underestimate the impact of air pollution on asthma exacerbation more broadly, as it excludes hospital admissions and less severe subclinical symptoms, such as respiratory symptoms and lung function decrements (Guarnieri and Balmes 2014).

Another important limitation is the potential mismatch between the exposure metrics we used versus those used in the epidemiology studies. For example, we used the annual average

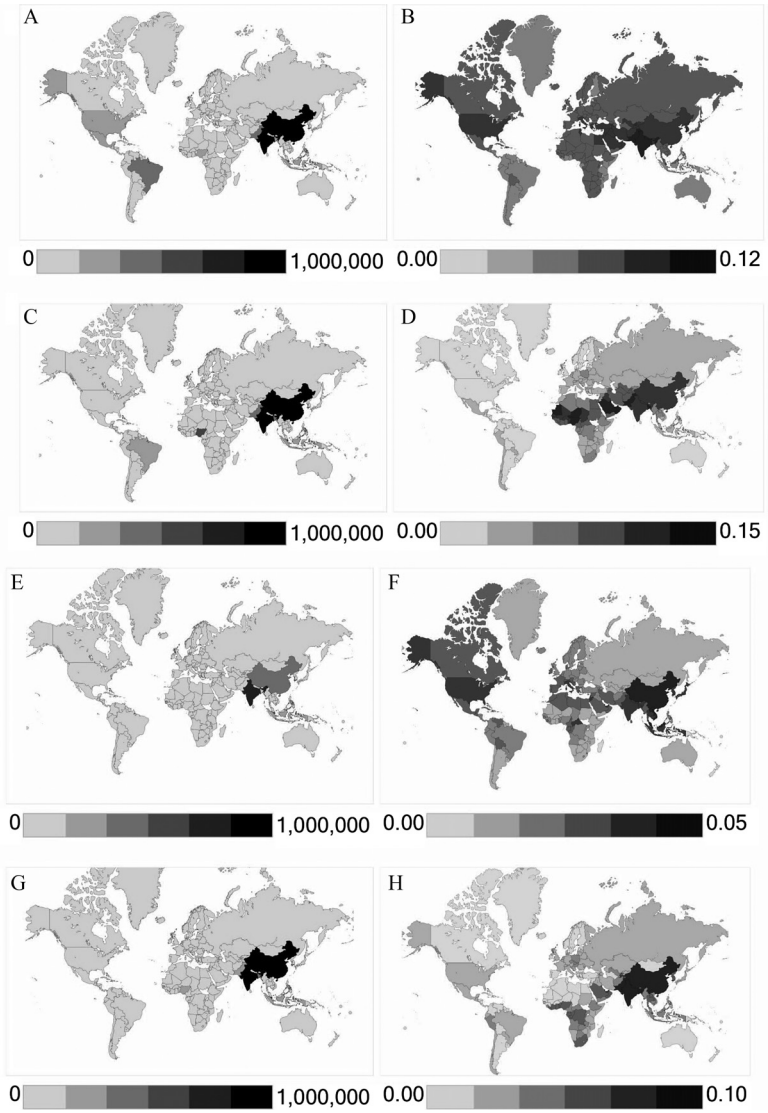

Figure 4. Asthma ERVs attributable to $PM_{2.5}$ and ozone in 2015, using Zheng et al. (2015) RR central estimates. Panels show asthma ERVs attributable to total: (*A*) ozone, number of cases; (*B*) ozone, fraction of national asthma ERVs; (*C*) $PM_{2.5}$, number of cases (*D*) $PM_{2.5}$, fraction of national asthma ERVs. Panels (*E–H*) show the same results but using anthropogenic concentrations.

of the 8-h daily maximum for ozone concentrations, because the meta-analyses did not clarify whether they used 1-h daily maximum, 24-h average, or some other metric. Our results may underestimate ozone asthma impacts if the RR estimates were derived from 1-h daily maximum but may overestimate impacts if the RR estimates were derived from 24-h averages. As has been shown elsewhere, the choice of concentration metric has important implications for health impact assessment (Malley et al. 2017). Additionally, although the asthma-exacerbation epidemiological studies examined daily exposures, following previous studies (e.g., Fann et al. 2012), we used annual average concentrations for computational efficiency and to leverage concentration datasets that assimilate satellite observations with chemical transport models. Using annual averages could lead to error in estimated pollution-attributable asthma ERVs, particularly for locations where daily concentrations are highly variable. Our approach is likely a reasonable approximation in many countries, because the concentration–response functions applied here are near-linear throughout a broad range of concentrations, and our assumption is supported by only 3–8% differences in estimated air pollution-attributable asthma ERVs using a linear model in comparison with the log-linear model used for the core results. However, it is possible that there is an adaptation of individuals to higher-than-average concentrations, such that only short-term fluctuations exacerbate asthma and that constant elevated levels do not. This possibility is not an issue for asthma incidence, which is related to long-term exposure. We used a multimodel ensemble for ozone concentration to leverage multiple model parameterizations, but all models were too coarse to sufficiently capture chemical nonlinearities in ozone formation and loss at urban and suburban scales (e.g., ozone titration). For NO_2, our spatial resolution of $0.1^\circ \times 0.1^\circ$ was too coarse to capture high near-road exposures. We also applied $PM_{2.5}$ concentration–response relationships regardless of particle type or mixture, as is commonly assumed to assess mortality impacts (Cohen et al. 2017). For asthma incidence, we estimated the impacts of $PM_{2.5}$ and NO_2 concentrations above the "natural background" as our main results, because the epidemiological studies focused on effects of within-city concentration variation, rather than between-city variation. This method could still overestimate asthma incidence from air pollution since background concentrations within communities are also influenced by regional anthropogenic emissions.

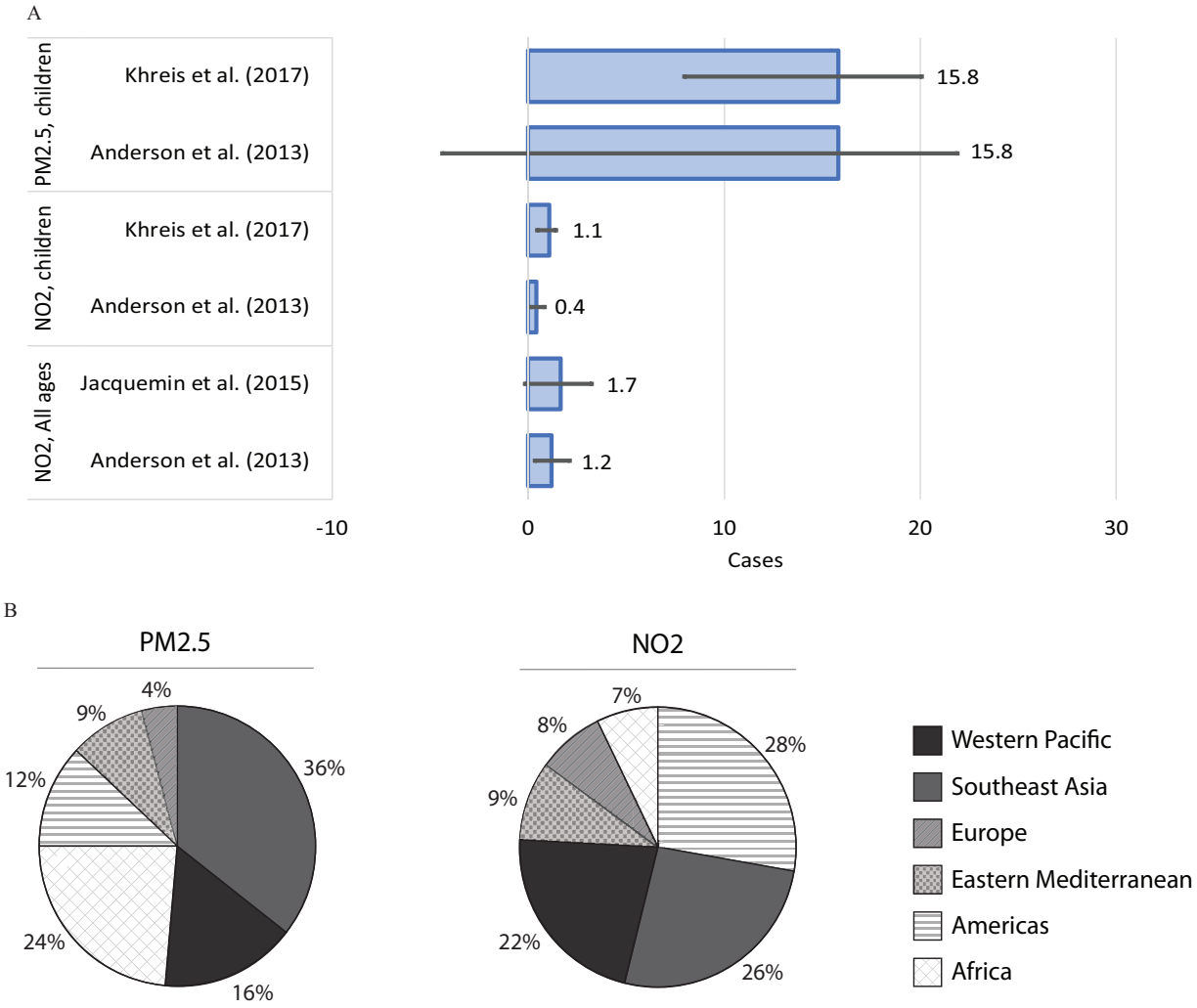

Figure 5. Asthma incidence attributable to anthropogenic $PM_{2.5}$ and NO_2 in 2015. (*A*) Number of new asthma cases (millions) associated with $PM_{2.5}$ and NO_2 for various age groups using RRs from multiple epidemiological meta-analyses. Confidence intervals (CI) (95%) reflect error in the RR estimate only. (*B*) Percent of pollution-attributable new asthma cases among children occurring in each region (for each pollutant, results are identical for all RR estimates applied).

We have provided first estimates of the global burden of ambient air pollution on asthma exacerbation and incidence, though they are subject to many assumptions and data limitations. We anticipate that future studies will further advance the input data and methods piloted here, for example by considering multipollutant epidemiological models. Improved epidemiological data, exposure estimates, and disease rates would enable refinements to analyses of air pollution's contribution to the large global asthma burden. Future studies should also strive to capture asthma impacts from high near-roadway $PM_{2.5}$ and NO_2 exposures at finer spatial scales (Khreis et al. 2018; Larkin et al. 2017). Nevertheless, these first estimates further demonstrate the range of global public health impacts that may be associated with ambient air pollution, already considered the leading environmental health risk factor globally (Cohen et al. 2017; GBD 2016 Risk Factors Collaborators 2017). These estimates also indicate the magnitude of the asthma burden that could be avoided by addressing air pollution.

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