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Updated Global Estimates of Respiratory Mortality in Adults ≥30 Years of Age Attributable to Long-Term Ozone Exposure

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Background: Relative risk estimates for long-term ozone (O_3) exposure and respiratory mortality from the American Cancer Society Cancer Prevention Study II (ACS CPS-II) cohort have been used to estimate global O_3-attributable mortality in adults. Updated relative risk estimates are now available for the same cohort based on an expanded study population with longer follow-up.

Objectives: We estimated the global burden and spatial distribution of respiratory mortality attributable to long-term O_3 exposure in adults ≥30 y of age using updated effect estimates from the ACS CPS-II cohort.

Methods: We used GEOS-Chem simulations ($2\times2.5^\circ$ grid resolution) to estimate annual O_3 exposures, and estimated total respiratory deaths in 2010 that were attributable to long-term annual O_3 exposure based on the updated relative risk estimates and minimum risk thresholds set at the minimum or fifth percentile of O_3 exposure in the most recent CPS-II analysis. These estimates were compared with attributable mortality based on the earlier CPS-II analysis, using 6-mo average exposures and risk thresholds corresponding to the minimum or fifth percentile of O_3 exposure in the earlier study population.

Results: We estimated 1.04–1.23 million respiratory deaths in adults attributable to O_3 exposures using the updated relative risk estimate and exposure parameters, compared with 0.40–0.55 million respiratory deaths attributable to O_3 exposures based on the earlier CPS-II risk estimate and parameters. Increases in estimated attributable mortality were larger in northern India, southeast China, and Pakistan than in Europe, eastern United States, and northeast China.

Conclusions: These findings suggest that the potential magnitude of health benefits of air quality policies targeting O_3, health co-benefits of climate mitigation policies, and health implications of climate change-driven changes in O_3 concentrations, are larger than previously thought. https://doi.org/10.1289/EHP1390

Introduction

Ground-level ozone (O_3) is formed photochemically in the atmosphere from nitrogen oxides, non-methane volatile organic compounds, methane, and carbon monoxide. Ozone exposure has been associated with a range of health impacts, including mortality (REVIHAAP 2013; U.S. EPA 2013). Relative risk estimates based on prospective data from the American Cancer Society Cancer Prevention Study II (ACS CPS-II) have been applied in previous analyses of the global burden of mortality attributable to long-term air pollution exposures. Jerrett et al. (2009) reported a relative risk estimate for respiratory mortality in association with long-term O_3 exposure in the CPS-II cohort (hereafter referred to as J2009), which was subsequently used to derive global estimates of O_3-attributable mortality ranging from 0.15 to 0.49 million deaths per year (Anenberg et al. 2010; Fang et al. 2013b; GBD 2013 Risk Factors Collaborators 2015; GBD 2015 Risk Factors Collaborators 2016; Lim et al. 2012; Silva et al. 2013, 2016a). In contrast, global estimates of mortality attributable to fine particulate matter ($PM_{2.5}$) exposure (from cardiovascular, respiratory, and lung cancer diseases) have been much higher, ranging from 1.6 to 4.2 million per year (Anenberg et al. 2010; Fang et al. 2013b; GBD 2013 Risk Factors Collaborators 2015; GBD 2015 Risk Factors Collaborators 2016; Lim et al. 2012; Silva et al. 2013, 2016a).

Turner et al. (2016) recently reported updated CPS-II cohort estimates of mortality risks associated with long-term O_3 exposure (hereafter referred to as T2016). The updated CPS-II estimates are based on a larger study population with longer follow-up (669,046 participants and 237,201 deaths during 1982–2004) (Turner et al. 2016) than the previous estimates (448,850 participants and 118,777 deaths during 1982–2000) (Jerrett et al. 2009). In addition to the differences noted above, the updated risk estimates reflect other changes from the original study, which are described in detail in Table S1. Importantly, there are differences in the O_3 exposure metric used in either study; in Jerrett et al. (2009), the summer average daily maximum 1-h O_3 concentration was used (average of April–June and July–September values), and in Turner et al. (2016), the annual average daily maximum 8-h O_3 concentration was used.

The purpose of the present analysis is to provide estimates of global respiratory mortality attributable to long-term O_3 exposure based on the updated T2016 relative risk estimate and exposure metric and compare them with estimates derived using the J2009 relative risk estimate and exposure metric. In addition, we report estimates of ozone-attributable deaths due to COPD mortality specifically.

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The evidence from epidemiological and toxicological studies for associations, and causal linkages, between O_3 exposure (short- and long-term) and specific health outcomes has been reviewed by the WHO and U.S. EPA (REVIHAAP 2013; U.S. EPA 2013). For respiratory mortality, REVIHAAP (2013) identified three cohort studies that linked long-term O_3 exposure and relevant outcomes, including respiratory mortality specifically (Jerrett et al. 2009), COPD mortality (Zanobetti and Schwartz 2011), and cardiopulmonary mortality (Smith et al. 2009b). The U.S. EPA (2013) concluded that there was "likely to be a causal relationship between long-term exposure to O_3 and respiratory effects" based on epidemiologic studies of respiratory mortality (Jerrett et al. 2009; Zanobetti and Schwartz 2011), respiratory morbidity (Jacquemin et al. 2012; Lin et al. 2008; Meng et al. 2010; Parker et al. 2009), and toxicological evidence of biologically plausible mechanisms for respiratory effects of O_3, including "pulmonary function decrement and increases in respiratory symptoms, lung inflammation, lung permeability, and airway hyper-responsiveness" (U.S. EPA 2013). Evidence for causal associations of O_3 with specific causes of respiratory mortality is more limited, with stronger evidence from studies of short-term O_3 and hospital admissions for both COPD and asthma compared with pneumonia (Medina-Ramón et al. 2006; U.S. EPA 2013; Zanobetti and Schwartz 2006), although a recent study reported an association between short-term O_3 exposure and hospital visits for pneumonia, as well as COPD (Malig et al. 2016).

Methods

Long-Term O_3 Exposure Estimation

Global gridded ($2\times2.5^\circ$, approximately 221×278 km at the equator) hourly O_3 concentrations were simulated using the GEOS-Chem Chemical Transport Model (Bey et al. 2001) driven by GEOS-5 meteorological fields for 2010 from the Global Modeling and Assimilation Office, with 47 vertical levels defined from the surface up to 0.01 hPa. Simulations used 2010 anthropogenic emissions from the Hemispheric Transport of Air Pollution version-2 inventory (Janssens-Maenhout et al. 2015). The model also considers additional emissions, described in further detail by Lapina et al. (2014), which include biogenic VOCs, soil NO_x, lightning NO_x, and monthly biomass burning emissions.

When estimating attributable deaths globally based on the J2009 relative risk estimates, we used an O_3 exposure metric that was consistent with the premise of the exposure metric for which the J2009 relative risk estimates were derived. Jerrett et al. (2009) used the average daily maximum 1-h O_3 concentration between April and September as the O_3 exposure metric in the United States alone, where O_3 concentrations are highest in spring and summer months. In other regions, the seasonal pattern of O_3 variation is different. To account for variability in the 6-mo period with highest daily maximum 1-h O_3 concentrations across regions, we estimated, for each grid, annual maximum 6-mo average daily maximum 1-h (6mDM1h) O_3 concentrations. The 6mDM1h metric calculated grid-by-grid accounts for differences in seasonal O_3 variation across the globe that affects the timing of the maximum 6-mo O_3 concentration (Anenberg et al. 2010; Silva et al. 2013, 2016a). When estimating attributable deaths using the T2016 risk estimates, we used the annual average daily maximum 8-h O_3 concentration (ADM8h) for each grid, consistent with the analysis from which the relative risk estimates were derived. For each day, 24 eight-hour rolling mean O_3 concentrations were calculated as the average O_3 concentration at the start hour and the following 7 h. The maximum of the 24 eight-hour O_3 concentrations on each day were selected and averaged across the year to derive the ADM8h concentration in each grid.

Exposure–Response Functions

Mortality attributable to long-term O_3 exposure was estimated for 181 countries in 2010 using Equations 1 and 2, consistent with methodologies used to estimate global health impacts of O_3 previously (Anenberg et al. 2010; Silva et al. 2013, 2016a):

$$\Delta\text{Mort} = y_0(1 - \exp^{-\beta\Delta X})\text{Pop}. \quad [1]$$

$$\text{HR} = \exp^{\beta\Delta Y} \quad [2]$$

ΔMort is the change in mortality attributable to long-term O_3 exposure, and was estimated separately for the population in each grid cell covering a particular country. In this study, we estimated ΔMort for each country in 2010 for respiratory mortality [*International Classification of Diseases* (ICD)-10 codes: J00–J98], consistent with the causes of death investigated in Jerrett et al. (2009) and Turner et al. (2016), and separately for chronic obstructive pulmonary disease (COPD) mortality (ICD-10 codes: J19–J46), a subset of respiratory mortality.

Pop. is the exposed population, which was the population in each country $\geq$30 y of age, estimated from UN Population Division population statistics disaggregated by age for each country (https://esa.un.org/unpd/wpp/DataQuery/) because participants in the ACS CPS-II cohort were required to be over 30 y of age at enrollment. The population was distributed to the grids covering each country using population count data for 2010 from the Gridded Population of the World (GPW) version 3 dataset (CIESIN-FAO-CIAT 2005). y_0 is the baseline mortality rate for each cause of death, derived as the ratio of the deaths of people $\geq$30 y of age from the cause and the number of people in each country $\geq$30 y of age estimated by the UN Population Division (https://esa.un.org/unpd/wpp/DataQuery/). For each country, the total number of deaths for each disease category (respiratory and COPD) for the population $\geq$30 y of age in 2010 were from the GBD 2015 estimates derived by the Institute of Health Metrics and Evaluation (GBD 2015 Mortality and Causes of Death Collaborators 2016). Uncertainty in y_0 was derived from the confidence intervals (CIs) reported by GBD 2015 Mortality and Causes of Death Collaborators (2016) for the number of deaths from each cause, as described below.

β is the effect estimate [natural log of the hazard ratio (HR)] for the association between long-term O_3 concentrations and respiratory or COPD mortality (Equation 2). In Jerrett et al. (2009), and Turner et al. (2016), the HRs are reported as the increased hazard of death for a 10-ppb increase in long-term O_3 exposure, which is ΔY in Equation 2. For J2009, in the main analysis we used the ln-HR for a 10-ppb increase in O_3 concentration (6mDM1h metric) from the two-pollutant model adjusted for $PM_{2.5}$ (HR = 1.040; 95% CI: 1.013, 1.067), which has been applied in several previous analyses (Anenberg et al. 2010; Fann et al. 2012; Silva et al. 2013, 2016a; West et al. 2013). For T2016, in the main analysis we used the ln-HR for a 10-ppb increase in O_3 concentration (ADM8h metric) from a model adjusted for near-source $PM_{2.5}$, regional $PM_{2.5}$, and NO_2 (HR = 1.12; 95% CI: 1.08, 1.16). This HR was used to estimate updated long-term O_3-attributable respiratory mortality [using two low-concentration cutoffs (LCCs) to reflect uncertainty in the concentration–response relationship below exposure levels in Turner et al. (2016) (see below)]. T2016 relative risk estimates for COPD mortality also were adjusted for $PM_{2.5}$ (near-source and regional) and NO_2 [HR = 1.14 (95% CI: 1.08, 1.21)].

Finally, ΔX is the long-term O_3 exposure (estimated using GEOS-Chem model output), expressed relative to a threshold exposure (low-concentration cutoff, or LCC), below which we assume there is no effect of O_3 exposure on mortality. The specific LCCs used corresponded to the minimum O_3 exposure or

the fifth percentile of O_3 exposure in the respective ACS CPS-II population on which each set of relative risk estimates (J2009 or T2016) were based because the validity of each risk estimate is uncertain for exposures below the actual levels experienced by each population. For analyses based on J2009 relative risk estimates and the 6mDM1h ozone exposure metric, LCCs for the minimum and fifth percentiles of exposure were set at 33.3 ppb and 41.9 ppb, respectively; for analyses using T2016 relative risk estimates and the ADM8h exposure metric, corresponding LCCs were set at 26.7 ppb and 31.1 ppb. For each grid cell, ΔX was calculated from the GEOS-Chem derived O_3 concentration (O3_GC) as

$$\Delta X = \begin{cases} 0, & \text{if O3_GC} \leq \text{LCC} \\ O3_GC - LCC, & \text{if O3_GC} > \text{LCC} \end{cases} \quad [3]$$

To derive central estimates of long-term O_3-exposure attributable respiratory, and COPD deaths for individual countries, we applied Equation 1 for the population ≥30 y of age assigned to each grid cell covering the country, using the central estimates of β and the national baseline mortality rate (y_0). To account for uncertainty in the relative risk estimate (β) and baseline mortality rates (y_0), we sampled 1,000 estimates of β and y_0 from normal distributions based on the 95% CIs for each variable, applied each resulting value to Equation 1 to derive 1,000 estimates of long-term O_3 attributable deaths, and used the resulting distribution to derive 95% CIs for attributable mortality in each grid cell. Estimates for individual grids were summed to derive national, regional, and global estimates, assuming dependence among the gridded estimates.

Sensitivity analyses were performed to estimate long-term O_3-attributable mortality using T2016 relative risk estimates derived using a single-pollutant model that did not adjust for near-source $PM_{2.5}$, regional $PM_{2.5}$, or NO_2 exposures [HR = 1.14 (95% CI: 1.10, 1.18)]. In addition, we also performed analyses using methods comparable with those used in previous studies to estimate O_3-attributable mortality. This allowed assessment of the consistency of results obtained in those studies, with comparable estimates using the O_3 exposure, baseline mortality, and population data used in this study. To make a direct comparison with the Global Burden of Disease (GBD) analyses, we also further estimated long-term O_3-attributable deaths using comparable methods. Specifically, GBD estimated long-term O_3-attributable deaths associated with chronic obstructive pulmonary disease (COPD) only, using the maximum 3-mo average daily maximum 1-h O_3 concentration, and the single-pollutant J2009 relative risk estimate [1.029 (95% CI 1.010, 1.048)] that was derived for total respiratory mortality (GBD 2013 Risk Factors Collaborators 2015; GBD 2015 Risk Factors Collaborators 2016; Lim et al. 2012).

Results

Globally, O_3 exposure ranged between 13.6 ppb and 84.6 ppb when quantified using the 6-mo daily maximum 1-h concentration (6mDMA1) relevant for the J2009 relative risk estimates, and between 11.3 ppb and 72.6 ppb when quantified as the annual daily maximum 8-h concentration (ADMA8) relevant for the T2016 relative risk estimates (Table 1; see also Figure S1). Both O_3 exposure metrics were elevated across Asia (particularly India and China) compared with other regions (Table 1).

Using the T2016 relative risk estimate (HR = 1.12) and ADM8h concentrations in each grid, we estimated that 1.23 million (95% CI: 0.85, 1.62 million) respiratory deaths among the global population ≥30 y of age were attributable to long-term O_3 exposure in 2010 using the minimum exposure in the T2016 cohort (26.7 ppb) as the low-concentration cutoff (LCC), and 1.04 million deaths (95% CI: 0.72, 1.37 million) using the fifth percentile LCC (31.1 ppb) (Table 2). Attributable deaths estimated using the T2016 relative risk estimate and the fifth percentile LCC represent 20.3% (95% CI: 14.5, 26.9%) of all respiratory deaths among those ≥30 y of age in 2010. In contrast, using the J2009 relative risk (HR = 1.04) and 6mDM1h concentrations, we estimated 0.55 million (95% CI: 0.20, 0.90) deaths attributable to long-term O_3 in 2010 using the minimum exposure in the J2009 cohort as the LCC (33.3 ppb) and 0.40 million (95% CI: 0.14, 0.65) million attributable respiratory deaths using the fifth percentile LCC (41.9 ppb).

The majority (79–81%) of our estimated long-term O_3-attributable respiratory deaths using the T2016 relative risk estimates were in Asia (Table 2, Figure 1), predominantly in India and China [37–39% of the global total for India depending on the LCC, and 26% for both LCCs for China (Table 2)]. Applying the T2016 relative risk estimates increased estimated long-term

Table 1. Range of O_3 concentrations (ppb) in grids covering world regions and selected countries estimated from GEOS-chem model simulations.

Region	Metric	Minimum	5th percentile	25th percentile	Median	75th percentile	95th percentile	Maximum
Asia	6mDMA1	13.6	26.5	50.4	59.2	66.1	75.9	84.0
	ADMA8	11.7	23.5	42.4	50.4	57.2	66.1	72.6
China	6mDMA1	46.2	51.7	59.9	64.4	70.2	78.5	84.0
	ADMA8	40.9	43.7	50.6	54.5	59.6	67.7	72.6
India	6mDMA1	36.1	45.0	62.4	67.2	73.2	78.3	80.1
	ADMA8	30.7	36.5	50.8	57.9	64.7	70.7	72.6
Europe	6mDMA1	36.9	38.7	40.2	42.6	48.9	57.8	66.0
	ADMA8	30.3	33.5	35.0	37.8	41.1	48.9	54.3
Africa	6mDMA1	25.8	34.7	44.6	50.2	56.3	67.4	84.6
	ADMA8	20.2	29.3	37.5	43.2	47.8	53.4	59.6
Latin America and the Caribbean	6mDMA1	15.8	22.3	29.9	38.7	49.5	59.0	78.5
	ADMA8	11.3	15.6	24.5	32.3	39.7	50.1	62.6
North America	6mDMA1	39.3	39.8	41.4	43.8	51.7	64.8	77.3
	ADMA8	34.1	35.6	37.0	39.4	44.0	54.4	58.8
United States	6mDMA1	39.6	40.3	43.3	51.8	60.1	68.8	77.3
	ADMA8	34.1	36.3	38.6	44.5	50.9	55.6	58.8
Oceania	6mDMA1	13.6	18.5	25.8	33.0	35.9	38.0	40.3
	ADMA8	11.7	15.0	20.1	29.2	32.7	34.5	37.6
Global	6mDMA1	13.6	26.8	39.8	44.8	54.8	68.9	84.6
	ADMA8	11.3	22.5	34.4	39.0	46.3	58.2	72.6

Note: The range of the maximum 6-mo daily maximum 1-h O_3 concentration (6mDMA1, relevant for J2009 relative risk estimates), and the annual average daily maximum 8-h concentrations (ADMA8, relevant for T2016 relative risk estimates) are shown. Ranges for China and India are shown because of the large health impacts estimated in these countries. Ranges from the United States are also shown because this is where the Jerrett et al. (2009) and Turner et al. (2016) studies were conducted.

Table 2. Global and regional estimates of respiratory deaths attributable to long-term O_3 exposure for adults ≥30 y of age.

Region	Estimates based on J2009[a]		Estimates based on T2016[b]		
	Low-concentration cutoff[c]	Attributable respiratory deaths J2009 (thousands)	Low-concentration cutoff[c]	Attributable respiratory deaths T2016 (thousands)	Proportion of total respiratory deaths (T2016 estimates, %)
Asia	33.3 ppb	430 (161, 699)	26.7 ppb	970 (686, 1,253)	28.0 (19.2, 35.8)
	41.9 ppb	328 (120, 536)	31.1 ppb	844 (593, 1,095)	24.3 (17.1, 31.9)
China	33.3 ppb	154 (59.9, 248)	26.7 ppb	316 (230, 403)	28.0 (20.5, 35.9)
	41.9 ppb	120 (45.6, 195)	31.1 ppb	274 (198, 351)	24.2 (17.2, 31.3)
India	33.3 ppb	193 (74.8, 311)	26.7 ppb	450 (329, 572)	32.2 (23.5, 41.3)
	41.9 ppb	151 (57.2, 246)	31.1 ppb	402 (291, 513)	28.7 (20.0, 37.3)
Europe	33.3 ppb	39.2 (13.9, 64.5)	26.7 ppb	78.9 (54.2, 104)	15.0 (10.4, 19.7)
	41.9 ppb	22.5 (7.7, 37.2)	31.1 ppb	55.9 (38.1, 73.8)	10.6 (6.9, 14.1)
Africa	33.3 ppb	33.6 (6.6, 60.6)	26.7 ppb	80.6 (37.1, 124)	15.9 (7.5, 24.6)
	41.9 ppb	18.8 (3.6, 34.1)	31.1 ppb	59.6 (27.5, 91.6)	11.7 (5.8, 19.1)
Latin America and the Caribbean	33.3 ppb	14.5 (5.1, 23.9)	26.7 ppb	39.9 (27.4, 52.4)	12.0 (8.2, 15.4)
	41.9 ppb	6.5 (2.3, 10.8)	31.1 ppb	27.2 (18.6, 35.7)	8.2 (5.4, 10.8)
North America	33.3 ppb	30.1 (11.5, 48.7)	26.7 ppb	63.8 (46.3, 81.3)	23.9 (17.3, 30.6)
	41.9 ppb	22.0 (8.2, 35.8)	31.1 ppb	53.5 (38.4, 68.5)	20.0 (14.5, 25.8)
Oceania	33.3 ppb	0.2 (0.06, 0.28)	26.7 ppb	1.0 (0.7, 1.3)	3.7 (2.4, 5.3)
	41.9 ppb	0[d]	31.1 ppb	0.4 (0.3, 0.6)	1.5 (1.0, 2.1)
Global	33.3 ppb	547 (198, 897)	26.7 ppb	1,234 (851, 1,616)	24.0 (16.9, 31.7)
	41.9 ppb	398 (142, 654)	31.1 ppb	1,040 (716, 1,365)	20.3 (14.5, 26.9)

Note: Estimates were calculated using relative risk estimates for long-term O_3 exposure and respiratory mortality derived in Jerrett et al. (2009) and Turner et al. (2016) and are also reported as a proportion of all respiratory deaths for the population aged ≥30 y in each region. Values in parentheses are 95% confidence intervals.
[a]J2009 estimates use HR = 1.040 (95% CI: 1.013, 1.067) as the relative risk estimate and the maximum 6-mo daily 1-h maximum O_3 concentration as the exposure metric (Jerrett et al. 2009).
[b]T2016 estimates use HR = 1.12 (95% CI: 1.08, 1.16) as the relative risk estimate and the annual daily 8-h maximum ozone concentration as the exposure metric (Turner et al. 2016).
[c]Lower value is the minimum ozone concentration, and the upper value is the 5th percentile of the ozone concentration for the population and ozone metric used to derive the J2009 and T2016 relative risk estimates.
[d]Estimated maximum 6-mo O_3 concentrations did not exceed the 5th percentile low-concentration cutoff in Oceania, and therefore no long-term O_3-attributable respiratory deaths were estimated.

O_3- attributable respiratory deaths everywhere in the world (Figure 2a), compared with the J2009 relative risk estimates (see Figure S2), reflecting the common increase in the HR. However, the increase in HR was offset to a different degree in different regions by the size of the decreases in the magnitude of the long-term O_3 exposure metric when quantified over the whole year (T2016) rather than 6 mo (J2009), and expressed as a daily 8-h maximum (T2016) rather than as a 1-h maximum (J2009). In those regions with relatively large reductions in the magnitude of the O_3 metric (Figure 2c), the increase in estimated attributable respiratory deaths was smaller than in those regions with a smaller reduction in the O_3 metric (Figure 2b). For example, there were larger reductions in the O_3 exposure metric, and smaller increases in estimated attributable respiratory deaths, at northern midlatitudes (eastern United States, northeast China, and central and northern Europe), compared with other regions (e.g., northern India). The spatial differences in the magnitude of the all-year compared with 6-mo metrics reflects different seasonal variability in O_3 concentrations at northern midlatitudes, compared with other regions (Monks et al. 2015).

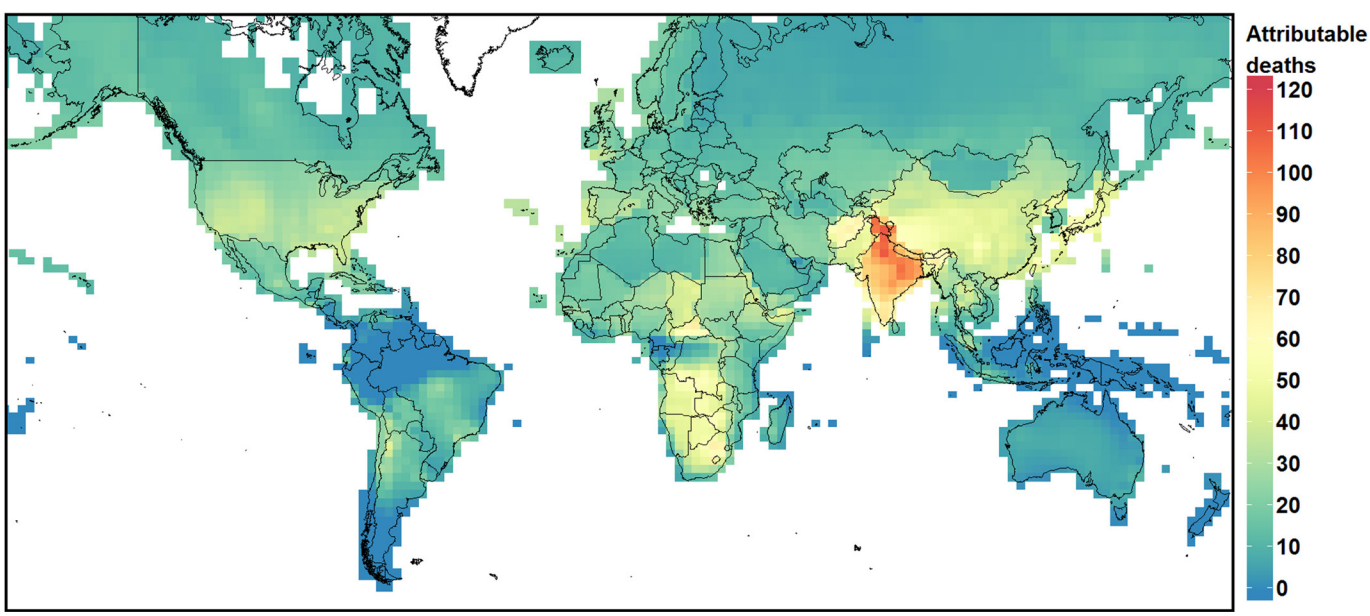

Figure 1. Estimated long-term O_3-exposure attributable respiratory deaths in 2010 for adults ≥30 y of age. Units are attributable deaths per 100,000 people, and estimates were derived using the T2016 relative risk estimate [HR = 1.12 (95% CI: 1.08, 1.16), adjusted for near-source and regional $PM_{2.5}$, and NO_2 exposure] and annual average daily maximum 8-h O_3 concentration as the O_3 exposure metric, with a low-concentration cutoff set at the minimum exposure in the Turner et al. (2016) cohort (26.7 ppb) (Map Data: © EuroGeographics for the administrative boundaries).

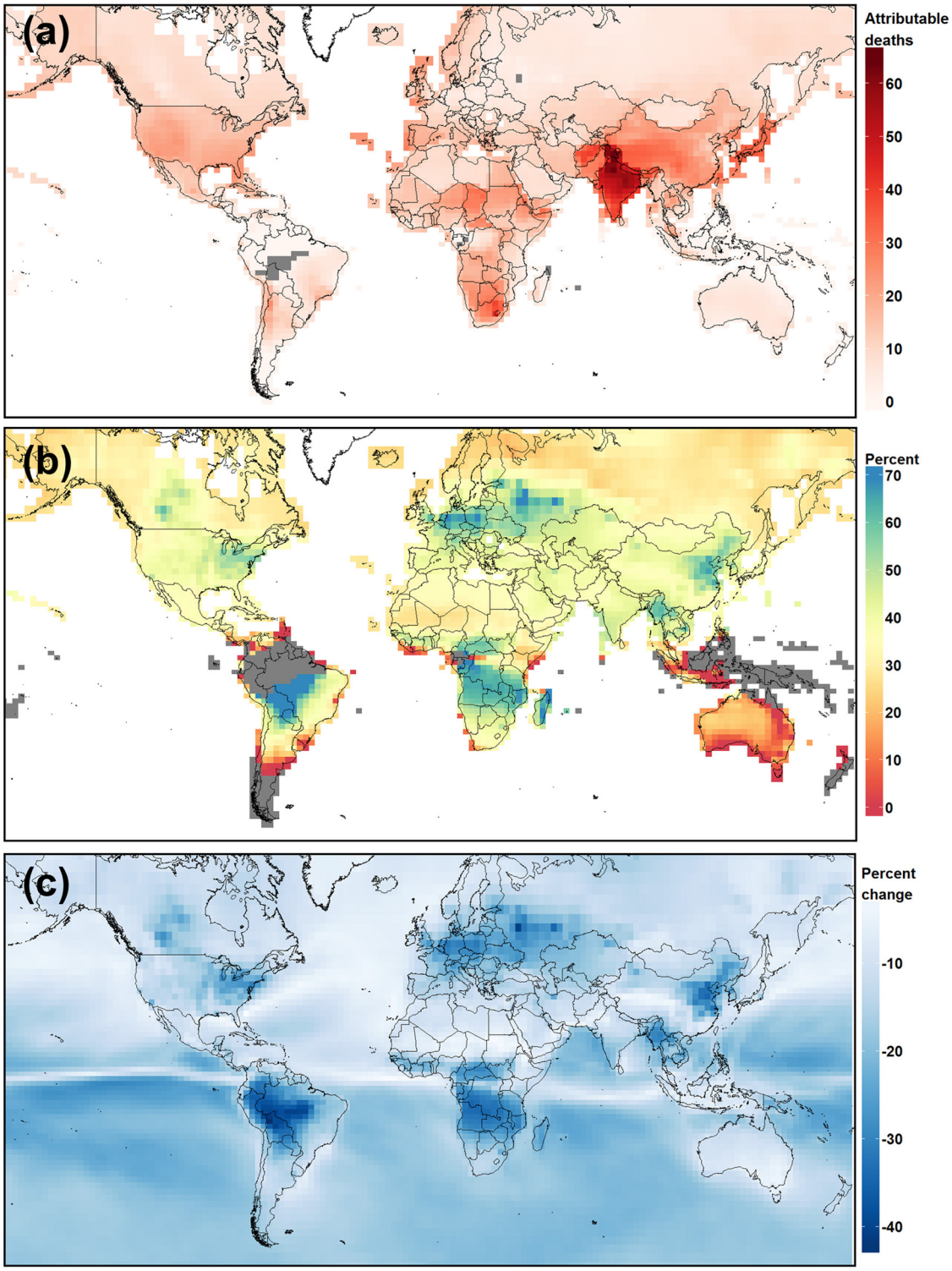

Figure 2. Spatial distribution of changes in estimated long-term O_3-attributable respiratory deaths when using the J2009 relative risk estimates [HR = 1.04 (95% CI: 1.013, 1.067), adjusted for total $PM_{2.5}$ exposure] and 6-mo daily maximum 1-h concentration as the O_3 exposure metric (33.3-ppb low-concentration cutoff), and T2016 relative risk estimates [HR = 1.12 (95% CI: 1.08, 1.16), adjusted for near-source and regional $PM_{2.5}$, and NO_2 exposure] and annual average daily maximum 8-h concentration as the O_3 exposure metric (26.7-ppb low-concentration cutoff). (*a*) shows the absolute difference in attributable respiratory deaths per 100,000 people estimated using the J2009 and T2016 relative risk estimates. (*b*) shows the percent of T2016-based attributable respiratory death estimates accounted for by J2009-based attributable respiratory deaths estimates (colder colors indicate a smaller increase in estimated O_3-attributable respiratory deaths when calculated using the T2016 relative risk estimate, warmer colors indicate a larger increase). (*c*) shows the percent decrease in the magnitude of the long-term O_3 exposure metric when using the annual average daily maximum 8-h metric (relevant for T2016 relative risk estimates), compared with the maximum 6-mo average daily maximum 1-h metric (relevant for J2009 relative risk estimates). Gray areas in each panel indicate those grids where the 6-mo or annual O_3 exposure metric was below the LCC, and therefore no O_3-attributable respiratory deaths were estimated (Map Data: © EuroGeographics for the administrative boundaries).

In addition, the T2016 relative risk estimates were also applied with different LCCs compared with the J2009 relative risk estimates. The use of an annual metric to characterize population O_3 exposure compared with a 6-mo metric shifts the distribution of the O_3 exposure metric in different regions, including in relation to the relevant LCCs. For example, the median ADM8h concentration across all grids globally was 46% greater than the minimum exposure LCC (26.7 ppb), compared with 35% greater for the median 6mDM1h concentration (33.3 ppb LCC), that is, a 33% larger exceedance of the minimum exposure LCC for the median ADM8h metric (Table 1). However, in Asia the exceedance of the LCC for the median ADM8h concentration was only 14% greater than for the median 6mDM1h concentrations, compared with 49% and 51% in Europe and North America, respectively (Table 1). Hence in different regions the change in the extent to which the O_3 exposure metrics exceed the LCC differs and contributes to regional differences in the increase in estimated O_3-attributable respiratory mortality when applying the T2016 relative risk estimates.

We performed a sensitivity analysis of estimated O_3-attributable respiratory deaths using a T2016 relative risk estimate derived from a single-pollutant model, instead of the multi-pollutant adjusted estimate used for the primary analyses. Estimated numbers of ozone-attributed respiratory deaths based on the single-pollutant model relative risk estimates were approximately 13% higher than the estimates derived using the multi-pollutant model relative risk estimates (see Table S2).

The O_3-attributable respiratory mortality estimates using the J2009 relative risk estimate, as described above (HR = 1.040; 95% CI: 1.013, 1.067; 33.3 ppb and 41.9 ppb LCCs), were comparable with previous estimates in Anenberg et al. (2010), Fang et al. (2013b), Silva et al. (2013), and Silva et al. (2016a) (see Table S4). In comparison with previous estimates of long-term O_3 attributable mortality by the Global Burden of Disease (GBD) project, our estimates using GBD-comparable inputs to Equation 1 (i.e., estimating O_3-attributable COPD mortality using the J2009 single-pollutant relative risk estimate for respiratory mortality and maximum 3-mo daily maximum 1-h O_3 exposure metric) had overlapping confidence intervals with GBD 2010, GBD 2013, and GBD 2015 long-term O_3-attributable deaths (GBD 2013 Risk Factors Collaborators 2015; GBD 2015 Risk Factors Collaborators 2016; Lim et al. 2012), but our central estimates were higher (see Table S3). Differences in the magnitude of O_3 exposure estimates, derived from the Tracer Model v5-FAst Scenario Screening Tool model in GBD (Brauer et al. 2016) and GEOS-Chem here, may contribute to this discrepancy. For example, in India and China, population-weighted 3-mo maximum daily 1-h concentrations were 5% (1.1-ppb), and 22% (14-ppb) higher for GEOS-Chem, respectively. Further work is required to evaluate the performance of both models in these regions, which have the largest estimated health burden, although currently there is relatively low number and spatial density of monitoring sites in these regions to achieve this (Cooper et al. 2014).

Application of the T2016 relationships for COPD mortality specifically resulted in an estimated 0.86 million (95% CI: 0.53, 1.18 million) O_3-attributable COPD deaths across the global population ≥30 y of age in 2010 using the minimum exposure in the T2016 cohort (26.7 ppb) as the LCC, and 0.74 million deaths (95% CI: 0.45, 1.02 million) using the fifth percentile LCC (31.1 ppb) (see Table S4, Figure S3). This indicates that estimated O_3-attributable COPD deaths were approximately 70–71% of total estimated O_3-attributable respiratory deaths. Hence, even when only focusing on COPD, long-term O_3 health impacts may be more significant than previously estimated [e.g., global long-term O_3 COPD deaths estimated by GBD 2015 were 6% of $PM_{2.5}$-associated attributable deaths, whereas our estimates using T2016 relationships are 17–20% of this $PM_{2.5}$-attributable death estimate (GBD 2015 Risk Factors Collaborators 2016)].

Discussion

Results of this study estimating the global burden and spatial distribution of long-term O_3 exposure on mortality applying the revised T2016 relative risk estimates estimated 1.04–1.23 million respiratory deaths among the global population ≥30 y of age were attributable to O_3 exposure in 2010. The more than doubling of estimated long-term O_3-attributable respiratory deaths obtained using the T2016 compared with J2009 relative risk estimates (0.40–0.55 million attributable respiratory deaths) increases the estimated contribution of O_3 to the global outdoor air pollution health burden. The respiratory mortality results for O_3 are 25–29% of the 4.2 million deaths estimated to be attributable to $PM_{2.5}$ exposure by the Global Burden of Disease (GBD) (GBD 2015 Risk Factors Collaborators 2016).

Previous long-term O_3 attributable mortality estimates have used O_3 exposure over a 6-mo period for consistency with the O_3 exposure estimates in Jerrett et al. (2009) (Anenberg et al. 2010; Fang et al. 2013b; Silva et al. 2013, 2016a) (the GBD studies have applied the J2009 relative risk estimates using a 3-mo metric (Brauer et al. 2016; Cohen et al. 2017)). The 3- and 6-mo metrics previously applied to estimate long-term O_3 health burdens do not account for O_3 exposure that occurs during the rest of the year, which varies differently between regions. For example, at northern midlatitudes, including North America, Europe, and northeast China, there is substantial annual O_3 variation, with a peak during spring months. In contrast, closer to the equator, there is less annual variation in O_3 concentrations (Monks et al. 2015). Hence annual averaged O_3 concentrations are substantially lower than 3- or 6-mo concentrations at northern midlatitudes compared with closer to the equator (Figure 2, Table 1). This work shows that when O_3 exposure across the whole year is taken into account the spatial distribution of estimated O_3-attributable respiratory mortality shifts in from the northern midlatitudes towards the equator, compared with previous analyses that quantified O_3 exposure only during part of the year. Consequently, the relative increase in estimated long-term O_3 attributable respiratory mortality using the T2016 compared with J2009 method was 134–165% for India, compared with 105–128% for China, 112–143% for North America and 101–148% for Europe.

The T2016 relative risk estimates used in the present analysis were derived using improved O_3 exposure estimates that combined monitored data with photochemical model output (Turner et al. 2016). In addition, we used T2016 relative risk estimates from multi-pollutant models adjusted for NO_2 and for "near-source" and "regional" $PM_{2.5}$ that have different correlation structures with O_3. In contrast, previous global estimates of long-term O_3-attributable deaths used J2009 relative risk estimates from a single-pollutant model [e.g., GBD 2015 Risk Factors Collaborators 2016), or a multi-pollutant model adjusted for total $PM_{2.5}$ concentrations only (e.g., Anenberg et al. (2010)], but within which there was a moderate correlation between O_3 and $PM_{2.5}$ exposure estimates. Hence the long-term O_3-attributable death estimates presented in this work should be more independent of health burdens associated with exposure to $PM_{2.5}$ and NO_2.

Additionally, the consistency of the association between exposure to fine particulate matter ($PM_{2.5}$) and mortality in multiple ACS CPS-II cohort analyses to different estimates of O_3 exposure suggests that the stronger relationship between long-term O_3 exposure and attributable mortality in Turner et al. (2016) may

represent an additional contribution to the outdoor air pollution health burden, as opposed to a reattribution of $PM_{2.5}$-associated premature deaths to long-term O_3 exposure. For example, the relative risk estimates derived in Turner et al. (2016) between long-term $PM_{2.5}$ exposure and all-cause mortality [HR for a 10-$\mu g\ m^{-3}$ increase in $PM_{2.5}$ concentration, single-pollutant model: 1.07 (95% CI: 1.06, 1.09) multipollutant model using alternative estimate of $PM_{2.5}$ exposure: 1.06 (95% CI: 1.04, 1.08)] was similar to that derived in the Krewski et al. (2009) [HR: 1.06 (95% CI: 1.04, 1.08)], and Pope et al. (2002) [HR: 1.06 (95% CI: 1.02, 1.11)] analyses of the ACS CPS-II cohort.

Turner et al. (2016) also calculated a significant association with cardiovascular mortality in addition to the significant association calculated between long-term O_3 exposure and respiratory mortality. This is in contrast to Jerrett et al. (2009) where a significant inverse relationship between long-term O_3 exposure and cardiovascular mortality was calculated. The evidence for associations, and causal linkages, between long-term O_3 exposure and cardiovascular mortality has been reviewed by the WHO and the U.S. EPA (REVIHAAP 2013; U.S. EPA 2013). REVIHAAP (2013) identified three cohort studies that estimated a significant relationship between long-term O_3 exposure and mortality, which includes, or is a subset of, cardiovascular mortality. One study calculated an association with ischemic heart disease (IHD) (Lipsett et al. 2011), one study with cardiopulmonary disease (Smith et al. 2009a), and one with congestive heart failure (Zanobetti and Schwartz 2011). Based on the evidence from a limited number of epidemiological and toxicological studies, the U.S. EPA concluded that the available evidence is only "suggestive of a causal relationship between long-term exposure to O_3 and cardiovascular effects" (U.S. EPA 2013), whereas Prueitt et al. (2014) concluded that the evidence from epidemiological, and human and animal toxicological studies is "below equipoise," that is, not sufficient to conclude that a causal relationship is as least as likely as not. Hence because the evidence for a causal association between long-term O_3 exposure and cardiovascular mortality is limited compared with respiratory mortality, we did not estimate the global impact of long-term O_3 exposure on cardiovascular mortality. However, if additional evidence shows that the T2016 relative risk estimate between long-term O_3 exposure and cardiovascular mortality is valid (Schwartz 2016), then the inclusion of cardiovascular mortality would increase the estimated O_3 health burden further.

Uncertainties

Limitations of this study include estimation of long-term O_3 exposure using a single global chemistry transport model at global grid resolution ($2 \times 2.5^\circ$, 221×278 km at the equator), that does not account for local-scale variability in O_3 concentrations (Monks et al. 2015). However, previous studies indicate only a modest effect of grid spatial resolution on O_3 attributable mortality estimates because the spatial gradients in O_3 concentrations are typically smoother than those of population distribution. Punger and West (2013) calculated a less than 6% increase in O_3 attributable mortality estimates in the United States, when derived using modeled O_3 concentrations at a 100–400 km grid scale compared with the finest (12 km) resolution. Furthermore, using GEOS-Chem, we obtained similar long-term O_3-attributable death estimates to previous studies using consistent methods (including the GBD, see Table S3), based on J2009 relationships, including those using chemical transport models with finer grid resolution (see Table S3).

Compared with 1,420 monitoring sites globally (85% of which were in the United States), a mean bias of $+10.8$ ppb was calculated for GEOS-Chem, which was consistent with biases estimated in other global models as part of multi-model comparison projects (Yan et al. 2016). This bias was identified by Yan et al. (2016) to be partly due to small scale nonlinear chemical processes that are not captured at the grid resolution of the GEOS-Chem model used here. Similarly, in China, where some of the highest health burdens were estimated, a positive bias was calculated in comparison with available measurements, for example, Zhu and Liao (2016): mean bias of $+11.6\%$ based on monitoring data from 10 Chinese sites (i.e., GEOS-Chem modeled O_3 concentrations were on average 11.6% higher than the measured concentration), and Lou et al. (2014): mean bias of $+9\%$ compared with data from 12 Chinese sites. Hence, accounting for these smaller-scale nonlinear processes in the GEOS-Chem global model, and in global models in general, may therefore yield somewhat lower estimates of O_3 exposure than estimated in this study. Ongoing efforts to harmonize and synthesize available measurement data worldwide will be particularly useful to extend model-measurement comparison with other regions (including those with the highest estimated O_3 health burdens) (Cooper et al. 2014; http://www.igacproject.org/TOAR), as is further work to increase global monitoring data coverage. Further evaluation of modeled O_3 exposure estimates through inter-model and measurement comparisons is also warranted.

Consistent with previous analyses of the GBD, we used relative risk estimates derived from a U.S. cohort to estimate mortality attributable to long-term O_3 exposure throughout the world. This assumes that the relative risk estimates for the ACS CPS-II population are transferable to all populations globally, for which the prevalence of other risk factors for respiratory mortality, such as socioeconomic status, access to health care, nutrition, race/ethnicity, education, and other competing risks may be different from the predominantly white, high-school educated CPS-II cohort population. Although Turner et al. (2016) adjusted for many of these confounders in analyzing the ACS CPS-II cohort, a limitation of this study is the application of the T2016 relative risk estimates to populations where the distribution of these risk factors is likely to be substantially different from the distribution across the ACS CPS-II population. The two European cohort studies that have assessed long-term O_3 exposure and mortality estimated null or negative associations between O_3 exposure and respiratory mortality (Bentayeb et al. 2015; Carey et al. 2013), and no such cohort studies have been conducted outside North America and Europe (Atkinson et al. 2016). In some regions, our modeled annual daily maximum 8-h O_3 concentrations (Table 1; see also Figure S1) were higher than for the Turner et al. (2016) cohort (maximum estimated exposure of Turner et al. (2016) cohort: 59.3 ppb). The T2016 HRs for ozone and mortality reported by Turner et al. (2016) were based on estimated O_3 exposures in the United States during 2002–2004, at the end of a 24-y period during which O_3 precursor emissions decreased substantially in the United States (Simon et al. 2015). Their application to regions with increasing O_3 precursor emissions since the 1980s is therefore uncertain (Monks et al. 2015). Further investigation is required to determine the relationship between changing long-term O_3 exposure and mortality in regions with increasing emissions.

Finally, potential interactions between exposure to O_3 and other pollutants (e.g., $PM_{2.5}$) and impacts on mortality were not considered by Turner et al. (2016). Hence long-term O_3-attributed mortality estimates reported here assume independence of effects of each pollutant. As additional epidemiological data becomes available on potential interactions between exposure to O_3 and $PM_{2.5}$ (and other pollutants), or on the transferability of effect estimates between regions, long-term O_3-attributable mortality estimates should be updated to account for the improved understanding of these aspects of O_3 impacts on mortality.

Conclusions

To evaluate the overall outdoor air pollution health burden, mortality attributable to O_3 and $PM_{2.5}$ exposure has been estimated at global (Anenberg et al. 2010; Fang et al. 2013b; GBD 2013 Risk Factors Collaborators 2015; Lelieveld et al. 2015; Likhvar et al. 2015; Silva et al. 2013), regional (Crippa et al. 2016), and national scales (Caiazzo et al. 2013; Fann et al. 2012; Kim et al. 2015), and many studies have used relative risk estimates derived from the ACS CPS-II cohort (Jerrett et al. 2009) to estimate mortality attributable to ozone air pollution in adults ≥30 y of age. Our findings suggest that the potential impact of long-term O_3 exposure on respiratory mortality is substantially higher when respiratory deaths attributable to long-term O_3 exposure are estimated using updated relative risks, exposure metrics, and low-concentration thresholds from the ACS CPS-II cohort (Turner et al. 2016). We estimated 1.04–1.23 million long-term O_3 attributable respiratory deaths using the updated assumptions, a 126–161% increase from estimates derived using assumptions based on an earlier analysis of the ACS CPS-II cohort (Jerrett et al. 2009). This study indicates that reducing O_3 exposure, for example, through reduction of precursor emissions (i.e., methane, NO_x, VOCs, and CO), could have substantially greater benefits than previously quantified in reducing the overall global burden of disease attributable to outdoor air pollution. Furthermore, human health co-benefits from climate mitigation policies (Anenberg et al. 2012; Shindell et al. 2012, 2016; West et al. 2013), and health burdens from climate-driven changes in O_3 concentrations (Fang et al. 2013a; Silva et al. 2016b; Zhu and Liao 2016) may also be greater than previously estimated.

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