Preterm birth associated with maternal fine particulate matter exposure: A global, regional and national assessment

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ABSTRACT

Reduction of preterm births (<37 completed weeks of gestation) would substantially reduce neonatal and infant mortality, and deleterious health effects in survivors. Maternal fine particulate matter ($PM_{2.5}$) exposure has been identified as a possible risk factor contributing to preterm birth. The aim of this study was to produce the first estimates of ambient $PM_{2.5}$-associated preterm births for 183 individual countries and globally. To do this, national, population-weighted, annual average ambient $PM_{2.5}$ concentration, preterm birth rate and number of livebirths were combined to calculate the number of $PM_{2.5}$-associated preterm births in 2010 for 183 countries. Uncertainty was quantified using Monte-Carlo simulations, and analyses were undertaken to investigate the sensitivity of $PM_{2.5}$-associated preterm birth estimates to assumptions about the shape of the concentration-response function at low and high $PM_{2.5}$ exposures, inclusion of provider-initiated preterm births, and exposure to indoor air pollution.

Globally, in 2010, the number of $PM_{2.5}$-associated preterm births was estimated as 2.7 million (1.8–3.5 million, 18% (12–24%) of total preterm births globally) with a low concentration cut-off (LCC) set at 10 μg m^{-3}, and 3.4 million (2.4–4.2 million, 23% (16–28%)) with a LCC of 4.3 μg m^{-3}. South and East Asia, North Africa/Middle East and West sub-Saharan Africa had the largest contribution to the global total, and the largest percentage of preterm births associated with $PM_{2.5}$. Sensitivity analyses showed that $PM_{2.5}$-associated preterm birth estimates were 24% lower when provider-initiated preterm births were excluded, 38–51% lower when risk was confined to the $PM_{2.5}$ exposure range in the studies used to derive the effect estimate, and 56% lower when mothers who live in households that cook with solid fuels (and whose personal $PM_{2.5}$ exposure is likely dominated by indoor air pollution) were excluded. The concentration-response function applied here derives from a meta-analysis of studies, most of which were conducted in the US and Europe, and its application to the areas of the world where we estimate the greatest effects on preterm births remains uncertain. Nevertheless, the substantial percentage of preterm births estimated to be associated with anthropogenic $PM_{2.5}$ (18% (13%–24%) of total preterm births globally) indicates that reduction of maternal $PM_{2.5}$ exposure through emission reduction strategies should be considered alongside mitigation of other risk factors associated with preterm births.

1. Introduction

Preterm birth (at <37 completed weeks of gestation) is a 'major cause of [postnatal] death and a significant cause of long-term loss of human potential' (Howson et al., 2012). There is a substantial long-term health impact from preterm birth due to increased risk both of death and of developing a wide range of chronic physical and neurological disabilities compared to full term births (Blencowe et al., 2013b; Calkins and Devaskar, 2011; Howson et al., 2012; Loftin et al., 2010;

Rogers and Velten, 2011). Liu et al. (2015) calculated that there were 965,000 deaths due to preterm birth complications globally in 2013, accounting for 35% of all neonatal deaths (<27 days after birth) and 15% of all deaths of children under 5. High preterm birth rates have been calculated for both high and low-income countries (Blencowe et al., 2012). Behrman and Butler (2007) estimated that preterm birth had an economic impact of $26.2 billion in the US in 2005 ($51,600 per preterm birth).

It is estimated that in 2010, 11.1% of the 135 million livebirths globally (14.9 million babies) were preterm, including both spontaneous and provider-initiated preterm births; preterm birth rates in countries vary between 4 and 5% in some European countries and 15–18% in

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some countries in Africa and South Asia (Blencowe et al., 2012). Spontaneous preterm birth is associated with multiple risk factors, including maternal age (young and old), multiple pregnancy (twins etc.), infection, previous preterm births, psychological health (e.g. depression) and social and personal/lifestyle factors such as poverty, maternal education, prenatal care, physical activity, diet, and alcohol and drug consumption (Behrman and Butler, 2007; Blencowe et al., 2013a; Gravett et al., 2010).

Maternal exposure to ambient concentrations of fine particulate matter (total mass of particles with an aerodynamic diameter <2.5 μm, $PM_{2.5}$) has also been identified as a risk factor for preterm birth (as reviewed in Shah et al., 2011), as well as for other related outcomes, such as low birth weight (e.g. Holstius et al., 2012; Rich et al., 2015). For example, significant associations between $PM_{2.5}$ exposure and preterm birth were detected in prospective cohort studies in Canada (Brauer et al., 2008) and China (Qian et al., 2016), in retrospective studies conducted in the US (Ha et al., 2014; Huynh et al., 2006) and China (Fleischer et al., 2014), and in a 'natural experiment' in the US (Parker et al., 2008). Proposed mechanisms for the effect of $PM_{2.5}$ on the risk of preterm birth include oxidative stress, pulmonary and placental inflammation, coagulopathy, endothelial dysfunction and hemodynamic responses (Kannan et al., 2006; Shah et al., 2011), and recently Nachman et al. (2016) showed a significant relationship between $PM_{2.5}$ exposure and intrauterine inflammation (IUI), that has been shown to increase the risk of preterm birth (Kemp, 2014). Exposure to $PM_{2.5}$ is spatially heterogeneous, with annual average $PM_{2.5}$ concentrations varying by an order of magnitude between rural areas of e.g. Europe, and urban areas in India and China (Kamyotra et al., 2012; Putaud et al., 2010; Wang et al., 2015). However, to date, no study has either assessed the implications of these differences in $PM_{2.5}$ exposure for the frequency of preterm births, or calculated the total number of preterm births that are associated with maternal exposure to elevated ambient $PM_{2.5}$ exposure globally.

Here, we present the first global estimates of ambient $PM_{2.5}$-associated preterm births, calculated using data for 183 countries. We used the relationship between $PM_{2.5}$ exposure during pregnancy and frequency of preterm births from the meta-analysis of Sun et al. (2015), because it was derived through the integration of studies conducted in Latin America, Asia and Africa, as well as North America and Europe. The odds ratio (OR) was combined with country-level population-weighted ambient $PM_{2.5}$ concentration estimates developed for the Global Burden of Disease (GBD) 2013 study (Brauer et al., 2016), in order to provide an estimate of exposure consistent with the GBD analysis, which calculated that 2.9 million premature deaths, primarily in older people, were associated with ambient $PM_{2.5}$ exposure globally (Forouzanfar et al., 2015). Finally, the number of preterm births in 183 countries was taken from a global analysis for 2010 (Blencowe et al., 2012). Uncertainty in these estimates was quantified using Monte-Carlo simulations. We also assess the contributions of anthropogenic versus natural fractions of ambient $PM_{2.5}$ to quantify the extent to which reductions in anthropogenic $PM_{2.5}$ and $PM_{2.5}$ precursor emissions could reduce the $PM_{2.5}$ risk factor associated with preterm birth. The impact of $PM_{2.5}$ on the frequency of preterm birth is further assessed in the context of spontaneous versus provider-initiated preterm births, and the contribution of household air pollution and smoking as other sources of maternal $PM_{2.5}$ exposure.

2. Methods

Calculation of the country, regional (GBD regional groupings shown in Fig. S1) and global cumulative incidence of preterm birth associated with $PM_{2.5}$ exposure (i.e. $PM_{2.5}$-associated preterm births) requires a relationship linking $PM_{2.5}$ exposure during pregnancy to preterm birth frequency, as well as the number of livebirths, the preterm birth rate, and maternal $PM_{2.5}$ exposure for each country (estimated here using annual mean population-weighted $PM_{2.5}$ concentrations as a proxy).

The most recent year for which all these variables were available was 2010. The change in cumulative incidence of preterm birth associated with $PM_{2.5}$ exposure (i.e. $PM_{2.5}$-associated preterm births) using the input variables was calculated using Eq. (1), which is based on a logistic model, and was selected because the coefficient (β) can be calculated directly from the OR using Eq. (2) (RTI International, 2015).

$$\Delta \text{Inc.} = y_0 \left(1 - \frac{1}{(1-y_0)e^{\beta \Delta X} + y_0} \right) \text{LB} \tag{1}$$

ΔInc. = Change in cumulative incidence of preterm birth. y_0 = baseline frequency of preterm birth. LB = number of live births. β = coefficient (derived from odds ratio). ΔX = change in $PM_{2.5}$ concentration (μg m^{-3}).

$$\beta = \frac{\ln(\text{OR})}{10} \tag{2}$$

OR = odds ratio

The odds ratio (OR) used (OR: 1.13 (95% confidence intervals (CI): 1.03–1.24) for a 10 μg m^{-3} change in $PM_{2.5}$ exposure) was derived in Sun et al. (2015) by meta-analysis of 13 studies. The majority of studies included in the Sun et al. (2015) meta-analysis adjusted for potential confounders that have previously been identified as risk factors for the incidence of preterm birth, including socioeconomic status/poverty, maternal smoking, race/ethnicity (Goldenberg et al., 2008; Muglia and Katz, 2010). However, the number of confounders adjusted for varied between studies. Table S1 summarises, for each of the studies included in the Sun et al. (2015) meta-analysis, the potential co-varying risk factors that were adjusted for. This relationship is similar (within confidence intervals) to the relationship derived in three other meta-analyses (Lamichhane et al., 2015; Sapkota et al., 2012; Zhu et al., 2015), see Table S2.

National, population-weighted annual average ambient $PM_{2.5}$ concentrations were those derived by Brauer et al. (2016), who adjusted the average of satellite and modelled gridded $PM_{2.5}$ concentrations using a global calibration model to optimise the fit to measurements at over 4000 surface monitoring sites. Brauer et al. (2016) then associated gridded $PM_{2.5}$ concentrations with population data to derive population-weighted $PM_{2.5}$ concentrations for each country in addition to confidence intervals accounting for uncertainty in the grid cell $PM_{2.5}$ estimates and calibration methods. Population-weighted $PM_{2.5}$ concentrations derived in Brauer et al. (2016) are shown in Fig. S2.

The number of livebirths (LB) and preterm births estimated by Blencowe et al. (2012) were used for the 183 countries. Blencowe et al. (2012) compiled data on preterm births from national registries, national surveys and peer-reviewed literature and then estimated the number of preterm births based on the prevalence of different predictor variables in that country, with confidence intervals estimated using bootstrap methods. For each country, the baseline frequency of preterm birth (y_0) was the ratio of preterm births to livebirths calculated in Blencowe et al. (2012). Fig. S3 shows the preterm birth rate estimated by Blencowe et al. (2012) for the 183 countries.

For each country, the number of $PM_{2.5}$-associated preterm births was calculated using Eq. (1). This value was also expressed as the percentage of all preterm births (as reported in Blencowe et al. (2012)). These calculations were repeated assuming different low concentration cut-off (LCC) 'counterfactual' ambient $PM_{2.5}$ exposures below which the excess risk of preterm birth was assumed to be zero. ΔX in Eq. (1) was the change in $PM_{2.5}$ concentration relative to a LCC (i.e. the difference between national population-weighted $PM_{2.5}$ concentration and the LCC). The LCC was set at 10 μg m^{-3} (the WHO air quality guideline (AQG) for $PM_{2.5}$ (WHO, 2006)), and 4.3 μg m^{-3} (the lowest population-weighted $PM_{2.5}$ concentration of any country). The number of $PM_{2.5}$-associated preterm births estimated using different LCCs reflect the uncertainty in the relationship between $PM_{2.5}$ exposure and

preterm births at low concentrations, due to the relatively fewer people exposed to lower $PM_{2.5}$ concentrations in those studies used to derive the Sun et al. (2015) OR (25th percentile $PM_{2.5}$ exposure varied between 6.3 and 19.7 µg m^{-3} for those studies included in Sun et al. (2015) that reported this statistic). We also used an LCC set at 0 µg m^{-3} as a sensitivity analysis to provide an upper bound to $PM_{2.5}$-associated preterm birth estimates assuming that the relationship between $PM_{2.5}$ and the frequency of preterm birth extends to zero. Further work is required to determine the shape of the concentration-response function at low $PM_{2.5}$ concentrations, including the existence and level of a threshold for effect.

Monte Carlo simulations were used to derive uncertainty estimates associated with each $PM_{2.5}$-associated preterm birth value. Normal distributions for each of the input variables to Eq. (1) were constructed using the confidence intervals reported in Brauer et al. (2016) for population-weighted $PM_{2.5}$ concentrations, in Blencowe et al. (2012) for the preterm birth rate and in Sun et al. (2015) for the OR and hence coefficient β. One thousand values of each input variable were randomly sampled from these distributions, and used to derive 1000 estimates of $PM_{2.5}$-associated preterm births in each country, from which 95% confidence intervals were calculated. Confidence intervals in regional and global estimates of $PM_{2.5}$-associated preterm births were calculated through 1000 random samples from the normal distribution of $PM_{2.5}$-associated preterm births in each country in the region. The contribution from uncertainty in each input variable to the total uncertainty in $PM_{2.5}$-associated preterm births was investigated by repeating the calculations three times, setting to zero the uncertainty in two of preterm birth rate, population-weighted $PM_{2.5}$ concentration and OR. To evaluate the sensitivity of $PM_{2.5}$-associated preterm births to the $PM_{2.5}$ concentration estimate, the calculation was also repeated with a different estimate of population-weighted $PM_{2.5}$ in each country (derived from gridded $PM_{2.5}$ concentrations reported in van Donkelaar et al. (2015), see Supplemental Information).

National, annual average, population-weighted $PM_{2.5}$ concentrations due to natural sources were calculated by associating gridded natural $PM_{2.5}$ concentrations, derived from GEOS-Chem chemical transport model (CTM) simulations (Bey et al., 2001) with zero anthropogenic emissions, with the Gridded Population of the World v3 dataset (Bey et al., 2001; CIESIN, 2005). Natural $PM_{2.5}$ was mainly composed of desert dust, but also included contributions from sea-salt, biogenic organic aerosol, natural sources of secondary inorganic aerosol (sulphate, nitrate and ammonium), as well as biomass burning. The anthropogenic $PM_{2.5}$ fraction was calculated using Eq. (3), and the anthropogenic $PM_{2.5}$ concentration (calculated by multiplying the population-weighted total $PM_{2.5}$ from Brauer et al. (2016) by the anthropogenic $PM_{2.5}$ fraction), was used as ΔX in Eq. (1). The population-weighted natural $PM_{2.5}$ fraction in each country was used as the LCC, in order to estimate the number of preterm births associated with only anthropogenic $PM_{2.5}$.

$$\text{Anthropogenic } PM_{2.5} \text{ fraction} = \left(1 - \frac{PM_{2.5\_nat\_GC}}{PM_{2.5\_tot\_GC}}\right) \quad (3)$$

$PM_{2.5\_nat\_GC.}$ = GEOS-Chem-derived Population-weighted natural $PM_{2.5\_tot\_GC.}$ = GEOS-Chem-derived Population-weighted total $PM_{2.5}$.

The calculation of national, regional and global $PM_{2.5}$-associated preterm births was then repeated to assess the sensitivity of these estimates to key assumptions. In the first sensitivity analysis, $PM_{2.5}$-associated preterm births were estimated for spontaneous preterm births only, with the number of spontaneous preterm births for each country estimated from the average proportion calculated for each Human Development Index (HDI) category of countries to which each country was assigned (Morisaki et al., 2014). In the second sensitivity analysis, $PM_{2.5}$-associated preterm births were estimated for only those livebirths to mothers who lived in households which do not use solid fuels for cooking (to exclude those mothers whose exposure to indoor air pollution is likely high). Hence the number of livebirths in each

country was multiplied by the proportion of the population in each country not using solid fuels for cooking (estimated in Bonjour et al. (2013)), and only these livebirths were included in the application of Eq. (1). Finally, we applied Eq. (1) assuming no increase in the risk to the cumulative incidence of preterm birth for $PM_{2.5}$ concentrations above 22.2 µg m^{-3}, i.e. $\beta\Delta X$ in Eq. (1) was fixed at the 22.2 µg m^{-3} value for $PM_{2.5}$ concentrations above 22.2 µg m^{-3}. This provided an assessment of the effect of $PM_{2.5}$ concentrations on the cumulative incidence of preterm birth within the range of $PM_{2.5}$ concentrations participants included in the studies used to derive the Sun et al. (2015) meta-analysis were exposed to, reflecting the uncertainty about the shape of the concentration-response functions at exposures above this value. The level of 22.2 µg m^{-3} was the maximum $PM_{2.5}$ exposure estimated in a large (>500,000 participants) cohort study in the US (Krewski et al., 2009), in which the most consistent evidence for the effect of $PM_{2.5}$ on preterm birth has been derived. This $PM_{2.5}$ concentration is consistent with maximum exposures reported in the US studies included in the Sun et al. (2015) meta-analysis (Chang et al., 2015; Ha et al., 2014; Huynh et al., 2006).

3. Results

3.1. Ambient $PM_{2.5}$-associated preterm births in 2010

3.1.1. Global and spatial distribution

In 2010, the global ambient $PM_{2.5}$-associated preterm birth estimates ranged from 2.7 million (95% CIs: 1.8–3.5 million) with a low concentration cut-off (LCC) of 10 µg m^{-3} to 3.4 million (2.4–4.2 million, 26% higher) with a 4.3 µg m^{-3} LCC (Table 1). Regardless of the LCC, the largest contribution to global $PM_{2.5}$-associated preterm births was from South Asia and East Asia, which together contributed 75%, and 65% of the global total with 10 µg m^{-3} and 4.3 µg m^{-3} LCCs, respectively. The West sub-Saharan Africa, and North Africa/Middle East regions also contributed >5% of the global total regardless of LCC. The large contribution of South and East Asia to global $PM_{2.5}$-associated preterm births was mainly due to $PM_{2.5}$-associated preterm births in India and China (1.1 million (0.3–1.8 million) and 0.5 million (0.1–0.7 million)

Table 1
Cumulative incidence of ambient $PM_{2.5}$-associated preterm births in 2010 (means with 95% confidence intervals) with two low $PM_{2.5}$ concentration cut-offs (LCCs).

Low $PM_{2.5}$ concentration cut-off	4.3 µg m^{-3}	10 µg m^{-3}
GBD region	Preterm births (Thousands)	Preterm births (Thousands)
South Asia	1693 (762–252)	1479 (671–2209)
East Asia	521 (189–832)	473 (154–763)
West Sub-Saharan Africa	362 (217–506)	281 (170–393)
North Africa/Middle East	219 (153–291)	173 (122–229)
East Sub-Saharan Africa	150 (105–202)	70.2 (41.6–100)
South East Asia	153 (92.9–220)	71.3 (42.4–101)
Central Sub-Saharan Africa	56.2 (20.2–95.9)	28.2 (9.2–51.0)
High Income North America	42.8 (15.3–73.2)	10.5 (3.2–17.9)
Western Europe	38.9 (28.5–48.7)	19.0 (13.9–24.1)
Central Latin America	32.8 (20.2–45.6)	9.6 (5.4–14.2)
Tropical Latin America	30.4 (7.7–56.8)	13.2 (3.6–24.3)
Central Asia	27.5 (17.2–38.1)	18.7 (11.5–27.5)
Eastern Europe	18.3 (8.0–30.1)	8.5 (3.3–13.6)
High Income Asia Pacific	19.8 (9.0–32.0)	13.4 (5.4–22.2)
South Sub-Saharan Africa	13.1 (4.7–22.5)	4.1 (0.6–8.1)
Central Europe	12.5 (8.8–16.6)	7.3 (4.9–9.7)
Southern Latin America	6.0 (3.0–8.8)	1.7 (0.6–2.8)
Andean Latin America	5.7 (2.7–9.2)	0.8 (0.3–1.4)
Caribbean	5.9 (2.7–9.2)	1.5 (0.5–2.5)
Australasia	0.9 (0.4–1.4)	0
Oceania	0.3 (0.1–0.5)	0
Global	3401 (2420–4208)	2683 (1783–3533)

respectively for the 10 µg m^{-3} LCC case) (Fig. S4, Table S3). In India, the large number of PM$_{2.5}$-associated preterm births resulted from elevated values of all input variables (the range of values for each input variable is shown in Table 2). For China, the preterm birth rate was relatively low (in the bottom quartile), but the large number of livebirths and a population-weighted PM$_{2.5}$ concentration above the 98th percentile resulted in the second largest contribution.

For the 10 µg m^{-3} LCC case, countries in the top 10% of national PM$_{2.5}$-associated preterm births accounted for 86% of the global total (Table S3). These countries were in South, East and South East Asia, sub-Saharan Africa, and the Middle East. There was substantial variation in population-weighted PM$_{2.5}$ concentrations between the top decile countries. For some countries, maternal exposure was to relatively moderate ambient PM$_{2.5}$ concentrations (e.g. population-weighted PM$_{2.5}$ < 20 µg m^{-3}: Democratic Republic of the Congo, Ethiopia), while in others the PM$_{2.5}$ concentrations were among the highest calculated for any country (>30 µg m^{-3}: Pakistan, Bangladesh, Iran, Egypt, Yemen, Nepal, Niger, Mali, Iraq, India and China), and there were some intermediate cases (20–30 µg m^{-3}: Nigeria, Sudan, Vietnam, Afghanistan). Hence, the global number of ambient PM$_{2.5}$-associated preterm births was not just dominated by countries with the highest population-weighted PM$_{2.5}$ concentrations, but countries with relatively moderate annual average PM$_{2.5}$ concentrations also contributed. When the LCC was decreased, other countries with moderate PM$_{2.5}$ concentrations, but large numbers of livebirths and relatively high preterm birth rates (e.g. Indonesia, US, Brazil, Uganda) were included in the top 10% of countries, and made substantial contributions to the global total.

3.1.2. Percentage of total preterm births

Globally, 18% (12–24%) of all preterm births were associated with PM$_{2.5}$ for a LCC of 10 µg m^{-3}. The countries with the largest percentage of PM$_{2.5}$-associated preterm births (i.e. above the 90th percentile of 30% (Table 2)) were located in the South and East Asia, North Africa/Middle East and West sub-Saharan Africa regions (Fig. 1a). Most of the countries with a larger proportion of PM$_{2.5}$-associated preterm births had relatively high population-weighted PM$_{2.5}$ concentrations. For example, 5 of the 7 countries making up the East Asia and South Asia regions were above the 90th percentile of 33 µg m^{-3} (Table 2), as were 8 of the 18 countries in North Africa/Middle East.

Decreasing the LCC to 4.3 µg m^{-3} increased the global percentage of PM$_{2.5}$-associated preterm births to 23% (16–28%). The percentage of PM$_{2.5}$-associated preterm births calculated for those countries with relatively high population-weighted PM$_{2.5}$ exposures were substantially less sensitive to changes in the LCC (Fig. 1b and c). For example, in India and China, population-weighted PM$_{2.5}$ concentrations were 43.4 and 54.1 µg m^{-3}, respectively, and decreasing the LCC to 4.3 µg m^{-3} increased the percentage of PM$_{2.5}$-associated preterm births by 14% in India and 10% in China. In contrast, the percentage of PM$_{2.5}$-associated preterm births in those countries with moderate PM$_{2.5}$ exposure (<20 µg m^{-3}, listed above) were on average 91% higher for the 4.3 µg m^{-3} LCC case compared to the 10 µg m^{-3} LCC case.

3.2. Anthropogenic PM$_{2.5}$-associated preterm births

The anthropogenic fraction of national population-weighted ambient PM$_{2.5}$, based on GEOS-Chem simulations, is shown in Fig. S5. For South and East Asia, the majority of PM$_{2.5}$ was anthropogenic (81 and 86% respectively). However, the value was smaller in other regions with elevated total PM$_{2.5}$-associated preterm births, e.g. in West sub-Saharan Africa, and North Africa/Middle East, the median anthropogenic fractions were both 21%.

Globally, 2.7 million (1.9–3.6 million) PM$_{2.5}$-associated preterm births were calculated when maternal exposure to only anthropogenic ambient PM$_{2.5}$ was considered (18% (13%–24%) of total preterm births globally), which is 81% of the total PM$_{2.5}$-associated preterm births with 4.3 µg m^{-3} LCC, and comparable to that with 10 µg m^{-3} LCC (Table 3). The contribution to this global total from West sub-Saharan Africa and North Africa/Middle East was substantially lower compared to total PM$_{2.5}$-associated preterm births (4.3 and 2.1% of anthropogenic PM$_{2.5}$-associated preterm births, respectively, compared to 10.6% and 6.4% of total PM$_{2.5}$-associated preterm births).

The median percentage of anthropogenic PM$_{2.5}$-associated preterm births (of all preterm births) was 5.1% for West sub-Saharan Africa, and 6.2% for North Africa/Middle East, compared to 18.1–26.7% and 20.7–29.1% (range across different LCCs) respectively for total PM$_{2.5}$-associated preterm births (Fig. 2 c.f. Fig. 1). In regions with high anthropogenic contributions to PM$_{2.5}$ exposures, the spatial distribution of anthropogenic PM$_{2.5}$-associated preterm births was similar to total PM$_{2.5}$-associated preterm births. For example, countries in South and East Asia had the highest anthropogenic PM$_{2.5}$-associated preterm births (Fig. 2), as well as the largest contributions to the global total (Table S4).

3.3. Uncertainty

The uncertainty in the relationship between maternal PM$_{2.5}$ exposure and preterm births, as derived in Sun et al. (2015), contributed the greatest uncertainty in the PM$_{2.5}$-associated preterm birth estimates. When the only uncertainty was in the OR, the uncertainty range (2.5–97.5th percentiles) in the resulting global PM$_{2.5}$-associated preterm births decreased by 14% and 5% for the 10 µg m^{-3}, and 4.3 µg m^{-3} LCC cases, respectively. In comparison, with uncertainty only in the number of preterm births, the uncertainty range in global PM$_{2.5}$-associated preterm births decreased by between 61% and 64% depending on the LCC. Finally, with uncertainty only in the Brauer et al. (2016) population-weighted PM$_{2.5}$ estimates included, the uncertainty range for global PM$_{2.5}$-associated preterm births decreased by between 93% and 94%. Using the alternative estimates of PM$_{2.5}$ exposure (derived from gridded PM$_{2.5}$ concentrations from van Donkelaar et al. (2015)), the global and regional estimates of PM$_{2.5}$-associated preterm births, were within the uncertainty range of the estimates derived using the Brauer et al. (2016) population-weighted PM$_{2.5}$ concentrations (see Supplementary Information Table S8).

Table 2
Variation between the 183 countries analysed in national PM$_{2.5}$-associated preterm births and input variables. The minimum, maximum and relevant percentiles are tabulated for each variable.

| Variable	Min	5th	25th	50th	75th	90th	95th	98th	Max
Livebirths (thousands)	1.1	3.2	43.9	153.7	611.5	1420	2586	4505	27,200
Preterm births (thousands)	0.1	0.2	4.4	153.7	57.4	153.3	277.7	701.8	3519
Preterm birth rate (%)	4.14	5.90	7.65	10.00	12.30	14.06	15.37	16.46	18.06
Population-weighted PM$_{2.5}$ (µg m^{-3})	4.3	6.6	9.9	15.4	21.3	33.2	41.4	47.0	65.6
PM$_{2.5}$ associated preterm births: 4.3 µg m^{-3} cut-off (thousands)	0	0.010	0.29	2.00	7.48	22.5	40.1	162.3	1224
PM$_{2.5}$ associated preterm births: 4.3 µg m^{-3} cut-off (% all preterm births)	0	2.5	5.8	11.6	17.0	27.0	33.9	37.7	48.5
PM$_{2.5}$ associated preterm births: 10 µg m^{-3} cut-off (thousands)	0	0	0	0.64	3.50	14.8	26.5	137.0	1073
PM$_{2.5}$ associated preterm births: 10 µg m^{-3} cut-off (% all preterm births)	0	0	0	5.7	11.6	22.3	29.6	33.5	45.1
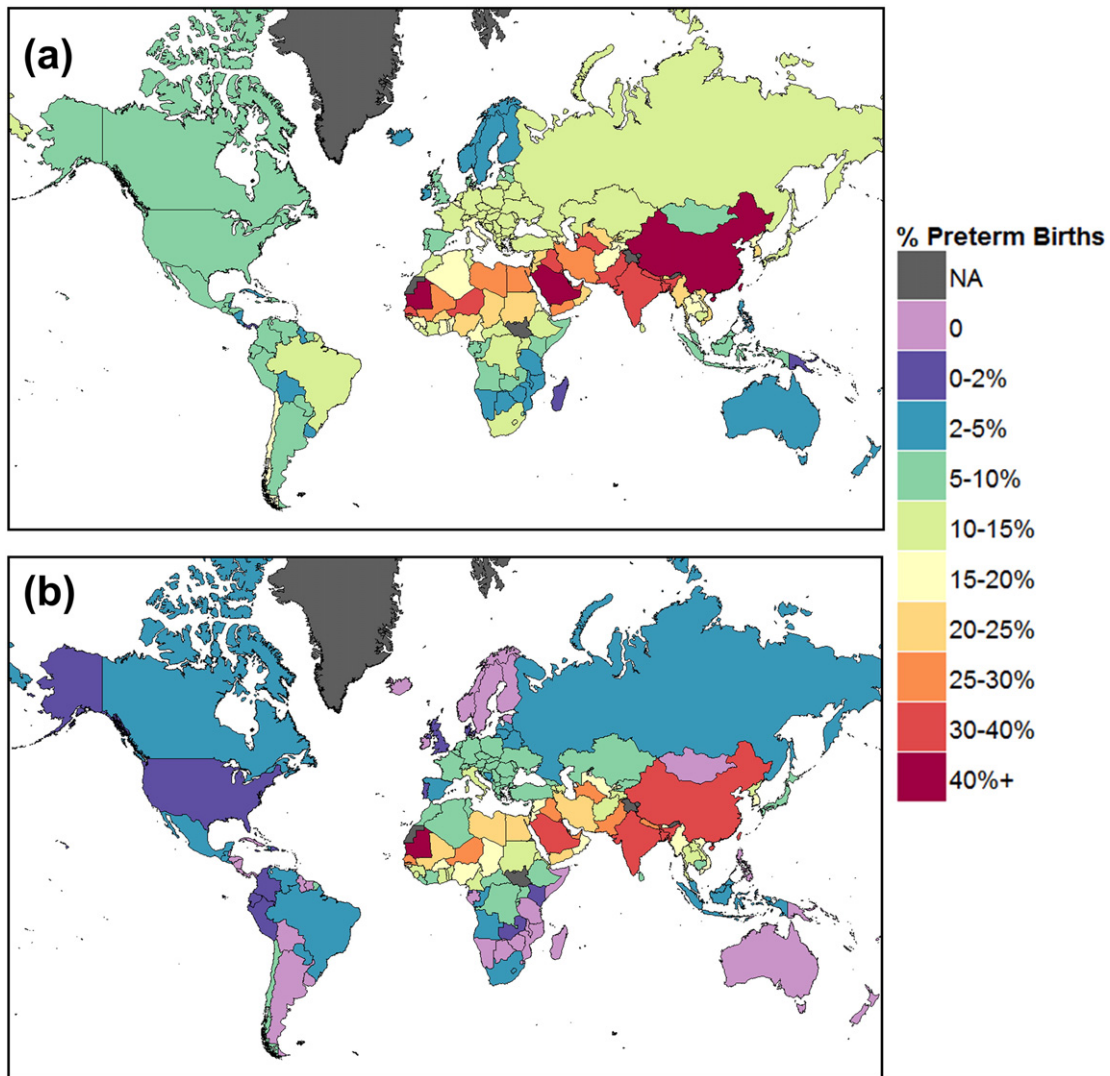
Fig. 1. Percentage of total preterm births which were associated with ambient $PM_{2.5}$ in 2010 using a low concentration cut-off of a) 4.3 µg m^{-3}, and b) 10 µg m^{-3}.

4. Discussion

4.1. Spontaneous vs provider-initiated preterm births

The ambient $PM_{2.5}$-associated preterm birth estimates (Table 1) were calculated based on total national preterm births, including spontaneous and provider-initiated. The number of preterm births calculated by Blencowe et al. (2012) were combined estimates due to a lack of data on the proportion of each type of preterm birth in individual countries, which has recently been re-emphasised (Smid et al., 2016). The majority of studies used to derive the Sun et al. (2015) OR did not exclude provider-initiated preterm births. The inclusion in our calculations of those provider-initiated preterm births for which $PM_{2.5}$ exposure is not a risk factor may have resulted in higher estimates of

Table 3

Global estimates of 2010 $PM_{2.5}$-associated preterm births calculated with different low concentration cut-offs (LCCs), modified to include the anthropogenic $PM_{2.5}$ fraction only, and spontaneous preterm births only.

| Low $PM_{2.5}$ concentration cut-off	0 µg m^{-3}	4.3 µg m^{-3}	10 µg m^{-3}	National population-weighted natural $PM_{2.5}$ concentration
	Preterm births (Thousands)	Preterm births (Thousands)	Preterm births (Thousands)	Preterm births (Thousands)
Total $PM_{2.5}$, All preterm births	3943 (2862–4855)	3401 (2420–4208)	2683 (1783–3533)	
Anthropogenic $PM_{2.5}$, All preterm births				2739 (1854–3572)
Total $PM_{2.5}$, Spontaneous preterm births	2999 (2213–3680)	2595 (1780–3272)	2047 (1387–2637)	
Total $PM_{2.5}$, risk levels off above 22.2 µg m^{-3}	2708 (2063–3268)	2117 (1640–2609)	1317 (951–1701)	
Total $PM_{2.5}$, only includes population not cooking with solid fuels	1762 (1275–2158)	1511 (1097–1874)	1166 (775–1488)	
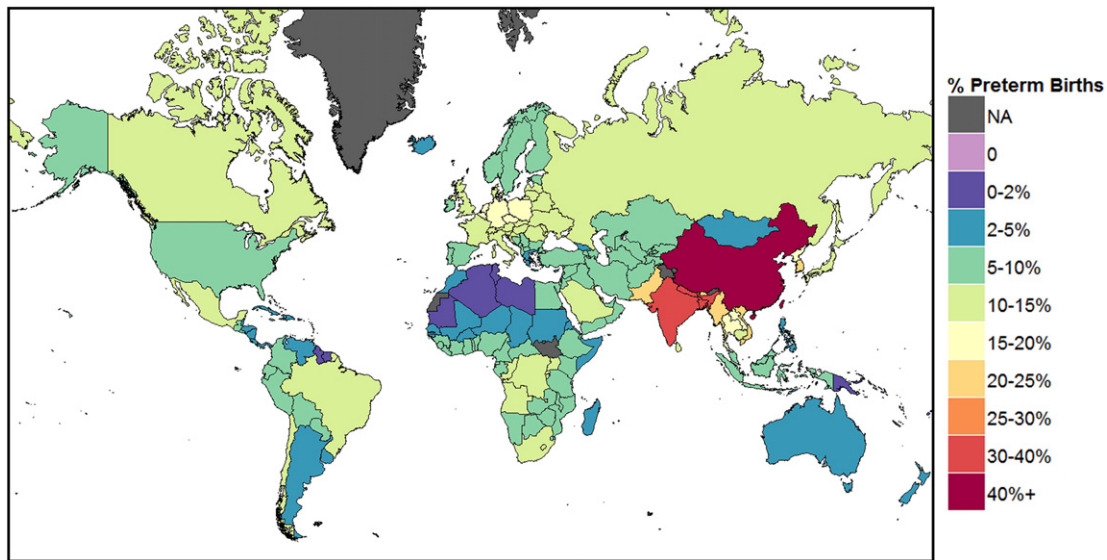
Fig. 2. Percentage of total preterm births which were associated with anthropogenic ambient PM$_{2.5}$ only in 2010.

PM$_{2.5}$-associated preterm births. However, the impact of their inclusion may be limited as provider-initiated and spontaneous preterm births are not independent, and the risk factors for each type increasingly overlap (Joseph et al., 2002). Provider-initiated preterm births are also linked to pregnancy complications, both maternal and fetal, including severe pre-eclampsia, placental abruption, uterine rupture, cholestasis, fetal distress and fetal growth restriction (Blencowe et al., 2013a). Hence the increasing ability to detect these conditions has meant that in settings with strong, well-resourced health systems, including good diagnostics, providers now monitor these babies closely and initiate delivery of a compromised baby at the point when the risk of remaining in-utero outweighs the risk of preterm delivery. In many cases, without intervention, the fetal or maternal conditions would have resulted in a stillbirth or spontaneous preterm birth at a later, but still preterm, gestational age (Joseph et al., 2002).

Nevertheless, we assessed the sensitivity of PM$_{2.5}$-associated preterm births estimates to exclusion of provider-initiated preterm births. An analysis of almost 300,000 preterm births across 29 countries produced estimates of the average proportion of preterm births that were provider-initiated in countries belonging to each Human Development Index (HDI) group (Morisaki et al., 2014; UNDP, 2015). The average proportions of provider-initiated preterm births were 40% in the Very High HDI group, 38% for High, 22% for Medium, and 20% for Low, but there was substantial variation between countries within the same HDI group (Morisaki et al. 2014). An indication of the impact of exclusion of provider-initiated preterm births on PM$_{2.5}$-associated preterm birth estimates was obtained by adjusting the Blencowe et al. (2012) total preterm births in each country by the relevant HDI-average initiated preterm birth proportion. Globally, PM$_{2.5}$-associated preterm births decreased by 24% (Table 3), with these reductions varying by a factor of 2 between regions (Table S5). The most conservative calculation of PM$_{2.5}$-associated preterm births, using a low concentration cut-off of 10 µg m^{-3} and excluding provider-initiated preterm births, resulted in an estimated 2.0 million (1.4–2.6 million) PM$_{2.5}$-associated preterm births in 2010, equivalent to 13% (9.4–17.4%) of all preterm births (Table S5).

4.2. Sources of PM$_{2.5}$ exposure

WHO REVIHAAP (2013) recommend quantification of long-term health-relevant PM as the total mass concentration (annual average), and the GBD studies report mortality associated with total PM$_{2.5}$, including both anthropogenic and naturally-derived PM$_{2.5}$ (Brauer et al., 2016). However, emission reduction strategies aimed at reducing ambient PM$_{2.5}$ concentrations (e.g. to attain the WHO air quality guideline of 10 µg m^{-3}) are largely limited to the anthropogenic sources of PM$_{2.5}$ and precursor emissions (Viana et al., 2008). Additionally, reduction in PM$_{2.5}$ concentrations through reduction in anthropogenic emissions during 'natural experiments' has been associated with reduction in adverse pregnancy outcomes, including the frequency of preterm birth, for example during the 2008 Beijing Olympics (Rich et al., 2015), and following the closure of a steel mill in Utah, US (Parker et al., 2008). Hence the number of PM$_{2.5}$-associated preterm births calculated using anthropogenic population-weighted PM$_{2.5}$ represents an estimate of the reduction in the PM$_{2.5}$ risk factor for preterm birth that could be achieved from implementing PM$_{2.5}$ and PM$_{2.5}$-precursor emission strategies. In the majority of regions, including those with the largest estimates of PM$_{2.5}$-associated preterm births, i.e. South and East Asia, the anthropogenic PM$_{2.5}$ fraction dominated, indicating that the majority of the PM$_{2.5}$ preterm birth risk factor could be mitigated from implementing emission control strategies in these regions. The exceptions were countries in North Africa/Middle East, and west Sub-Saharan Africa, for which the dominant PM$_{2.5}$ fraction was the natural component. The substantial percentage of preterm births that we calculate are associated with anthropogenic PM$_{2.5}$ indicates that reduction of maternal PM$_{2.5}$ exposure should be considered alongside mitigation of other risk factors associated with preterm births.

Additionally, the majority of studies (including most of those used to derive the Sun et al. (2015) OR) which have calculated significant associations between maternal PM$_{2.5}$ exposure and preterm birth have been conducted in regions where the anthropogenic PM$_{2.5}$ fraction dominates (i.e. North America, Europe, China, Fig. S5). Evidence that the natural PM$_{2.5}$ fraction contributes to the PM$_{2.5}$ preterm birth risk factor remains more limited. The number of PM$_{2.5}$-associated preterm births calculated using total population-weighted PM$_{2.5}$ concentrations (0 µg m^{-3} LCC) and anthropogenic population-weighted PM$_{2.5}$ therefore represent estimates for scenarios where all PM$_{2.5}$ is a risk factor associated with preterm birth, and only the anthropogenic component is a risk factor, respectively. The sensitivity of PM$_{2.5}$-associated preterm birth estimates to exclusion of natural PM$_{2.5}$ was relatively low for those regions where the anthropogenic PM$_{2.5}$ fraction dominates, but much higher for North Africa/Middle East, and west Sub-Saharan Africa (>70% reduction in estimated PM$_{2.5}$-associated preterm births for these regions when only the anthropogenic fraction was included). Further study of the association between preterm birth and PM$_{2.5}$ exposure in regions with dominant natural PM$_{2.5}$ fractions is required to assess the

similarity of the effect to that in those regions where the anthropogenic $PM_{2.5}$ fraction dominates.

In addition to ambient $PM_{2.5}$, household air pollution (quantified as e.g. solid fuel use or $PM_{2.5}$ concentration) has been identified as an additional risk factor associated with adverse pregnancy outcomes, including preterm birth (Amegah et al., 2014; Patelarou and Kelly, 2014). The studies used to derive the Sun et al. (2015) OR did not adjust for household $PM_{2.5}$ exposure. The majority of these studies were conducted in North America, Europe and Australia where the confounding effect of household air pollution is likely to be low due to the small fraction of the populations using solid fuels (<5% in 2010 (Bonjour et al., 2013)). However, in Fleischer et al. (2014), data from countries in Latin America, Africa and Asia were integrated to calculate the association between preterm birth and $PM_{2.5}$ exposure. In these regions a substantially larger fraction of the populations use solid fuels (77% and 61% in Africa and South East Asia in 2010 (Bonjour et al., 2013)). Household air pollution is therefore a potential additional contributor to maternal $PM_{2.5}$ exposure not accounted for here, and in those countries with substantial populations using solid fuels, it may be a significant, additional risk factor for preterm birth. In these regions, indoor air pollution sources may dominate overall personal $PM_{2.5}$ exposure for those mothers living in households where there are substantial indoor $PM_{2.5}$ emissions. Therefore, the sensitivity of the global ambient $PM_{2.5}$-associated preterm birth estimates to the inclusion of livebirths to mothers living in households that cook with solid fuels was evaluated by calculating ambient $PM_{2.5}$-associated preterm births including only those mothers living in households that do not cook with solid fuels in each country (i.e. by multiplying total livebirths in each country by the proportion of the national population not using solid fuels for cooking, as estimated by Bonjour et al. (2013)). Ambient $PM_{2.5}$-associated preterm birth estimates for only mothers living in non-solid fuel burning households was 43–45% of the total $PM_{2.5}$-associated preterm birth estimates described in Section 3 (Table 3). As expected, the greatest reduction in predicted $PM_{2.5}$-associated preterm births was in sub-Saharan Africa and, to a lesser extent, in South East Asia, where use of solid fuels for cooking is greatest. However, even assuming that only mothers in households that do not burn solid fuels are affected by ambient $PM_{2.5}$, these results still indicate that ambient $PM_{2.5}$ is a substantial global risk factor for preterm birth (i.e. estimates of $PM_{2.5}$-associated preterm births to mothers in non-solid fuel burning households were 7.5–10.1% of total preterm births globally, depending on the LCC).

Similarly, maternal smoking is an additional source of $PM_{2.5}$ exposure which has also been linked to preterm birth, and between 11 and 13% of women in a subset of high-income countries were estimated to smoke during pregnancy (Ion and Bernal, 2014). However, the majority of studies used to derive the Sun et al. (2015) OR (7 out of 10) did adjust for maternal smoking. In addition, in middle and low-income countries the prevalence of smoking for women in general is substantially lower, and on average 4% and 3% of women in middle and low-income countries, respectively, were estimated to smoke (WHO, 2015). Hence in those regions where the largest number of preterm births associated with ambient $PM_{2.5}$ exposure was estimated, the confounding effect of $PM_{2.5}$ exposure from maternal smoking is likely to be small.

4.3. Application of Sun et al. (2015) odds ratio

In this work, the Sun et al. (2015) OR was applied globally to estimate $PM_{2.5}$-associated preterm births, assuming transferability to all regions and across the range of population-weighted annual average $PM_{2.5}$ concentrations. The Sun et al. (2015) OR was mainly derived from studies in North America (7 of 13 studies) and Europe (2 studies), but it also included studies conducted in other regions (an Australian study and a study covering 22 countries in Latin America, Africa and Asia (Fleischer et al. (2014)). However, the OR for preterm birth derived in Fleischer et al. (2014) across the 22 countries was not statistically significant (OR: 0.96 (0.90–1.02) for a 10 µg m^{-3} increase in $PM_{2.5}$).

Sun et al. (2015) identified significant heterogeneity in the studies used to derive the OR applied here. By conducting additional meta-analyses using only a subset of the 13 studies, Sun et al. (2015) identified sources of this heterogeneity to include the method of exposure assessment, the study location (US and non-US studies), and the type of study (retrospective or prospective). However, significant heterogeneity remained in the majority of these additional meta-analyses that combined a subset of the studies, indicating that there were additional, unidentified sources of heterogeneity that require additional epidemiological studies to investigate.

One of the tests of heterogeneity conducted by Sun et al. (2015) split studies conducted in the US from those outside the US; the resulting OR for the latter showed no significant effect of ambient $PM_{2.5}$ exposure on the cumulative incidence of preterm birth (OR: 0.95 (0.95–1.01) for a 10 µg m^{-3} increase in $PM_{2.5}$ based on 5 non-US studies). Sun et al. (2015) note that this result may be due to the small number of studies (5) included in this meta-analysis, and emphasise the need for additional studies in other regions to assess the consistency of effect in other regions compared to US studies. There was also no qualitative difference in studies conducted in and outside the US in the confounders that were considered (Table S1).

Since the cut-off date for inclusion in Sun et al. (2015) (December 2014), we have identified 10 studies that have quantified the effect of ambient total $PM_{2.5}$ exposure on preterm birth (Table S7). Six of these studies showed a significant effect of entire pregnancy $PM_{2.5}$ on preterm birth risk, while 8 showed a significant effect over some gestational window. The three studies conducted outside of North America (two retrospective analyses in Madrid, Spain, and a prospective study in Wuhan, China) showed significant relationships between $PM_{2.5}$ exposure and preterm birth (Arroyo et al., 2016a, 2016b; Qian et al., 2016). Despite the significant relationships detected in these three studies conducted outside the US, the small number of studies conducted outside the US limits assessment of the transferability of the Sun et al. (2015) OR to other regions of the world. We therefore reemphasise the conclusion of Sun et al. (2015) on the need for additional studies in other regions, especially China, where only one study has been published since Sun et al. (2015), and India, and Asia and Africa generally, where the largest burdens have been estimated. Additional studies in these regions would allow for a substantially more comprehensive assessment of the global applicability of the OR derived in Sun et al. (2015) than is currently possible with the suite of studies published to date.

We also identified 25 studies that have assessed the effect of PM_{10} ($PM_{2.5}$ plus coarse particulate matter) on the cumulative incidence of preterm birth. Of these, 15 detected a significant relationship, including 3 studies in the US (Ritz et al., 2000; Sagiv et al., 2005; Wu et al., 2011), and 12 studies outside the US in China (Jiang et al., 2007; Qian et al., 2016; Zhao et al., 2015), South Korea (Leem et al., 2006; Suh et al., 2009; Yi et al., 2010), Australia (Hansen et al., 2006), Uruguay (Balsa et al., 2016), and Europe (Candela et al., 2013; Schifano et al., 2016, 2013; van den Hooven et al., 2012). However, other studies in the US (Le et al., 2012; Lee et al., 2013; Pereira et al., 2016; Salihu et al., 2012; Wilhelm and Ritz, 2005), Europe (Capobussi et al., 2016; Dibben and Clemens, 2015; Hannam et al., 2014), and China (Huang et al., 2015) did not detect a significant association.

Evidence of transferability of the Sun et al. (2015) meta-analysis to other regions is provided by comparison with ORs calculated using data from China in Fleischer et al. (2014) (OR: 1.11 (1.04–1.17) for a 10 µg m^{-3} increase in $PM_{2.5}$ exposure), and Qian et al. (2016) (OR: 1.06 (1.04–1.10)), in which annual average $PM_{2.5}$ exposures were up to approximately 100 µg m^{-3}. Fleischer et al. (2014) also estimated the effect of $PM_{2.5}$ exposure on preterm birth in India, where the exposure range was greater than in other countries, but the effect here was non-significant (OR: 0.96 (0.91–1.03) for a 10 µg m^{-3} increase in $PM_{2.5}$). However, for China, the ORs calculated in these studies were within the uncertainty bounds of the Sun et al. (2015) OR (1.03–1.24). Table S6 also shows that the confidence intervals of $PM_{2.5}$-associated

preterm births estimated using the Sun et al. (2015) OR span the number of $PM_{2.5}$-associated preterm births estimated using the Fleischer et al. (2014), and Qian et al. (2016) ORs. This indicates that the Sun et al. (2015) OR is transferable to China, and also relevant to $PM_{2.5}$ exposures up to the maximum Brauer et al. (2016) national population-weighted annual average $PM_{2.5}$ concentration of 66 μg m^{-3}, including other countries in South and East Asia where the percentage of $PM_{2.5}$-associated preterm births was estimated to be high.

We also applied the Sun et al. (2015) OR varying linearly across the range of national population-weighted $PM_{2.5}$ exposures estimated by Brauer et al. (2016). As outlined above, locally derived ORs for China, derived across substantially higher $PM_{2.5}$ exposures, provided estimates of $PM_{2.5}$-associated preterm births that are consistent with those derived using the Sun et al. (2015) ORs applied in this way. However, there is evidence for some health outcomes (e.g. premature mortality due to ischemic heart disease and stroke) that the relationship with $PM_{2.5}$ exposure is steeper at lower $PM_{2.5}$ concentrations, and tends to level off at higher concentrations (Burnett et al., 2014; Pope et al., 2015). A lower increase in risk at higher concentrations would reduce estimates of $PM_{2.5}$-associated preterm births in those regions with highest $PM_{2.5}$ exposure. We assessed the sensitivity of our $PM_{2.5}$-associated preterm birth estimates to this assumption by repeating the calculations assuming no additional risk above 22.2 μg m^{-3} (the highest concentrations estimated for the US where most consistent evidence for an effect of $PM_{2.5}$ on preterm birth is available). The change in global $PM_{2.5}$-associated preterm birth estimates under this assumption was a 38–51% reduction, depending on LCC. The greatest reduction in $PM_{2.5}$-associated preterm births was in East and South Asia (57–67%, and 49–59% reduction, respectively), followed by North Africa/Middle East (30–40% reduction), where highest ambient $PM_{2.5}$ exposures were estimated. Conversely there was almost no change in $PM_{2.5}$-associated preterm birth estimates in Europe, North America and Latin America. This sensitivity analysis is conservative as significant levelling off of risk estimates for other health outcomes occurs at much higher $PM_{2.5}$ concentrations (Burnett et al., 2014). However, even when the effect of $PM_{2.5}$ on preterm birth is only quantified within the range of exposures experienced by mothers in the studies used to derive the OR, the resulting global $PM_{2.5}$-associated preterm birth estimates indicate it to be a substantial risk factor for preterm birth (9–14% of total preterm births globally) that should be considered alongside other risk factors when considering effective strategies to reduce the incidence of preterm birth.

Finally, there is also uncertainty in the shape of the concentration-response function at low $PM_{2.5}$ exposures, as substantially fewer mothers were exposed to low concentrations (below ~5 μg m^{-3}) compared to more moderate concentrations in the studies used to derive the Sun et al. (2015) OR. To reflect this uncertainty, we therefore estimated $PM_{2.5}$-associated preterm births with two LCCs, set at 4.3 and 10 μg m^{-3}. However, to provide an upper bound to estimates of $PM_{2.5}$-associated preterm births, we repeated the analysis with a LCC set at 0 μg m^{-3}, i.e. assuming the entire range of $PM_{2.5}$ concentrations contributes to the overall burden of ambient $PM_{2.5}$ on preterm birth. Globally, $PM_{2.5}$-associated preterm birth estimates were 34% higher than for the 10 μg m^{-3} case (Table 3) (3.9 million (2.9–4.9 million)), equivalent to 26% (19–33%) of total preterm births. The relative increase in $PM_{2.5}$-associated preterm births for the 0 μg m^{-3} LCC case was greatest in those regions with relatively low $PM_{2.5}$ concentrations, including Latin America and the Caribbean, and North America.

5. Conclusions

The estimated 14.9 million annual preterm births globally have been identified as a major global health issue due to their substantial contribution to neonatal and infant mortality, and the long-lasting health effects in survivors. An identified potential risk factor associated with preterm birth is maternal exposure to $PM_{2.5}$ during pregnancy. Estimates of global $PM_{2.5}$-associated preterm births varied, ranging

between 2.7 million (1.8–3.5 million) when the low $PM_{2.5}$ concentration cut-off was set at 10 μg m^{-3} (18% (12–24%) of global preterm births), to 3.4 million (2.4–4.2 million) with a 4.3 μg m^{-3} cut-off (23% (17–19%)). The majority of the $PM_{2.5}$-associated preterm births occurred in South and East Asia, as well as North Africa/Middle East and West sub-Saharan Africa, due to above average $PM_{2.5}$ exposures, livebirths and preterm birth rates. Despite the uncertainties in our estimates, they clearly show that maternal $PM_{2.5}$ exposure is a potentially substantial global risk factor associated with preterm birth. Global Burden of Disease studies have identified the global significance of $PM_{2.5}$ exposure for premature mortality, but our analysis emphasises the importance of also considering its contribution to effects in utero that lead to increased postnatal mortality and lifetime morbidity. Efforts aimed at reducing the frequency of preterm births should therefore consider reduction of maternal exposure to $PM_{2.5}$ alongside mitigation of other identified preterm birth risk factors.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.envint.2017.01.023.

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