Prenatal $PM_{2.5}$ Exposure and the Risk of Adverse Births Outcomes: Results from Project ELEFANT

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Abstract

Background: Studies investigating the impact of fine particulate matter ($PM_{2.5}$) exposure during pregnancy upon adverse birth outcomes have primarily been performed in Western nations with low ambient $PM_{2.5}$ levels. We examined associations between high levels of $PM_{2.5}$ exposure during pregnancy and risk of adverse birth outcomes by timing and level of exposure in a Chinese population.

Methods: We analysed data from 10,738 live births within the Project ELEFANT study based in Tianjin, China. Personal mean daily $PM_{2.5}$ exposures were estimated using data from 25 local monitoring sites across the city, used to compute the days exceeding 50, 100, 150, 200 and 250 $\mu g/m^3$. Relative risk of pre-term birth (<37 weeks) and low birthweight (<2500 g) were estimated by generalised additive distributed lag models, adjusted for maternal age, sex, region, paternal smoking, parity, maternal occupation, season, temperature and dew point.

Results: A dose-response was exhibited for $PM_{2.5}$ exposure and relative risk (RR) of adverse birth outcomes, with exposure in the second and third trimesters of pregnancy associated with greatest risk of adverse birth outcomes. The RRs of pre-term birth with exposures of >50, >150 and >250 $\mu g/m^3$ $PM_{2.5}$ in the third trimester were 1.09 (95%CI: 1.03-1.16), 1.30 (1.09-1.54) and 2.73 (2.03-3.66) respectively. For low birthweight, exposures of >50, >150 and >250 $\mu g/m^3$ $PM_{2.5}$ in the third trimester were associated with RRs of 0.99 (0.88-1.11), 1.37 (1.04-1.81) and 3.03 (1.75-5.23) respectively.

Conclusions: Exposure to high levels of $PM_{2.5}$ from the second trimester onwards were most strongly associated with increased risk of pre-term birth and low birthweight, with a dose-response relationship. Our data demonstrates the need to account for both level and timing of exposure in analysis of $PM_{2.5}$-associated birth outcomes.

Keywords: Air pollution; particulate matter; $PM_{2.5}$; pre-term birth; low birthweight.

Introduction

Exposure to air pollution during pregnancy has been widely reported to be associated with adverse birth outcomes such as low birth weight and pre-term birth (Ha et al, 2014; Li et al, 2017; Stieb et al, 2016), with the latter the predominant cause of perinatal death in developed countries (Goldenberg et al, 2008). In particular, exposure to fine particulate matter under 2.5 μm ($PM_{2.5}$), including metals and carbonaceous species, is believed to be a significant factor. The basis of this association is likely to be multifactorial, with exposure leading to increased intrauterine inflammation (Nachman et al, 2016), oxidative stress (Weldy et al, 2014), and epigenetic changes (Janssen et al, 2015). Exposure to $PM_{2.5}$ is associated with IL4-mediated placental inflammation (de Melo et al, 2015) and disrupted placental functional morphology (Veras et al, 2008) that impairs foetal nutrition, thereby potentially leading to foetal growth restriction (Liu et al, 2007). However, while the association between $PM_{2.5}$ exposure and intrauterine inflammation is strongest with exposure in the first trimester (Nachman et al, 2016), there is conflicting evidence regarding the relative risk of adverse birth outcomes by exposure period.

Studies examining the effect of $PM_{2.5}$ exposure upon the risk of low birth weight have variously reported the greatest effect of exposure during the second (Ha et al, 2014; Mannes et al, 2005) or the third trimester (Bell et al, 2007; Stieb et al, 2016), while others have reported no difference by trimester (Parker et al, 2005) or significant associations only when considering total exposure across the entire duration of pregnancy (Li et al, 2017). Similarly, the risk of pre-term birth has been reported to be greatest with exposures at different points of the pregnancy, including the first (Pereira et al, 2014) and second trimester (Ha et al, 2014). Other studies have reported similar effect sizes for exposure in the first month and last two weeks (Huynh et al, 2006), and a minority have reported no association whatsoever between exposure and pre-term birth risk (Johnson et al, 2016). The reasons for such discrepancies between studies may in part be due to heterogeneity in study design, with exposure being modelled by trimester, by uniquely defined time period, or across the entirety of the pregnancy. Further, there is evidence that the risk of adverse birth outcomes is modified by ethnicity. The prevalence of $PM_{2.5}$-associated pre-term births is higher among black (Basu et al, 2017; Bell et al, 2007), Asian (Basu et al, 2017) and Hispanic (Pereira et al, 2014) women than Caucasians. Such effects may in part be through other factors associated with differences in socio-economic status in addition to differential $PM_{2.5}$ exposure (Benmarhnia et al, 2017). Nonetheless, the modifying effect of ethnicity may further have contributed to the contrasting findings of studies examining the effects of $PM_{2.5}$ by timing of exposure as study cohorts differ in their ethnic composition.

Most studies examining the effect of maternal exposures on adverse birth outcomes have been conducted in Western populations, especially the USA, where ambient $PM_{2.5}$ levels are significantly lower than found in regions such as China, India, the Middle East and Northern Africa. Indeed, in Western countries other factors such as maternal smoking during pregnancy are greater determinants of adverse birth outcomes than $PM_{2.5}$ exposure, with the latter estimated to account for <10% of pre-term births (Malley et al, 2017). Subsequently, much of the work in the field to date cannot be extrapolated to regions where ambient $PM_{2.5}$ levels are higher and a greater contributing factor to the risk of adverse birth outcomes.

Here we have examined the relative risk of pre-term birth and low birthweight by the timing and level of exposure to $PM_{2.5}$, using data from 10,738 live births within the Project ELEFANT study based in Tianjin, China. We assessed the association of extreme exposures exceeding 50, 100, 150, 200 and 250 $\mu g/m^3$ upon these adverse birth outcomes. Further, we examined the impact of exposures in the three months prior to conception.

Materials & Methods

Study population and design

Project Environmental and LifEstyle FActors iN metabolic health throughout life-course Trajectories (ELEFANT) is a longitudinal population study based in Tianjin, China. It is comprised of >429,000 participants categorised into three age-based cohorts: Baby ELEFANT (mean age: 0; n=48,762); Young ELEFANT (age 20-40; n=366,474); and Elderly ELEFANT (age>61; n>13,000). For this study, we leveraged data from the Baby ELEFANT cohort collected between January 2014 and June 2016 (n=10,738 live births). Of these, 5,421 (50%) were male and 5,317 (50%) were female. The mean age of the mothers was 29.5 ± 4.4 and the mean BMI was 22.4 ± 3.1. No mothers were reported to be active smokers during pregnancy, while 20.3% of husbands were active smokers. The population were near-exclusively Han Chinese (98.8%). All procedures and study protocols were approved by the ethical committee of Tianjin Medical University (reference number: TMUhMEC2016022; approved 15th November 2016) and were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All study participants provided written informed consent.

Assessment of birth outcomes

Birth outcomes were recorded by obstetricians at participating clinics within Tianjin city. Pre-term birth was defined as those occurring before 37 weeks and low birthweight defined as less than 2500 grams, in accordance with the definitions of the World Health Organization (1977).

Air pollution modelling

Hourly measurements of $PM_{2.5}$ concentrations were collected from 25 monitoring sites within Tianjin city for the period of January 2014 to June 2016. Hourly concentrations were then used to calculate daily means as a 24-hour window. $PM_{2.5}$ concentrations at the nearest monitoring station of maternal residence was estimated for individual's exposure assessment. Extreme $PM_{2.5}$ exposure were divided by >50, >100, >150, >200 and >250 μg/m^3. Meteorological parameters including temperature and dew point were obtained from the China Meteorological Data Service Center (CMDC) (http://data.cma.cn/en). Meteorological data were averaged to daily values as ambient $PM_{2.5}$ concentration.

Covariates

The model was adjusted for maternal age, child sex, maternal education (years), maternal occupation (manual, non-manual, unemployed), region (urban/rural), paternal smoking (yes/no), parity, time from date of last menstruation to birth, temperature, and dew point.

Statistical analysis

The numbers of days participants were exposed to daily $PM_{2.5}$ levels over 50, 100, 150, 200 and 250 μg/m^3 were computed by each trimester and month of pregnancy. The exposure-response relationship between extreme exposure days and adverse birth outcomes (birth term and weight as dependent variables) were estimated using a generalized additive distributed lag models including $PM_{2.5}$ exposure level of critical periods as lag effect variables.

$$Y = \alpha_0 + \alpha_1 x_1 + \cdots + \alpha_i x_i + \alpha_j z_j + s(time, df) + s(weather, df)$$

In the equation, Y corresponds to binomial distribution function of birth outcomes, α_0 to the intercept, $\alpha_i x_i$ to the $PM_{2.5}$ exposure level of ith month/trimester during pregnancy, $\alpha_j z_j$ to the covariates that were adjusted for, $s(time, df)$ and $s(weather, df)$ to the smooth function of last menstruation date and meteorological factors, which adjust for the periodically fluctuation.

The degree of freedom was selected using generalized cross validation (GCV). We estimated the adjusted relative risks (RRs) and 95% confidence interval (95%CI) of adverse birth outcomes associated with average and extreme $PM_{2.5}$ exposure level in different periods of pregnancy.

A significant P value was defined as <0.05 (two-sided). All analyses were performed in SAS v9.4 (SAS Institute, Cary, NC).

Results

Prevalence of pre-term births and low birth weight within Project ELEFANT participants

We analysed data from 10,738 live births within the Baby ELEFANT cohort. Of these, a total of 231 pre-term births and 72 cases of low birthweight were recorded. The prevalence of pre-term births (2.2%) was in line with other reports from Tianjin (1.1%) (Christian et al, 2013), but lower than observed nationally (Lee et al, 2013a). The prevalence of low birthweight (0.7%) was similarly in line with previous reports in Tianjin (1.0%) (Christian et al, 2013).

Pre-term births were significantly associated with advanced maternal age, longer time in education, non-manual work or unemployment, residence in urban locations, paternal smoking and previous births (all $p<0.0001$), but not the gender of the child ($p=0.11$) or the BMI of the mother prior to pregnancy ($p=0.62$) (*Table 1*). Low birthweight was associated with advanced maternal age ($p=0.02$), longer in education ($p<0.0001$), non-manual work or unemployment ($p<0.0001$), urban residence ($p<0.0001$) and paternal smoking ($p<0.0001$), but not the gender of the child ($p=0.43$), parity ($p=0.87$) or maternal BMI prior to pregnancy ($p=0.24$) (*Table 2*).

Ambient $PM_{2.5}$ levels in Tianjin

Ambient daily $PM_{2.5}$ levels in the period January 2014 to June 2016 ranged from 9.6 $\mu g/m^3$ to 369.9 $\mu g/m^3$, with substantial variation in daily means by season and by location within Tianjin (*Figure 1*). Seasonal $PM_{2.5}$ levels across Tianjin were typically 70-120 $\mu g/m^3$ in the winter while receding to 40-70 $\mu g/m^3$ in the summer. The frequency of exposure to $PM_{2.5}$ concentrations above threshold (>50, >100, >150, >200 and >250 $\mu g/m^3$) during pregnancy term are presented in *Figure 2*.

Risk of pre-term birth by $PM_{2.5}$ exposure level and trimester

The relative risk of pre-term birth showed variation by timing and level of exposure to $PM_{2.5}$. The most profound effects were observed with exposure during in the second trimester and final three months of pregnancy, and relative risk consistently increased with higher levels of exposure (*Figure 3*). In the second trimester, the relative risk (RR) of pre-term birth ranged from 1.07 (95% CI: 0.99 – 1.16) with exposures above 50 $\mu g/m^3$ to 3.18 (2.25 – 4.50) with exposures above 250 $\mu g/m^3$. Similarly, in the final three months of pregnancy, exposures of >50 $\mu g/m^3$ were associated with RR of 1.09 (1.03 – 1.16), while the highest levels of exposure of >250 $\mu g/m^3$ were associated with RR of 2.79 (2.03 – 3.66). Exposures in the first trimester were associated with a variable pattern of risk by $PM_{2.5}$ level, with exposures exceeding 150 and 200 $\mu g/m^3$ associated with decreased risk of pre-term birth (RR >150 $\mu g/m^3$: 0.64, 0.56 – 0.73; RR >200 $\mu g/m^3$: 0.61, 0.48 – 0.77), while the highest levels (>250 $\mu g/m^3$) of exposure were associated with substantially increased risk (RR: 1.67, 1.18 – 2.37).

Analysis by month of pregnancy revealed a similar pattern of increasing risk with high exposures later during the course of the gestation (*Table 3*). The highest estimated risk was for exposures exceeding 250 $\mu g/m^3$ in the final month of pregnancy (RR: 1.53, 1.32 – 1.79). Furthermore, in each of the sixth and final three months of pregnancy, a clear trend for increasing risk was observed with higher levels of exposure.

Risk of low birthweight by $PM_{2.5}$ exposure level and trimester

Similar to the risk of pre-term birth, the relative risk of low birthweight was highest with $PM_{2.5}$ exposure in more advanced pregnancies (*Figure 4*). In the second trimester, the RR increased from 0.97 (0.84 – 1.12) with exposures exceeding 50 $\mu g/m^3$ to 3.09 (1.79 – 5.35) with exposures of >250 $\mu g/m^3$. Highly similar relative risks were observed with exposure levels in the final three months of pregnancy, ranging from 0.99 (0.88 – 1.11) for exposures of >50 $\mu g/m^3$ to 3.03 (1.75 – 5.23) for those of >250 $\mu g/m^3$. Interestingly, a more pronounced decrease in risk was observed with high levels of $PM_{2.5}$ exposure in the first trimester in comparison to the risk of pre-term birth, with relative risk of 0.22 (0.13 – 0.38) for exposures of >200 $\mu g/m^3$.

Analysis by month of pregnancy revealed a consistent trend for increased risk of low birthweight with high levels of exposure from the fifth month onwards (*Table 4*), with the strongest effect again present for exposures in the final month (RR: 2.05, 1.51 – 2.78). Furthermore, a dose-response was again exhibited where increasing exposure levels were associated with higher relative risks. More moderate increases in risk (RR<1.20) were observed with lower thresholds of exposure.

Effect of $PM_{2.5}$ exposures prior to conception

Further to analysis of the effect of exposures during pregnancy, we examined the effect of ambient $PM_{2.5}$ exposure across the three months preceding conception. The relative risk of pre-term birth was significantly elevated with exposures of >250 $\mu g/m^3$ (RR: 4.30, 3.04 – 6.08) (*Figure 5A*). Conversely, decreases in risk were observed with exposures of >150 $\mu g/m^3$ (RR: 0.72, 0.63 – 0.82) and >200 $\mu g/m^3$ (RR: 0.62, 0.49 – 0.80). The risk of low birthweight was also raised with the highest level of exposure (RR: 3.70, 1.60 – 8.56), while substantially reduced risk was observed with exposures of >150 $\mu g/m^3$ (RR: 0.36, 0.27 – 0.49) and >200 $\mu g/m^3$ (RR: 0.32, 0.18 – 0.58) (*Figure 5B*). These patterns were similarly observed for both pre-term birth and low birthweight when each of the three months were analysed separately (data not shown).

Discussion

Maternal exposure to pollutants has been linked to a number of adverse birth outcomes, including pre-term birth (Ha et al, 2014; Li et al, 2017), low birthweight (Ha et al, 2014; Kim et al, 2007; Li et al, 2017; Stieb et al, 2016), congenital heart defects (Stingone et al, 2014) and other congenital abnormalities (Dolk et al, 2010). However, there remains a significant knowledge gap regarding the impact of exposures by their timing during the pregnancy. Studies have variously measured total exposure across the pregnancy (Dolk et al, 2010), by trimester (Kim et al, 2007) or uniquely defined time periods (Stingone et al, 2014), which has inhibited the clear identification of windows of susceptibility. Furthermore, most studies have been conducted in Western populations, where ambient air pollution levels are comparatively low and are not the pre-eminent risk factor for such events (Malley et al, 2017). Here, we have examined the impact of $PM_{2.5}$ upon the risk of pre-term birth and low birthweight by both timing and level of exposure in a Chinese cohort with severe air pollution. Our analysis has identified the second trimester and final month of pregnancy as critical periods of exposure and has demonstrated a dose-effect of $PM_{2.5}$ levels upon risk.

Daily mean $PM_{2.5}$ exposures reported by studies conducted in Western populations are typically below 15 $\mu g/m^3$ and often below the World Health Organization 24-hour mean guideline of 25 $\mu g/m^3$ (Ha et al, 2014; Johnson et al, 2016; Mannes et al, 2005; Stieb et al, 2016). In comparison, in 2016-17 the annual mean $PM_{2.5}$ level in China was 47 $\mu g/m^3$ (Huang et al, 2018), far exceeding the annual mean guideline of the World Health Organization of 10 $\mu g/m^3$. While commendable efforts have been made to reduce air pollution in China, studies conducted in Western populations will not adequately reflect the true impact of ambient air pollution upon public health across the globe. Importantly, our study has revealed a dose-effect of exposure to $PM_{2.5}$ and the risk of adverse birth outcomes. We report that exposures exceeding the lowest threshold of 50

$\mu g/m^3$ were associated with moderate increases in risk of pre-term birth of 1.07 and 1.09 in the second trimester and final three months of pregnancy, while exposures far exceeding those seen in the West (>150 and >200 $\mu g/m^3$) were associated with much sharper increases in risk of 1.30 and 1.36 respectively. While our use of monitoring site data has enabled us to model personal exposure levels, land-use or satellite data could have reduced measurement errors by offering higher resolution data and more accurate personal exposure estimates, and so it is possible that the effect sizes have been underestimated in our study. Our observations are therefore in agreement with studies conducted in low-exposure (<20 $\mu g/m^3$ $PM_{2.5}$) Western populations that have reported relative risks in the order of 1.05 for pre-term birth and low birth weight (Mannes et al, 2005; Stieb et al, 2016) or even no significant associations (Johnson et al, 2016), while simultaneously underlining the need for further studies in more highly-exposed populations. Indeed, in the West substantially fewer incidences of pre-term births are attributable to $PM_{2.5}$ exposure (<10%) in comparison to China, India and Northern Africa (20-40%) (Malley et al, 2017), and therefore the need for examination is greater in such regions. While we report substantially higher levels of risk with exposures of >250 $\mu g/m^3$, well beyond estimates previously reported for the impact of $PM_{2.5}$ on birth outcomes, caution must be taken. The number of days on which participants were exposed to such levels were very few, and therefore such estimates are subject to considerable variability.

To date there has been substantial heterogeneity in the findings of studies examining effects by timing of exposure. While exposures in the second and third trimesters have often showed the strongest associations with risk of pre-term birth and low birthweight (Bell et al, 2007; Ha et al, 2014; Mannes et al, 2005; Stieb et al, 2016), there have been contrasting reports of stronger associations between first trimester exposures and the risk of pre-term birth (Lee et al, 2013b), and similar risk of pre-term birth by exposures in the first month and final two weeks of pregnancy (Huynh et al, 2006). Recent studies in Chinese populations have conflictingly reported greatest association between exposure and pre-term birth risk in the first and second trimesters (Li et al, 2018), in the final month of pregnancy (Cheng et al, 2016), and no substantial influence of the timing of exposure whether analysed by trimester or by month (Liu et al, 2019). Our study provides evidence for exposures in the second and third trimesters being particularly critical in moderating the risk of pre-term birth and low birthweight, as has been similarly reported in Western populations (Bell et al, 2007; Ha et al, 2014; Mannes et al, 2005; Stieb et al, 2016).

Interestingly, Cheng *et al* (Cheng et al, 2016) reported that exposures exceeding 75 $\mu g/m^3$ in the second week prior to birth were particularly associated with the risk of pre-term birth. It may therefore be that cumulative exposure is not as influential as more acute exposure to spikes in air pollution levels. Our model assessed the effect of exposure to extreme levels of $PM_{2.5}$, computing the number of days individuals were exposed to levels exceeding a defined threshold. The estimated relative risks were more pronounced than those reported through assessment of cumulative exposures by trimester or year (Johnson et al, 2016; Stieb et al, 2016), and we therefore speculate that more precise focus on fluctuations in ambient $PM_{2.5}$ levels may prove more insightful in elucidating the impact of exposure upon risk of adverse birth outcomes.

Our study also examined the impact of $PM_{2.5}$ exposure prior to conception. While increased risk of adverse birth outcomes was again observed with exposures of >250 $\mu g/m^3$, reduced risk was observed with more frequent exposures of >150 and >250 $\mu g/m^3$. This may in part be the product of residual confounding due to the seasonality of ambient $PM_{2.5}$ levels (i.e. low levels of exposure immediately prior to conception are likely to be paired with high levels of exposure in the crucial second and third trimesters), and therefore caution must be taken in interpreting these observations. Further studies will be required to examine the impact of high exposure levels prior to conception, in both fathers and mothers.

With regard to the limitations of our study, the prevalence of pre-term births and low birthweight in the Tianjin region are comparatively low and have therefore reduced the power of the study to examine the risk of such outcomes by exposure. It is possible that the high levels of exposure present within the study cohort could be associated with more severe birth outcomes, such as stillbirth, that may in part explain the comparatively low prevalence of pre-term birth and low birthweight. As our study does not currently have data on such outcomes, we have been unable to examine this further. Our analysis also cannot account for behavioural changes taken by the participants designed to offset the potential effects of air pollution exposure. In particular, on days when $PM_{2.5}$ levels were especially high, the study participants may have subsequently decided to remain indoors, to use anti-pollution masks, or to use air purifiers that may have reduced the inhalation of particulate matter. Finally, while our model adjusted for paternal smoking behaviours, we could not account for maternal smoking during pregnancy. Maternal smoking is a known risk factor for pre-term birth and low birthweight, but for cultural reasons the number of women self-reporting as smokers within the Project ELEFANT study is likely to underrepresent the true number of smokers, and we were therefore unable to account for this risk factor in our analysis.

Conclusions

Our study of 10,738 live births in a Chinese population exposed to high levels of ambient air pollution has demonstrated differential effects of $PM_{2.5}$ upon the risk of pre-term birth and low birthweight by both dose and timing of exposure. Our findings underline the need to address this global health issue by examination in populations away from Western nations in order to more fully understand its impact upon public health.

Author contributions

PHL, LG and HMB are the steering committee members of Project ELEFANT and conceived the study. RZ, YZ, CL, HL, PHL, LG and HMB were involved in organisation and collection of data and samples. JF, CMK, COY, TMB, LG and HMB performed data analysis and interpretation. TMB led writing of the manuscript, and all authors had final approval of the submitted manuscript.

Declaration of interests

All authors declare no competing interests.

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Variable	Class	Full-term	Pre-term	Total	t / χ^2	P-value
Maternal age	-	29.4 ± 4.4	31.4 ± 4.3	-	-7.23	<0.0001
Gender	Female	5191	126	5317	2.52	0.11
	Male	5266	155	5421		
Maternal education	<9 years	5448	58	5506	114.55	<0.0001
	9-16years	4889	213	5102		
	≥17 years	120	10	130		
Maternal occupation	Manual work	8734	151	8885	170.04	<0.0001
	Non-manual / unemployed	1723	130	1853		
Region	Urban	1933	140	2073	172.50	<0.0001
	Rural	8524	141	8665		
Paternal smoking	Non-smoker	8383	180	8563	43.97	<0.0001
	Smoker	2074	101	2175		
Parity	0	6240	129	6369	21.49	<0.0001
	≥1	4217	152	4369		
BMI prior to pregnancy	Underweight	751	23	774	1.78	0.62
	Normal weight	7254	196	7450		
	Overweight	1924	45	1969		
	Obese	528	17	545		
Gestation period (days)	P25	280	229			
	Median	281	248			
	P75	283	254			

Table 1: Characteristics of Baby ELEFANT participants by full-term and pre-term birth. Data are presented as *n* for all variables with the exception of maternal age (mean ± standard deviation).

Variable	Class	Normal birthweight	Low birthweight	Total	t / χ^2	P-value
Maternal age	-	29.47±4.40	30.69±4.39	-	-2.35	0.02
Gender	Female	5278	39	5317	0.627	0.43
	Male	5388	33	5421		
Maternal education	<9 years	5489	17	5506	24.417	<0.0001
	9-16years	5177	55	5232		
	≥17 years	130	0	130		
Maternal occupation	Manual work	8840	45	8885	20.804	<0.0001
	Non-manual / unemployed	1826	27	1853		
Region	Urban	2043	30	2073	23.267	<0.0001
	Rural	8623	42	8665		
Paternal smoking	Non-smoker	8522	41	8563	23.329	<0.0001
	Smoker	2144	31	2175		
Parity	0	6327	42	6369	0.029	0.87
	≥1	4339	30	4369		
BMI prior to pregnancy	Underweight	767	7	774	4.238	0.24
	Normal weight	7399	51	7450		
	Overweight	1961	8	1969		
	Obese	539	6	545		
Birthweight (g)	P25	3250	1800			
	Median	3400	2150			
	P75	3600	2320			

Table 2: Characteristics of Baby ELEFANT participants by birthweight. Data are presented as *n* for all variables with the exception of maternal age (mean ± standard deviation).

Exposure (μg/m³)	Month of pregnancy 1	2	3	4	5	6	3rd last	2nd last	Final
Ex50	0.98 (0.94, 1.02)	1.01 (0.97, 1.05)	1.03 (0.98, 1.07)	1.05 (1.01, 1.10)	1.02 (0.98, 1.06)	1.00 (0.96, 1.04)	1.03 (0.99, 1.07)	1.02 (0.99, 1.06)	1.04 (1.00, 1.07)
Ex100	0.98 (0.92, 1.03)	1.01 (0.95, 1.07)	0.99 (0.94, 1.05)	1.07 (1.01, 1.13)	0.97 (0.92, 1.02)	1.04 (1.00, 1.10)	1.04 (0.99, 1.10)	1.06 (1.01, 1.11)	1.08 (1.04, 1.13)
Ex150	0.84 (0.76, 0.94)	0.90 (0.81, 0.99)	0.81 (0.74, 0.88)	0.94 (0.87, 1.03)	0.95 (0.88, 1.02)	1.05 (0.98, 1.13)	1.09 (1.01, 17)	1.08 (0.99, 1.15)	1.12 (1.03, 1.21)
Ex200	0.75 (0.64, 0.89)	0.92 (0.80, 1.05)	0.82 (0.72, 0.95)	0.84 (0.73, 0.96)	1.04 (0.95, 1.14)	1.09 (1.00, 1.18)	1.15 (1.05, 1.26)	1.05 (0.95, 1.16)	1.13 (1.02, 1.25)
Ex250	1.04 (0.81, 1.34)	1.43 (1.17, 1.76)	1.23 (1.00, 1.51)	1.26 (1.03, 1.53)	1.45 (1.27, 1.65)	1.24 (1.10, 1.40)	1.47 (1.30, 1.67)	1.19 (1.02, 1.40)	1.53 (1.32, 1.79)

Table 3: Association between daily $PM_{2.5}$ exposure level and relative risk of pre-term birth by month of pregnancy. Relative risks (95% CI) were estimated by non-linear lag distributed model, adjusted for maternal age, offspring sex, region, paternal smoking, parity, maternal occupation, season, temperature and dew point.

Exposure (μg/m³)	Month of pregnancy								
	1	2	3	4	5	6	3rd last	2nd last	Final
Ex50	1.00 (0.94, 1.07)	0.96 (0.90, 1.03)	0.95 (0.88, 1.02)	1.02 (0.94, 1.11)	0.92 (0.85, 1.00)	1.03 (0.94, 1.12)	0.95 (0.88, 1.02)	0.97 (0.90, 1.03)	1.07 (1.00, 1.14)
Ex100	1.01 (0.91, 1.12)	1.01 (0.91, 1.13)	0.92 (0.83, 1.02)	0.97 (0.87, 1.07)	0.96 (0.87, 1.06)	1.03 (0.94, 1.12)	0.98 (0.90, 1.06)	1.03 (0.95, 1.11)	1.05 (0.97, 1.15)
Ex150	0.92 (0.78, 1.10)	0.86 (0.73, 1.02)	0.71 (0.61, 0.83)	0.84 (0.73, 0.96)	0.94 (0.84, 1.05)	1.06 (0.95, 1.18)	1.04 (0.93, 1.16)	1.15 (1.02, 1.29)	1.20 (1.04, 1.37)
Ex200	0.74 (0.56, 0.97)	0.61 (0.44, 0.85)	0.53 (0.39, 0.72)	0.82 (0.66, 1.02)	1.01 (0.87, 1.17)	1.09 (0.95, 1.24)	1.03 (0.88, 1.20)	1.10 (0.92, 1.32)	1.11 (0.87, 1.42)
Ex250	1.12 (0.73, 1.72)	0.74 (0.44, 1.25)	0.76 (0.51, 1.13)	1.04 (0.76, 1.44)	1.30 (1.07, 1.59)	1.34 (1.12, 1.61)	1.34 (1.07, 1.67)	1.53 (1.18, 1.98)	2.05 (1.51, 2.78)

Table 4: Association between daily $PM_{2.5}$ exposure level and relative risk of low birthweight by month of pregnancy. Relative risks (95% CI) were estimated by non-linear lag distributed model, adjusted for maternal age, offspring sex, region, paternal smoking, parity, maternal occupation, season, temperature and dew point.

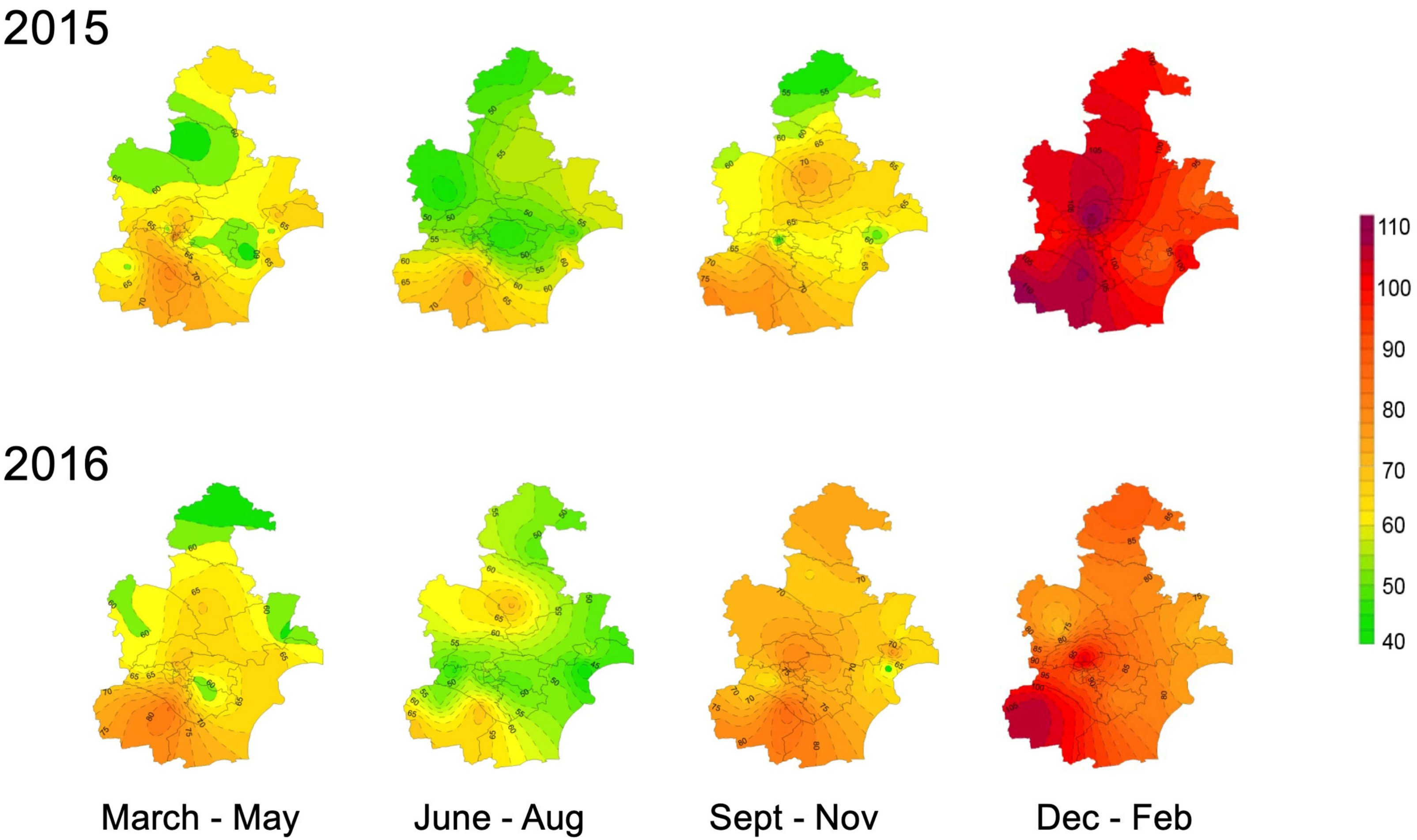

Figure 1: Spatio-temporal distribution of ambient $PM_{2.5}$ levels in Tianjin, China. Seasonal $PM_{2.5}$ ($\mu g/m^3$) averages were calculated from hourly data from 25 monitoring sites across the Tianjin region.

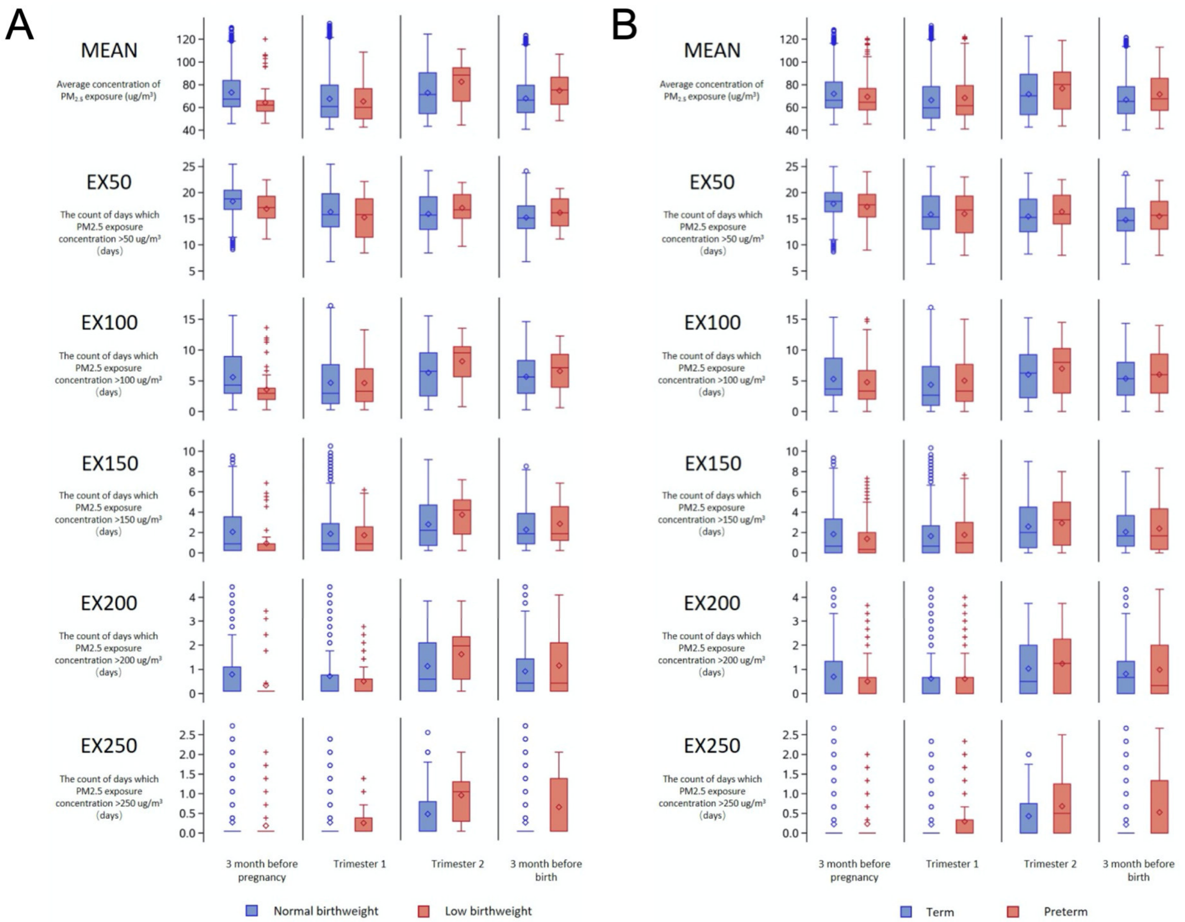

Figure 2: $PM_{2.5}$ exposure incidence by threshold and birth outcome. Frequency (days) of exposure to $PM_{2.5}$ concentrations exceeding threshold (>50, >100, >150, >200 and >250 μg/m³) among study participants by stage of pregnancy. A: frequencies of exposure among normal term (red) and pre-term (blue) live births. B: frequencies of exposure among normal (blue) and low (red) birthweight live births.

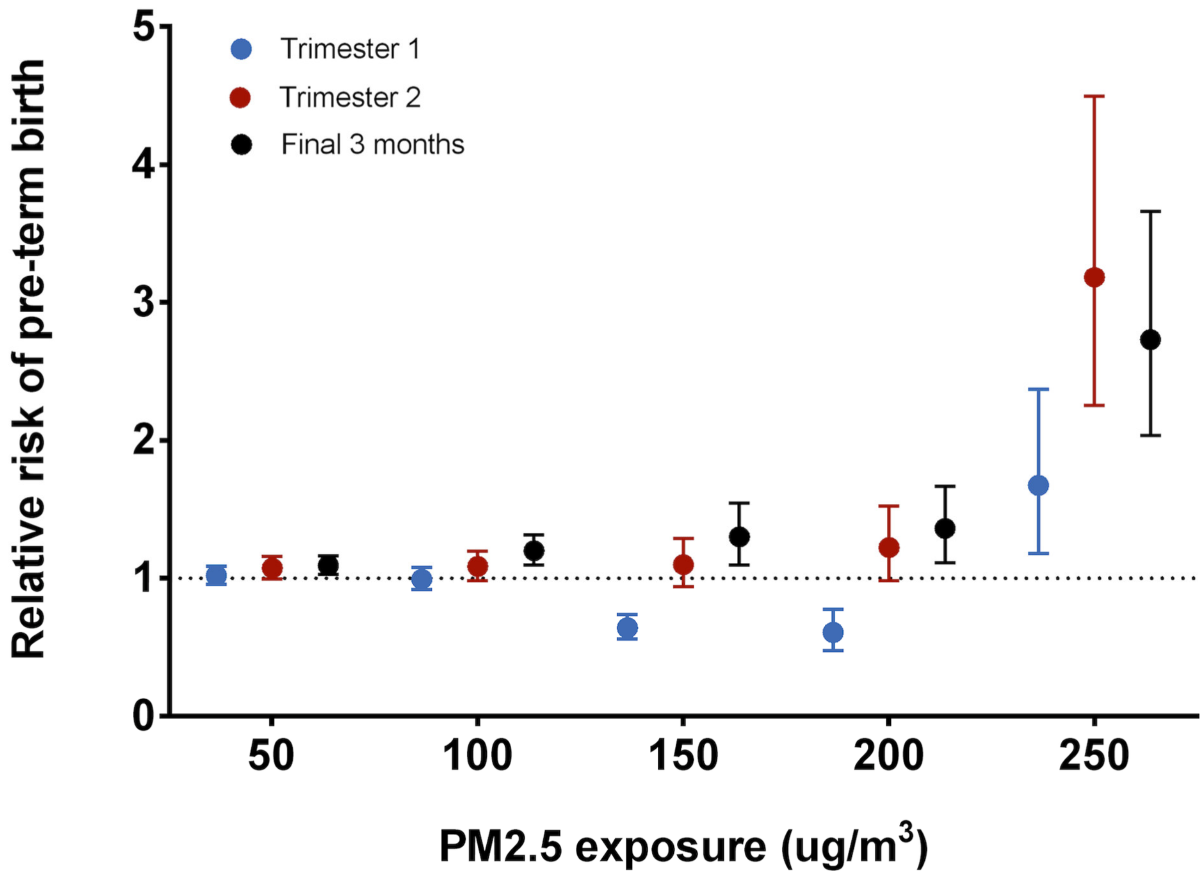

Figure 3: Relative risk of pre-term birth by daily $PM_{2.5}$ exposure level and trimester. Relative risks (95% CI) for the relationship between extreme exposure days (exceeding 50, 100, 150, 200 and 250 μg/m^3) and pre-term birth were estimated by non-linear lag distributed model, adjusted for maternal age, offspring sex, region, paternal smoking, parity, maternal occupation, season, temperature and dew point.

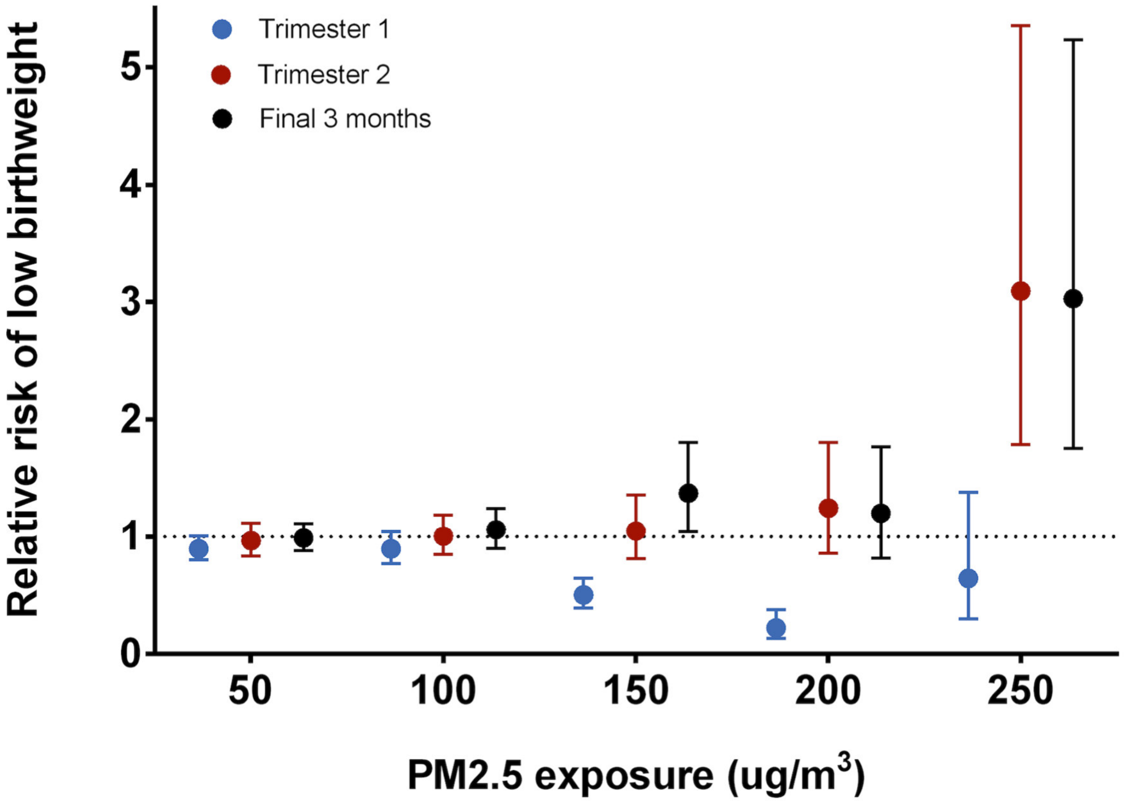

Figure 4: Relative risk of low birthweight by daily PM2.5 exposure level and trimester. Relative risks (95% CI) for the relationship between extreme exposure days (exceeding 50, 100, 150, 200 and 250 μg/m3) and low birthweight were estimated by non-linear lag distributed model, adjusted for maternal age, offspring sex, region, paternal smoking, parity, maternal occupation, season, temperature and dew point.

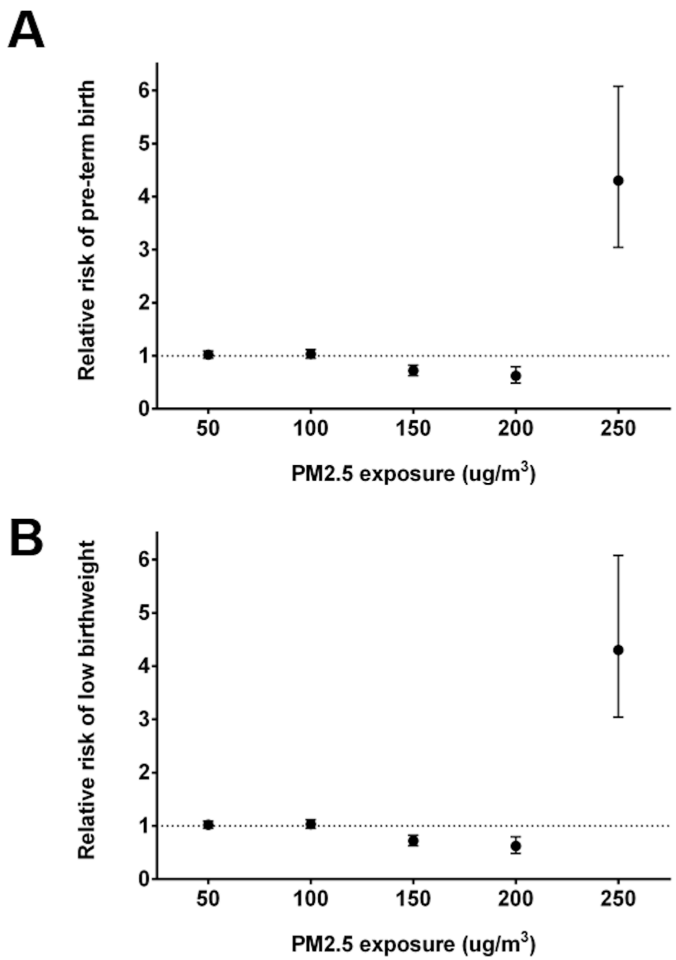

Figure 5: Effect of pre-conception PM2.5 exposure upon risk of adverse birth outcomes. Relative risks (95% CI) for the relationship between extreme exposure days (exceeding 50, 100, 150, 200 and 250 μg/m3) in the three months preceding conception and incidence of pre-term birth (A) and low birthweight (B) were estimated by non-linear lag distributed model, adjusted for maternal age, offspring sex, region, paternal smoking, parity, maternal occupation, season, temperature and dew point.