

Air pollution exposure during pregnancy and reduced birth size in a mother and child cohort study in Valencia, Spain.

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Abstract

Background: Maternal exposure to air pollution has been related to fetal growth in a number of recent scientific studies. The objective of this study was to assess the association between exposure to air pollution during pregnancy and anthropometric measures at birth in a cohort in Valencia, Spain.

Methods: Seven hundred and eighty-five pregnant women and their singleton newborns participated in the study. Exposure to ambient nitrogen dioxide (NO₂) was estimated by means of land use regression. NO₂ spatial estimations were adjusted to correspond to relevant pregnancy periods (whole pregnancy and trimesters) for each woman. Outcome variables were birth weight, length, and head circumference (HC), along with being small for gestational age (SGA). The association between exposure to residential outdoor NO₂ and outcomes was assessed controlling for potential confounders and examining the shape of the relationship using generalized additive models (GAM).

Results: For continuous anthropometric measures, GAM indicated a change in slope at NO₂ concentrations of around 40 µg/m³. NO₂ exposure >40 µg/m³ during the first trimester was associated with a change in birth length of -0.27 cm (95% CI: -0.51 to -0.03) and with a change in birth weight of -40.3 grams (-96.3 to 15.6); the same exposure throughout the whole pregnancy was associated with a change in birth HC of -0.17 cm (-0.34 to -0.003). The shape of the relation was seen to be roughly linear for the risk of being SGA. A 10 µg/m³ increase in NO₂ during the second trimester was associated with being SGA-weight, OR: 1.37 (1.01-1.85). For SGA-length the estimate for the same comparison was OR 1.42 (0.89-2.25).

Conclusions: Prenatal exposure to traffic-related air pollution may reduce fetal growth. Findings from this study provide further evidence of the need for developing strategies to reduce air pollution in order to prevent risks to fetal health and development.

Background

In recent years a growing body of epidemiological research has focused on the potential impact of prenatal exposure to air pollution on birth outcomes. Several outcomes have been related to exposure to air pollution during pregnancy, including low birth weight, reduced birth size, and intrauterine growth retardation [1-4]. Moreover, reduction in fetal growth has been associated with poor neurological development as well as with an increased risk for chronic diseases later in life [5,6].

A cohort study is the design of choice for evaluating the impact of air pollution on fetal growth as pregnancy is a process in which the relationship between a given type of exposure and an associated effect may be observed in a limited period of time [7]. Some of the studies carried out on this topic have included large populations using birth data from health care registries [8-10] whereas other cohort studies had smaller samples, but more detailed, primary data [11-13]. Authors of recent methodological reviews [7, 14-16] agree that new prospective studies should allow for adequate assessment of air pollution exposure, consider different time windows of exposure, and collect sufficient information on confounding variables.

Nitrogen dioxide (NO₂) is the air pollutant most frequently used as a surrogate for traffic-related pollution in prospective studies, both in adults and in children [17,18]. This is due to the fact that outdoor NO₂ levels correlate well with pollutants generated by traffic, they can be easily measured using passive samplers, and they are routinely measured by air quality networks, which allows for correction for seasonality.

The INMA study (Spanish Children's Health and Environment) is a prospective multi-centre pregnancy and birth cohort study that seeks to evaluate the role of the environment on fetal development and children's health in the general population in Spain [19]. The objective of this report is to assess the association between residential exposure to outdoor NO₂ during pregnancy and anthropometric measures at birth.

Methods

Study design and population

The present study was based on data from the INMA cohort in Valencia. Between November 2003 and June 2005, 855 pregnant women attending the prenatal population-based screening program at the reference hospital were included in the study. Thirty-five of these women had a spontaneous abortion or fetal death, 33 withdrew from the study or were lost to follow up, and 787 delivered a live, singleton infant. Exposure to outdoor NO₂ was assessed for 785 of the 787 mother-child pairs in the study, thus making up the final study population. Deliveries took place between May 2004 and February 2006. The study area covered the home addresses of all participants. Approximately 10% lived in a typically urban zone (city of Valencia), 50% lived in the metropolitan zone, 35% in a semi-urban zone, and the rest in a typically rural zone. The study area covers 1372 km² including 34 municipalities and has a reference population of almost 300,000 inhabitants with a broad socio-demographic and environmental heterogeneity. The study protocol was approved by the Ethics Committee of the reference hospital and informed consent was obtained from every participating woman. The mothers' recruitment and follow up procedures have been previously reported [19].

Birth outcome assessment

Outcome variables were birth weight (in grams), birth length, and head circumference (in centimetres). Birth weight was measured by the midwife that attended the birth, whereas birth length and head circumference were measured by a nurse when the newborn arrived in the hospital ward within the first twelve hours of life. The three measures were standardized for gestational age and sex using the residuals method [20]. An early ultrasound of the crown-rump length was also available and used for gestational dating when the difference with the last menstrual period was equal to or greater than 7 days. This happened in 11.9% of the cases. We defined small for gestational age (SGA) as a birth weight or length below the 10th percentile according to standard percentile charts for sex and gestational age in the Spanish population [21]. We did not classify SGA in terms of head circumference because our measurement procedure was different from that used in the published charts. Of all the births, 6.4% were classified as preterm births (i.e. gestational age < 37 weeks) in the studied cohort.

Assessment of air pollution exposure

A procedure was designed to assess individual exposure to NO₂ as a marker of outdoor air pollution considering both spatial and temporal variations on exposure. Ambient NO₂ concentrations for 93 sampling points covering the study area were obtained using radial symmetry passive samplers (Radiello®, Fondazione Salvatore Maugeri, Padua /Italy) which remained exposed for four sampling periods of 7 days each. The campaigns took place in April, June, and November 2004 and February 2005. The passive samplers were distributed over the area according to geometrical criteria, taking into account the expected pollution gradients and the expected number of births. For obtaining estimates of the NO₂ spatial distribution in the study area, a two step approach was used. First, universal kriging was used to predict NO₂ levels at unmonitored sites, i.e. the women's residences. Then, geographical information system (GIS) data (traffic, i.e. vehicle density and distance to a main road, land use, and altitude) were used to improve predictions with the aid of land use regression (LUR).

In addition, in order to take into account temporal variations in exposure, we used daily information from seven stations of the monitoring network within 5 km or less of the study area to adjust NO₂ spatial estimations to correspond with the pregnancy period for each woman. Thus, the NO₂ spatial estimation for each woman's residence was multiplied by the ratio between the NO₂ monitoring network average during the pregnancy period of that particular woman divided by the NO₂ monitoring network average for the entire study period. In order to explore critical exposure windows, an air pollution exposure indicator for each trimester of pregnancy was constructed using the same procedure as that utilized for the entire pregnancy. Address changes were taken into consideration when they accounted for a relevant fraction of each exposure window (>2/9). The methodology and results for assignment of personal air pollution exposure have been described elsewhere [22].

Covariates and potential confounders

The mothers completed a detailed questionnaire about socio-demographic characteristics, environmental exposures, and life style variables twice during their pregnancy (weeks 10-13 and 28-32). The questionnaires were administered during personal interviews by previously trained interviewers. Potential confounders included maternal variables (see Table 1), infant's sex, paternal

height, and season of delivery. Body mass index (BMI) and gestational weight gain were further classified following the Institute of Medicine guidelines [23]. Socio-economic status (SES) was classified using an adaptation of the British SES classification. Environmental tobacco smoke exposure was assessed as both passive exposure at home and global exposure.

Statistical Methods

We first performed bivariate analysis to determine parental and pregnancy characteristics associated with birth outcomes. We also examined individual NO₂ levels and maternal and pregnancy characteristics. Association between exposure to residential outdoor NO₂ and anthropometric measures was assessed by means of linear regression for continuous variables and logistic regression for SGA. In order to avoid excessive influence of extreme values, robust methods were applied. For continuous variables, we checked for the shape of the relation using graphical smoothing techniques. The height of both parents showed a linear relation and was therefore included as a continuous variable in the models. The rest of the continuous variables were categorized to account for non-linear associations. Covariates were retained in the final model if they were related to the outcome based on likelihood ratio (LR) tests with a *p* value of <0.10 or if they changed effect estimates for the exposure of interest by ≥10% when excluded from the model. The mother's age was included in all models in spite of its statistical significance. Zone of residence was not included in the multivariate analyses because it was highly correlated with NO₂ levels. To assess the shape of the relationship between measures at birth and NO₂ levels, we used adjusted GAM models to evaluate the linearity of the relation between NO₂ levels and the reproductive outcomes, comparing models with NO₂ levels in a linear and non-linear manner (a cubic smoothing spline with 2, 3, and 4 degrees of freedom) by means of graphical examination and an LR test (*p*<0.05).

Results

Characteristics of the newborns, the mothers and their pregnancy, and the fathers' height in relation to size measures and SGA are described in Table 1. In brief, older mothers, mothers who had higher pre-pregnancy weight and/or BMI, who were taller, of higher social class, non-smokers, and of Latin

American origin had infants with a higher birth weight and a lower proportion of SGA (in weight) babies. Primiparous mothers, those with low weight gain, those with only primary school education, and those who still smoked at week 12 had infants with a lower birth weight and a higher proportion of SGA (in weight) babies. Boys weighed more than girls. Similar patterns were found for birth length and head circumference adjusted for gestational age, and for SGA (in length) except that there were no differences by country of origin, and in the case of length, no differences by either social class or education were observed. Finally, taller fathers had bigger babies and a lower proportion of SGA babies.

The spatial distribution of NO₂ levels throughout the study area showed a gradient from the urban zone to the rural one with the two motorways crossing the area playing an important role (Figure 1). The mean residential outdoor NO₂ level corresponding to the 785 pregnancy periods was 36.9 µg/m³ (Table 2). For 43.2% of the women, the outdoor NO₂ levels at their residences during the pregnancy period were above 40µg/m³, the World Health Organization guideline for annual NO₂ concentration [24]. Individual NO₂ levels for each trimester correlated well with NO₂ levels for the whole pregnancy, and moderately between themselves (Table 2).

Air pollution exposure and anthropometric measures

Unadjusted analysis considering the variables in their continuous form showed a negative relationship between individual exposures to ambient NO₂ and anthropometric measures at birth (Table 3). This relation was statistically significant for first trimester exposure and for both birth length and head circumference, as well as for second trimester exposure and head circumference. After adjustment for covariates and potential confounders, the same temporal pattern persisted (Table 3). Although 95% confidence intervals yielded results that do not reject the null hypothesis, birth head circumference and NO₂ exposure in the first trimester were marginally associated. Specifically, an increase in 10 µg/m³ in NO₂ levels during the first trimester of pregnancy was associated with a decrease in head circumference by -0.07 cm (95% CI: -0.14 to 0.005).

When the shape of the relation between NO₂ exposure and anthropometric measures was assessed, a non-linear relationship was observed. In most cases in the multivariate analysis, the best fit was obtained when NO₂ was introduced as a cubic smoothing spline with 3 or 4 degrees of freedom (Table 3). Graphic examination of the relation between NO₂ exposure during the first trimester and birth weight and length, and between NO₂ exposure during the second trimester and head circumference suggested a change in slope around 40 µg/m³ (Figure 1). For this reason, the association between NO₂ exposure and weight, length, and head circumference at birth was also analyzed considering NO₂ as a categorical variable, i.e. >40 µg/m³ versus ≤40 µg/m³ (Table 4). Results of the multivariate analysis indicated that NO₂ exposure above 40 µg/m³ during the first trimester was associated with a reduction in birth length of -0.27 cm (95%CI -0.51 to -0.03). Birth weight was just marginally associated with NO₂ exposure; i.e. a reduction of -40.3 grams in birth weight (95%CI: -96.3 to 15.6) for the same comparison. Also a significant reduction in head circumference was found for exposures above 40 µg/m³ throughout the entire pregnancy.

Analysis of the relationship with small for gestational age (SGA)

In the bivariate analysis, although all the odds ratios (OR) were higher than 1, no significant association was found for either of the two measures of SGA and exposure to NO₂ during pregnancy (Table 5). After adjustment for potential confounders, a clearer association emerged with the second trimester being the most relevant window of exposure. A 10 µg/m³ increase in NO₂ during the second trimester was thus associated with the risk of SGA-weight, OR: 1.37 (95%CI: 1.01-1.85). For SGA-length the association estimate for the same comparison was OR: 1.42 (95%CI: 0.89-2.25). No significant improvement in the model was obtained with non-linear models for SGA (Figure 2); therefore, we have only included the results for the relationship with NO₂ exposure as a continuous variable (Table 5).

Discussion

Results from this mother and child cohort living in a large, heterogeneous area in Valencia, Spain, suggest an association between maternal exposure to outdoor air pollution and birth outcomes. The

odds of being SGA-weight increased by 37% when ambient NO₂ levels increased 10 µg/m³ during the second trimester of pregnancy. For anthropometric measures in continuous form, an association with air pollution appeared for women living in zones with ambient NO₂ levels above 40 µg/m³. The first and second trimesters seem to be the relevant window of exposure.

Results for the different air pollutants varied in the different studies. Besides particulate matter (PM) [either of diameter <10 µm -PM₁₀- or <2.5 µm -PM_{2.5}-] and carbon monoxide (CO), NO₂ appears as one of the pollutants more frequently associated with birth outcomes. In a previous review [2] we identified six articles reporting associations between NO_x or NO₂ with either birth weight, low birth weight (LBW, measured as birth weight <2500 g), or SGA. The three articles that included nitrogen oxides (NO_x) were ecological in design and used data from central monitors. None of them found an association between NO_x and birth weight. For NO₂, results from the literature reviewed suggested some association with birth weight, but were still not conclusive [8, 25, 26]. In recent years a considerable number of articles have been published in this field. We have identified 12 articles studying the association of NO₂ exposure with birth weight that were published after our previous review (Table 6) [10, 12, 27-36]. Of the four studies analyzing birth weight, an association was found in three of them: Bell et al. in Massachusetts and Connecticut (USA) [10], Mannes et al. in Sydney (Australia) [32], and Gouveia and cols in Brazil [29], but no relationship was observed in the Children's Health Study [31]. Interestingly, all but one of the articles [36] studying SGA found an association with NO₂; in the study in question, however, NO₂ was the only pollutant studied to be associated with head circumference. As an example, in their study in Vancouver, Brauer et al. [35] estimated residential exposures to air pollution and the risk of SGA. Of the seven air pollutants studied, the association with NO₂ was the most robust. On the other hand, only three studies found an association between LBW and NO₂ [10, 28, 35]. This discrepancy may be due to the fact that the number of cases of SGA is greater than that of LBW term babies, which gives the study more statistical power. Moreover, the use of SGA, calculated for each week of gestation, enables the effect of gestational length to be more effectively controlled than LBW, which is estimated simply by selecting births that take place after a certain period of gestation (i.e. between weeks 37- 44).

Few studies have examined the relation between air pollution exposure during pregnancy and other anthropometric indicators such as birth length or head circumference (HC). Studies of two cohorts of pregnant women in Poland and in New York described a relationship between prenatal exposure to airborne polycyclic aromatic hydrocarbons (PAH) and fetal growth [37]. Regarding prenatal NO₂ exposure and birth length or HC, a birth register-based study assessed birth length and HC among 26,617 term births in Brisbane, Australia [36]. An IQR range increase in NO₂ (11.1 µg/m³), but not in other pollutants, during the third trimester was associated with a reduction in crown-heel length: -0.15 cm (95%CI: -0.25 to -0.05). Moreover, in the French Eden cohort [38] a reduction of -0.31 cm in HC at birth was found when comparing NO₂ exposure in the highest tertile (>31.4 µg/m³) to that in the lowest tertile. Our results are consistent with the findings of these two studies.

Up to now a clear window of susceptibility for growth retardation has not been identified. In our study we found that exposure during the first trimester is most closely related to a decrease in birth weight and length. In the case of SGA (both, in weight and in length) however, the strongest relationship was found with exposure in the second trimester. Regarding reduced HC, when exposure was evaluated above vs. below 40 µg/m³, exposure throughout the pregnancy was the most clearly related. This may indicate that exposure during the entire pregnancy plays the most important role for reduction in the growth of the infant head.

Very few studies have completely assessed the shape of the relationship between air pollution exposure and reproductive outcomes. Instead, most have analyzed the relation using air pollution variables in the continuous form or comparing only two levels. Some have attempted to examine the shape using tertiles or quartiles and observed an increased risk of LBW at higher quartiles [12, 28]. Regarding NO₂ exposure and birth weight only, Ha et al. [25] examined this relationship using GAM models, as did we in the present study. In the former study, although the authors considered the relationship to be relatively linear, a change in the slope may be observed in the figures, with a higher negative gradient after NO₂ values of around 32 ppb (60 µg/m³). In our study, we found some indication of a reduction in birth length starting at a threshold of approximately 40 µg/m³. For HC and the risk of SGA we found a monotonic relationship with air pollution exposure.

The biological mechanisms by which air pollutants may affect fetal growth are still unclear. There is some evidence that NO₂ alters fetal growth and thus may play a causal role. NO₂ is a potent oxidant and increased lipid peroxidation in the maternal and/or fetal compartment has been found in preterm births [39]. Tabacova et al. investigated the relationship between exposure to nitrogen-oxidizing species and pregnancy complications in an area in Bulgaria highly polluted by oxidized nitrogen compounds [40]. Methemoglobin, a biomarker of individual exposure, was determined, and glutathione balance and lipid peroxide levels were used as measures of oxidant/antioxidant status. A high percentage of women suffered from pregnancy complications, the most common being anaemia (67%), threatened abortion/premature labour (33%), and signs of preeclampsia (23%). Methemoglobin was significantly elevated in all three conditions, in comparison with normal pregnancies. Reduced:total glutathione, an indicator of maternal antioxidant reserves, decreased, whereas cell-damaging lipid peroxide levels increased. More recently, Mohorovic found similar results for methemoglobin in a polluted area of Croatia [41]. These results suggest that maternal exposure to environmental oxidants can increase the risk of pregnancy complications through stimulation of methemoglobin formation, which may lead to hypoxia and hypoxemia in pregnant women and has an important influence on maternal health as well as on placental and fetal development.

Our study has several limitations. The number of women participating in the study is small compared with that in other studies. Subsequently, not only is the power of the study fairly low, but the estimates have wide confidence intervals. In addition, we had no information available on other important pollutants such as PM₁₀, PM_{2.5}, sulphur dioxide (SO₂), and CO, all of which have been shown to play an important role in fetal growth in other studies. Consequently, we cannot affirm that NO₂ is the air pollutant definitively associated with birth measurements. Due to the colinearity between pollutants, NO₂ may simply be a proxy for other toxins. Still, NO₂ has been shown to be a marker of air pollution from road traffic [42] and could be a reasonable marker of ultrafine particulates or PAH from this source. Unfortunately, we did not have information on indoor levels of air pollutants. However we did have information on environmental tobacco smoke exposure, an important source of indoor air pollution, and we controlled for this.

Notwithstanding the aforementioned weaknesses, our study has several important strengths. In this prospective study we followed a pregnant cohort from early pregnancy and assessed exposure, health outcomes, and covariates in great detail. In addition, the statistical approach using GAM models allows us to examine the shape of the relationship while the use of robust methods permits the minimization of the influence of extreme values. Moreover, we developed a protocol combining measurements from NO₂ passive samplers, kriging, and LUR in order to obtain estimates of individual exposure to ambient NO₂ for each woman. We also performed four different campaigns to assess the stability over time of the spatial NO₂ distribution in the study area, as recommended by Ritz and Wilhelm [15]. Our method allowed us to address local heterogeneity in order to assign an individual estimate of the exposure, a problem that has been reported to affect other studies [15, 30]. Lastly, our study had access to detailed information about each woman's residence throughout pregnancy, including changes of location and address.

Conclusions

Findings from this mother and birth cohort study in Valencia, Spain, suggest that prenatal exposure to NO₂ affects the anthropometric development of the fetus, reducing its length and head circumference and increasing the risk of having a small for gestational age (in weight) baby.

We found an association between exposure to levels of NO₂ above 40 µg/m³ during the first trimester of pregnancy and a reduction in birth weight. This association was only marginal for birth length.

For head circumference (HC) reduction and the risk of SGA, a monotonic relationship with air pollution exposure was observed. The relevant period of exposure for the risk of SGA was the second trimester. Exposure throughout the pregnancy played the most important role in decreased HC.

Compared with other recent studies, NO₂ levels in the study area occupy an intermediate position; therefore, the results are not due to extreme exposure conditions. Taking into account the relationship between fetal growth reduction and child development and health, strategies should be developed to reduce air pollution in order to prevent these risks.

List of abbreviations:

BMI: Body mass index; BSP: Black smoke particles; CI: confidence interval; CO: carbon monoxide; GAM: generalized additive models; GIS: geographical information system; HC: head circumference; INMA: Spanish Children's Health and Environment study; IQR: Interquartile range; LBW: low birth weight (measured as birth weight <2500 g); LR: likelihood ratio; LUR: land use regression; NO₂: nitrogen dioxide; NO_x: nitrogen oxides; OR: odds ratio; PAH: polycyclic aromatic hydrocarbons; PM: particulate matter; PM₁₀: particulate matter of diameter <10 µm; PM_{2.5}: particulate matter of diameter <2.5 µm; ppb: parts per billion; PR: prevalence ratio; SES: socio-economic status; SGA: small for gestational age; SO₂: sulphur dioxide.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors contributed to the article as follows: FB conceived the study, supervised the data collection and data analysis, and prepared the manuscript. ME contributed to data collection, conducted the data analysis of the association of interest, and helped with manuscript preparation. CI prepared the outcome variables, developed the land use regression analysis, assisted with data analysis, and helped with data interpretation and manuscript preparation. SL, AE, RR, ML, and MR contributed to data collection, provided critical revision of the manuscript, and helped with data interpretation and manuscript preparation. All authors have read and given final approval of the version to be published.

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Figure legends

Figure 1: Relationship between individual NO₂ exposure during the first trimester and anthropometric measures at birth. Graphical estimation of the association and 95% confidence intervals for the non-linear model with lower AIC (degrees of freedom: df).

Figure 1(A). Birth weight (gr) and NO₂ exposure (3 df)

Figure 1(B). Birth length (cm) and NO₂ exposure (4 df).

Figure 1(C). Birth head circumference (cm) and NO₂ exposure (4 df)

Footnote for Figure 1(C): For birth head circumference the model with the best adjustment was the linear model.

Figure 2: Relationship between individual NO₂ exposure during the second trimester and small for gestational age, in birth weight and in birth length in a multivariate analysis. Graphical estimation of the association and 95% confidence intervals for the non-linear model with lower AIC (degrees of freedom: df).

Figure 2(A). Logit of small for gestational age in birth weight and NO₂ exposure (2 df).

Footnote for Figure 3(A): For SGA (in birth weight) the model with the best adjustment was the linear model.

Figure 2(B). Logit of small for gestational age in birth length and NO₂ exposure (2 df)

Footnote for Figure 3(B): For SGA (in birth length) the model with the best adjustment was the linear model.

Table 1. Characteristics of pregnant women and their association with birth outcomes in the INMA-Valencia cohort, 2004-2006.

Characteristics				Birth weight (gram) ^b		SGA ^d (weight)		Birth length (cm) ^b			SGA ^d (length)		Birth head circumference (cm) ^b			
		N ^a	(%)	Mean	(SD)	p ^c	%	p ^e	Mean	(SD)	p ^c	%	p ^e	Mean	(SD)	p ^c
Maternal age (years)	<25	85	(11)	3236.9	(414.6)	0.012	10.6	0.198	50.2	1.6	0.167	7.1	0.281	34.0	1.3	0.006
	25-29	274	(35)	3301.4	(417.0)		11.7		50.5	1.9		6.2		34.2	1.4	
	30-34	301	(38)	3329.9	(442.7)		13.7		50.6	2.0		6.4		34.4	1.3	
	≥35	125	(16)	3424.1	(435.6)		6.4		50.7	1.7		2.4		34.5	1.3	
Prepregnancy Weight (Kg)	<50	57	(7)	3077.2	(396.5)	<0.001	26.3	0.006	49.9	2.1	<0.001	12.3	0.014	33.7	1.2	0.001
	50-59	313	(40)	3264.5	(383.1)		11.9		50.3	1.7		7.7		34.2	1.3	
	60-69	235	(30)	3394.6	(415.6)		8.1		50.8	1.9		3.0		34.4	1.3	
	≥70	180	(23)	3417.2	(495.4)		10.6		50.8	1.9		3.9		34.5	1.3	
Gestational weight gain^f	Low	190	(24)	3234.1	(440.6)	0.001	18.0	0.011	50.3	2.0	0.045	9.5	0.053	34.2	1.3	0.357
	Normal	286	(37)	3320.2	(390.7)		9.4		50.6	1.8		4.2		34.3	1.3	
	High	300	(39)	3382.5	(457.3)		9.7		50.7	1.8		5.0		34.4	1.4	
Pre-pregnancy BMI^f	<19.8	116	(15)	3231.2	(423.0)	0.010	16.4	0.202	50.3	1.8	0.187	7.8	0.563	34.1	1.3	0.099
	19.8-26	479	(61)	3323.3	(408.5)		10.3		50.5	1.9		5.7		34.3	1.4	
	>26	189	(24)	3384.9	(484.6)		11.6		50.7	1.9		4.8		34.3	1.3	
Parity	0	433	(55)	3254.3	(422.6)	<0.001	14.8	0.001	50.4	1.8	0.012	6.7	0.188	34.2	1.4	0.005
	≥ 1	352	(45)	3411.7	(428.0)		7.4		50.7	1.9		4.5		34.5	1.2	
Education	Incomplete	26	(3)	3488.9	(445.4)	0.102	3.8	0.477	51.0	2.0	0.540	0.0	0.201	34.3	1.1	0.005
	Primary school	240	(31)	3329.9	(450.3)		12.9		50.6	2.0		7.1		34.1	1.4	
	Secondary school	334	(43)	3293.9	(427.9)		11.4		50.5	1.7		4.8		34.4	1.3	
	University	185	(24)	3351.3	(408.4)		10.9		50.5	1.8		6.6		34.5	1.4	

Working status in the first trimester	Employed	546	(70)	3319.88	(430.7)	0.580	11.0	0.523	50.6	1.9	0.135	5.1	0.270	34.3	1.3	0.292
	Unemployed	238	(30)	3338.45	(435.1)		12.6		50.4	1.8		7.2		34.2	1.4	
Working status in the third trimester	Employed	486	(63)	3319.05	(431.9)	0.644	10.9	0.448	50.6	1.9	0.459	5.1	0.317	34.4	1.3	0.104
	Unemployed	291	(37)	3333.88	(434.9)		12.7		50.5	1.9		6.9		34.2	1.4	
Socio-economic status	I+II	124	(16)	3406.2	(409.3)	0.034	9.8	0.782	50.7	1.7	0.326	4.9	0.684	34.6	1.4	0.013
	III	185	(24)	3276.4	(427.6)		11.4		50.4	1.8		7.0		34.2	1.4	
	IV+V (lower)	476	(61)	3322.5	(437.1)		12.0		50.6	1.9		5.5		34.3	1.3	
Country of origin	Spain	693	(89)	3311.9	(431.2)	0.003	12.1	0.054	50.5	1.9	0.157	5.8	0.850	34.3	1.3	0.599
	Latin American	60	(8)	3496.2	(396.0)		3.3		51.0	1.8		6.7		34.5	1.3	
	European	27	(3)	3232.7	(434.8)		14.8		50.3	1.7		3.7		34.2	1.1	
Living with baby's father	Yes	763	(97)	3328.7	(430.7)	0.142	11.3	0.350	50.5	1.9	0.830	5.9	0.104	34.3	1.3	0.962
	No	22	(3)	3191.6	(464.1)		18.2		50.5	1.9		0.0		34.3	1.5	
Smoking during pregnancy	No	459	(59)	3365.2	(417.7)	<0.001	9.8	0.052	50.7	1.8	<0.001	4.8	0.023	34.4	1.3	0.003
	Yes, but gave up before week 12	126	(16)	3374.0	(448.7)		10.3		51.0	1.9		3.2		34.3	1.4	
	Still smoking at week 12	193	(25)	3195.9	(433.3)		16.6		50.0	1.9		9.8		34.0	1.3	
Global passive smoking	Not exposed	199	(26)	3373.7	(443.3)	0.048	10.6	0.593	50.6	1.8	0.358	7.1	0.412	34.5	1.4	0.069
	Exposed	569	(74)	3303.6	(425.8)		12.0		50.5	1.9		5.4		34.3	1.3	
Passive smoking at home	Not exposed	409	(53)	3341.8	(421.6)	0.248	10.3	0.263	50.6	1.9	0.622	6.4	0.482	34.4	1.4	0.040
	Exposed	366	(47)	3305.8	(444.6)		12.8		50.5	1.8		5.2		34.2	1.2	
Alcohol consumption (daily mean in g.)	0	433	(56)	3310.7	(433.4)	0.264	12.0	0.582	50.5	1.9	0.595	6.0	0.928	34.2	1.2	0.030
	0-1	260	(34)	3359.8	(433.5)		10.0		50.6	1.8		5.4		34.5	1.5	
	>=1	80	(10)	3290.7	(416.1)		13.8		50.6	1.8		6.3		34.2	1.3	

Infant sex	Boys	415	(53)	3393.6	(446.5)	<0.001	12.1	0.578	50.9	1.9	<0.001	5.3	0.594	34.6	1.3	<0.001
	Girls	370	(47)	3247.8	(401.8)		10.8		50.1	1.7		6.2		34.0	1.3	
Season of last menstrual period	Winter	259	(33)	3328.4	(425.3)	0.683	10.8	0.203	50.6	1.9	0.468	5.0	0.113	34.4	1.4	0.151
	Spring	190	(24)	3298.4	(417.6)		11.6		50.5	1.8		9.0		34.3	1.3	
	Summer	161	(21)	3354.5	(426.5)		8.1		50.7	1.8		3.1		34.3	1.4	
	Fall	175	(22)	3321.2	(462.6)		15.4		50.4	1.8		5.7		34.1	1.3	
Residence	Urban	70	(9)	3339.2	(422.5)	0.714	14.3	0.071	50.4	1.6	0.515	5.7	0.548	34.3	1.2	0.579
	Metropolitan	384	(49)	3306.6	(441.7)		12.5		50.5	1.9		5.5		34.2	1.4	
	Semi-urban	283	(36)	3341.8	(431.1)		11.0		50.7	1.9		6.8		34.4	1.3	
	Rural	48	(6)	3350.5	(372.9)		2.1		50.6	1.6		2.1		34.4	1.4	
Total		785	100	3224.9	(431.9)		11.5		50.5	1.9		5.7		34.3	1.3	

Continuous variables	β^g	(SE) ^g	p^e	OR ^f	(95% CI) ^f	β^g	(SE) ^g	p^e	OR ^f	(95% CI) ^f	β^g	(SE) ^g	p^e
Maternal height (cm)	11.00	(2.4)	<0.001	0.96	(0.93,0.99)	0.04	(0.01)	<0.001	0.94	(0.89;0.98)	0.03	0.01	0.001
Paternal height (cm)	6.99	(2.1)	0.001	0.97	(0.94,1.00)	0.02	(0.01)	0.011	0.96	(0.92;1.00)	0.01	0.01	0.065

^a Number may not sum up 785 in all variables because some values missing. N for birth length: 784. N for birth head circumference: 782.

^b Standardized for gestational age.

^c p-value from ANOVA in univariate analysis.

^d SGA = small for gestational age.

^e p-value from chi-square (likelihood ratio test) in univariate analysis.

^f According to 1990 Institute of Medicine guidelines (Abrams et al., 2000). BMI = body mass index (Kg/m²).

^g Beta coefficient (and standard error) from simple linear regression.

^f Odds ratio (95% confidence interval).

Table 2. Descriptive statistics of the estimates of individual exposure to ambient NO₂ during the different pregnancy periods

Pregnancy period	Mean (µg/m ³).	Percentiles (µg/m ³)			Pearson's correlation (r) between periods		
		25	50	75	First trimester	Second trimester	Third trimester
First trimester	37.9	28.2	38.1	48.5			
Second trimester	35.9	26.5	35.2	44.2	0.69		
Third trimester	37.0	27.3	37.0	46.1	0.34	0.65	
Whole pregnancy	36.9	29.4	37.9	45.6	0.80	0.92	0.83

Table 3. Individual exposure to ambient NO₂ in different time periods during pregnancy and anthropometric measures at birth. Estimates are expressed as the change in birth anthropometric measures for a 10 µg/m³ increase in the mean NO₂ levels at each woman's residence during the corresponding period. Unadjusted and adjusted models.

NO ₂ exposure period	Birth weight (in g) ^a (n:785)			Birth length (in cm) ^a (n:784)			Birth head circumference (in cm) ^a (n:782)		
	β	95% CI	Linearity (df) ^b	β	95% CI	Linearity (df) ^b	β	95% CI	Linearity (df) ^b
Unadjusted									
First trimester	-3.564	-23.698, 16.570	L	-0.092	-0.177, -0.008	NL (4)	-0.069	-0.133, -0.004	L
Second trimester	-4.464	-25.175, 16.248	NL (3)	-0.050	-0.137, 0.037	NL (2)	-0.071	-0.137, -0.004	L
Third trimester	-5.740	-26.553, 15.072	L	-0.010	-0.096, 0.077	NL (4)	-0.017	-0.084, 0.049	L
Whole pregnancy	-5.792	-30.065, 18.481	NL (3)	-0.063	-0.165, 0.038	L	-0.074	-0.152, 0.003	L
Adjusted^c									
First trimester	-12.782	-34.537, 8.972	NL (3)	-0.066	-0.149, 0.017	NL (4)	-0.066	-0.137, 0.005	L
Second trimester	-9.961	-32.594, 12.671	NL (4)	-0.040	-0.125, 0.044	NL (3)	-0.060	-0.133, 0.014	NL (3)
Third trimester	-4.294	-25.923, 17.335	L	-0.005	-0.089, 0.079	NL (2)	-0.028	-0.099, 0.042	L
Whole pregnancy	-9.729	-33.218, 13.760	L	-0.047	-0.146, 0.052	NL(2)	-0.058	-0.134, 0.018	NL (3)

^aStandardized for gestational age.

^b Shape of the relationship after contrast between model with NO₂ in non-linear vs. linear form; L: linear; NL: non-linear (and degrees of freedom of the selected model).

^c Adjusted for:

-Birth weight = maternal age, maternal pre-pregnancy weight, maternal height, paternal height, gestational weight gain, parity, maternal education, smoking during pregnancy, country of origin, sex of the infant, and season of last menstrual period.

-Birth length = maternal age, maternal height, gestational weight gain, parity, maternal education, smoking during pregnancy, working status in the first trimester, country of origin, and sex of the infant.

-Birth head circumference: maternal age, maternal pre-pregnancy weight, maternal height, gestational weight gain, parity, maternal education, smoking during pregnancy, country of origin, sex of the infant, and season of last menstrual period .

Table 4. Individual exposure to ambient NO₂ >40 µg/m³ in different time periods during pregnancy and anthropometric measures at birth. Estimates are expressed as the change in birth anthropometric measures comparing NO₂ exposure levels >40 µg/m³ vs. exposure levels ≤40 µg/m³ at each woman residence during the corresponding period. Unadjusted and adjusted models.

NO ₂ exposure period	Birth weight (in g) ^a (n:785)		Birth length (in cm) ^a (n:784)		Birth head circumference (in cm) ^a (n:782)	
	β	95% CI	β	95% CI	β	95% CI
Unadjusted						
First trimester	-24.309	-78.256, 29.638	-0.300	-0.526, -0.075	-0.104	-0.276, 0.069
Second trimester	-9.648	-65.156, 45.860	-0.100	-0.333, 0.133	-0.173	-0.352, 0.005
Third trimester	28.325	-26.475, 83.126	0.150	-0.079, 0.379	0.051	-0.123, 0.226
Whole pregnancy	-16.912	-71.233, 37.410	-0.170	-0.398, 0.058	-0.152	-0.326, 0.022
Adjusted^b						
First trimester	-40.349	-96.267, 15.568	-0.271	-0.514, -0.028	-0.074	-0.257, 0.108
Second trimester	-37.546	-96.231, 21.140	-0.190	-0.447, 0.066	-0.177	-0.368, 0.014
Third trimester	26.656	-28.239, 81.551	0.077	-0.161, 0.315	0.011	-0.167, 0.190
Whole pregnancy	-33.292	-84.874, 18.290	-0.199	-0.424, 0.027	-0.171	-0.339, -0.003

^a Standardized for gestational age.

^b Adjusted for:

-Birth weight: maternal age, maternal pre-pregnancy weight, maternal height, paternal height, gestational weight gain, parity, maternal education, smoking during pregnancy, country of origin, sex of the infant, and season of last menstrual period.

-Birth length: maternal age, maternal height, gestational weight gain, parity, maternal working status in the first trimester, smoking during pregnancy, country of origin, sex of the infant, and season of last menstrual period.

-Birth head circumference: maternal age, maternal pre-pregnancy weight, maternal height, gestational weight gain, parity, maternal education, smoking during pregnancy, working status in the third trimester, sex of the infant, and season of last menstrual period.

Table 5. Individual exposure to ambient NO₂ in different time periods during pregnancy and Small for Gestational Age. Estimates are expressed as the change in odds for SGA (birth weight) and SGA (birth length) for a 10 µg/m³ increase in the mean NO₂ levels at each woman's residence during the corresponding period. Unadjusted and adjusted models.

NO ₂ exposure period	SGA – weight (n: 785)			SGA – length (n:784)		
	OR	95% CI	Linearity (df) ^a	OR	95% CI	Linearity (df) ^a
Unadjusted						
First trimester	1.013	0.992, 1.035	L	1.001	0.968, 1.035	L
Second trimester	1.013	0.992, 1.034	L	1.006	0.972, 1.041	L
Third trimester	1.004	0.983, 1.026	L	1.013	0.979, 1.049	L
Whole pregnancy	1.014	0.988, 1.040	L	1.010	0.970, 1.052	L
Adjusted^b						
First trimester	1.182	0.894, 1.563	L	1.137	0.741, 1.744	L
Second trimester	1.369	1.013, 1.849	L	1.416	0.890, 2.254	L
Third trimester	1.186	0.906, 1.552	L	1.103	0.750, 1.623	L
Whole pregnancy	1.281	0.942, 1.743	L	1.230	0.778, 1.945	L

^a Shape of the relationship after contrast between model with NO₂ in non-linear vs. linear form; L: linear; NL: non-linear (and degrees of freedom of the selected model).

^bAdjusted for:

-SGA in weight: maternal age, maternal pre-pregnancy weight, paternal height, gestational weight gain, parity, maternal education, country of origin, smoking during pregnancy, and season of last menstrual period.

-SGA in length: maternal age, maternal pre-pregnancy weight, maternal education, parity, smoking during pregnancy, gestational weight gain, country of origin, alcohol consumption during pregnancy, and season of last menstrual period.

Table 6. Results from studies assessing NO₂ effect on birth weight published between 2003-2008

Study	Location (time period)	Design N° of births	Outcome(s)	Exposure				Results β (95% CI) grams OR (95% CI)	Adjusted for ^a	Other outcomes/ air pollutants studied / comments
				Assessment: -data source; -individual	Mean (SD) NO ₂ levels, in	Pregnancy periods	NO ₂ increase assessed			
Present study	Valencia; Spain (2004-2006)	Cohort of pregnant women 785	Birth weight SGA	-4 campaigns using passive samplers at 93 sites, monitoring network, and GIS; -residential prediction using Kriging + LUR temporally adjusted	36.9 (11.1)	Trimester; Entire pregnancy	10 $\mu\text{g}/\text{m}^3$ (5.3 ppb)	- β for birth weight 1st trimester: -12.8 (-34.5 to 9.0) Entire pregnancy: -9.7(-33.2 to 13.8) -OR for SGA 2nd trimester: 1.37 (1.01-1.85) Entire pregnancy: 1.28 (0.94-1.74)	1-19	Association with birth length and birth head circumference See tables 2-4 for complete results
Brauer et al., 2008 [35]	Vancouver, Canada (1999-2002)	Birth register-based study 70249	SGA LBW excluded <37 wg	-Monitoring network and 2 campaigns using passive samplers at 116 sites; -nearest and inverse-distance weighting (IDW) area monitors, LUR temporally adjusted	32.5 (range:15.3; 53.6)	Month; Entire pregnancy	10 $\mu\text{g}/\text{m}^3$ (5.3 ppb)	Entire pregnancy: NO ₂ IDW OR for SGA:1.14 (1.09-1.18) OR for LBW:1.11 (1.01-1.23)	1,2,7,8,13,18-22	SGA also associated with CO, SO ₂ , and PM _{2.5} but not with O ₃ .
Slama et al., 2007 [12]	Munich, Germany (1998,1999)	Cohort of pregnant-women 1016	BW<3000 g among births>2500g and >37 <44 weeks	- 2 campaigns with passive samplers at 40 sites and GIS; -residential prediction using LUR.	35.8 (P5th:28.3 ; P95th: 42.5)	Trimester; Entire pregnancy	10 $\mu\text{g}/\text{m}^3$ (5.3 ppb) Quartiles	PR 1st trimester: 0.96 (0.73- 1.20) 2nd trimester: 1.18 (0.95- 1.44) 3rd trimester: 1.13 (0.91- 1.35) Entire pregnancy: 1.21 (0.86-1.68) No significant associations by quartiles	1,3,5-7,13,14,18, 19	Significant associations with PM _{2.5} and PM _{2.5} absorbance
Bell et al., 2007 [10]	Massachusetts and Connecticut, USA (1999-2002)	Birth register-based study 358504	Birth weight LBW excluded <37 wg	Average county-level concentration from monitoring networks	32.7 (9.4)	Trimester; Entire pregnancy	9.0 $\mu\text{g}/\text{m}^3$ (4.8 ppb)	β for birth weight 1st trimester: nr (-9.6 to -8.8) Entire pregnancy: -8.9(-10.8 to -7.0) OR for LBW Entire pregnancy: 1.027 (1.002-1.051) Associations for other trimesters were less consistent	1,2,8,13,18,21,23-28	Exposures to CO, PM _{2.5} , and PM ₁₀ also lowered birth weight. SGA was also associated with CO, PM _{2.5} , PM ₁₀ , and SO ₂ .
Hansen et al., 2007 [36]	Brisbane, Australia (2000-2003)	Birth register-based study 21432	SGA	-4 monitoring stations -average of measurements	16.5 (7.7)	Trimester; Month	IQR: 11.1 $\mu\text{g}/\text{m}^3$ (5.9 ppb) Quartiles	No association between NO ₂ and SGA	1,2,10,18,19,20,23,24,29	Effect of NO ₂ (IQR:11.1 $\mu\text{g}/\text{m}^3$) third trimester on crown-heel length : -0.15cm (95%CI: -0.25

										to -0.05). No effects for PM ₁₀ , BSP, O ₃
Liu et al., 2007 [33]	Calgary, Edmonton, and Montreal, Canada (1985-2000)	Birth register-based study 386202	SGA among born between wg37-42	-2, 4, 8 monitoring stations in each city, respectively; -mean of measurements in the residential area	45.1 (IQR:32.9; 55.5)	Trimester; Month	37.6 µg/m ³ (20 ppb)	OR for Trimester 1st: 1.16 (1.09-1.24) 2nd: 1.14 (1.06- 1.21) 3rd: 1.16 (1.09- 1.24)	1,2,7,18, 19,21,30	Also associated with CO and PM _{2.5} . In multipollutant models only CO showed robustness while effects of NO ₂ and PM _{2.5} were no longer observed. No effects for SO ₂ and O ₃ .
Mannes et al., 2005 [32]	Sydney, Australia (1998-2000)	Birth register-based study 138056	Birth weight SGA	Average of the monitoring stations in the city	43.6 (13.9)	Trimester; one month before birth	1.88 µg/m ³ (1 ppb) increase among women living <5 km from a monitoring station	β for birth weight 1st trimester: -26.2(-35.4 to -17.0) 2nd trimester: -28.9(-51.0 to -6.8) 3rd trimester: -22.9(-44.6 to -1.2) Month before pregnancy: -19.7(-27.8 to -11.5) OR for SGA 1st trimester: 1.06 (0.99- 1.14) 2nd trimester: 1.14 (1.07- 1.21) 3rd trimester: 1.13 (1.05- 1.21) Month before pregnancy: 1.07 (1.00-1.14)	1,2,10,13,18,19, 20	Also associated with CO and PM ₁₀ . In multipollutant models NO ₂ appeared as the most important pollutant.
Salam et al., 2005 [31]	California, USA (1975-1987)	Birth register-based study 3901	Birth weight SGA <P15 born between wg 37-44 LBW born between wg 37-44	Spatial interpolation from the 3 nearest monitoring stations (in <50 km) When there are available stations in <5 km, the nearest station data are assigned	67.9 (29.0)	Trimester; Entire pregnancy	47 µg/m ³ (25 ppb)	β for birth weight Entire pregnancy: -7.2 g (-34.7 to 20.4) OR for SGA 1st Trimester: 1.2 (1.0-1.4) Entire pregnancy: 1.1 (0.9-1.3) No association for other trimesters or LBW	1,2,10,12,13,18, 27,31	O ₃ exposure during 2nd and 3rd trimester and CO exposure during 1 st trimester were associated with reduced birth weight.
Wilhelm and Ritz, 2005 [30]	Los Angeles County, CA, USA (1994-2000)	Birth register-based study 106483	LBW at term Born between 90-320 days; excluded weight <500g or >5000g	15 monitoring stations for the county-level analysis 11 stations for the address-level analysis	73.5 (range:38.7- 116.6)	First month; Trimester; 6 weeks before birth; Entire pregnancy	nr	Results from one pollutant models for NO ₂ are not provided. No association between NO ₂ and LBW after adjusting for CO and/or PM ₁₀ .	1,2,7,8,18,19,23, 27,32,33	Association of LBW with CO and PM ₁₀ but not with O ₃ . Clearer association for women residing 1 mile from a station

						ncy				
Gouveia et al., 2004 [29]	Sao Paulo, Brasil (1997)	Birth register-based study 179460	Birth weight LBW at term; excluded <37wg or weight <1000g >5500g	Mean of the hourly maximum from between 4-12 NO ₂ monitoring stations in the city	117.9 (51.2)	Trimester	10 µg/m ³ (5.3 ppb)	β for birth weight 1st trimester: -7.0 g (-14.3 to 0.3) No association between NO ₂ and LBW	1,2,7,10, 18,23,24	An association between LBW and CO and PM _{2.5} exposure during 1 st trimester was found
Lee et al., 2003 [28]	Seoul, Korea (1996-1998)	Birth register-based study 388105	LBW born between wg37-44	Daily mean of the 20 monitoring stations in the city	61.1 (19.2)	Month; Trimester; Entire pregnancy	IQR: 27.6 µg/m ³ (14.7 ppb)	OR for LBW 1st trimester: 1.02 (0.99-1.04) 2nd trimester: 1.03 (1.01-1.06) 3rd trimester: 0.98 (0.96-1.00) Entire pregnancy: 1.04 (1.00-1.08)	1,8,18,19,21,25,34	An association between LBW and CO, PM ₁₀ , and SO ₂ exposure was found except for 3 rd trimester for all pollutants, and for 1 st trimester for SO ₂ .
Liu et al., 2003 [27]	Vancouver, Canada (1986-1998)	Birth register-based study 229085	SGA born between wg 37-44 LBW excluded <500g or <22wg	Mean of the monitoring stations in the residential area of each mother	36.5(P5th: 21.6; P95th: 60.0)	First Month; Last month; Trimester	18.8 µg/m ³ (10 ppb)	OR for SGA First month: 1.05 (1.01-1.10) Last month: 0.98 (0.92-1.03) 1st trimester: 1.03 (0.98-1.10) 2nd trimester: 0.94 (0.88-1.00) 3rd trimester: 0.98 (0.92-1.06) OR for LBW First month: 0.98 (0.90-1.07) Last month: 0.94 (0.85-1.04)	1,2,7,18,19	An association between SGA and CO and SO ₂ first month exposure was also found

Abbreviations: β (95% CI): regression coefficient for birth weight (in grams) and 95% confidence interval; OR: odds ratio; PR: prevalence ratio; SGA: small for gestational age: <10th percentile from population charts unless otherwise indicated in the table; LBW: birth weight <2500gr unless otherwise indicated in the table. LBW at term: LBW among those born ≥37 weeks of gestation; nr: not reported; wg: weeks of gestation; BSP: black smoke particles; ppb: parts per billion; P5th: Percentile 5th. P95th: Percentile 95th; IQR: Interquartile range.

◦ Covariates considered: 1: Gestational age; 2: Maternal age; 3: Maternal pre-pregnancy weight; 4: Gestational weight gain; 5: Maternal height; 6: Maternal body mass index; 7: Parity; 8: Maternal education; 9: Maternal working status; 10: Maternal socio-economic status; 11: Mother's country of origin; 12: Living with partner; 13: Maternal smoking during pregnancy; 14: Maternal environmental tobacco exposure at home; 15: Maternal environmental general tobacco exposure; 16: Maternal alcohol consumption; 17: Paternal height; 18: Infant sex; 19: Season; 20: Country of origin; 21: Year of birth; 22: Income; 23: Prenatal care; 24: Type of delivery; 25: Birth order; 26: Weather; 27: Mother's ethnicity; 28: Marital status; 29: Previous abortions; 30: Location of residence; 31: Diabetes; 32: Time since last delivery; 33: Previous preterm; 34: Paternal education.

Spatial model prediction

• Women addresses

NO2

High : 54.27

Low : 3.02

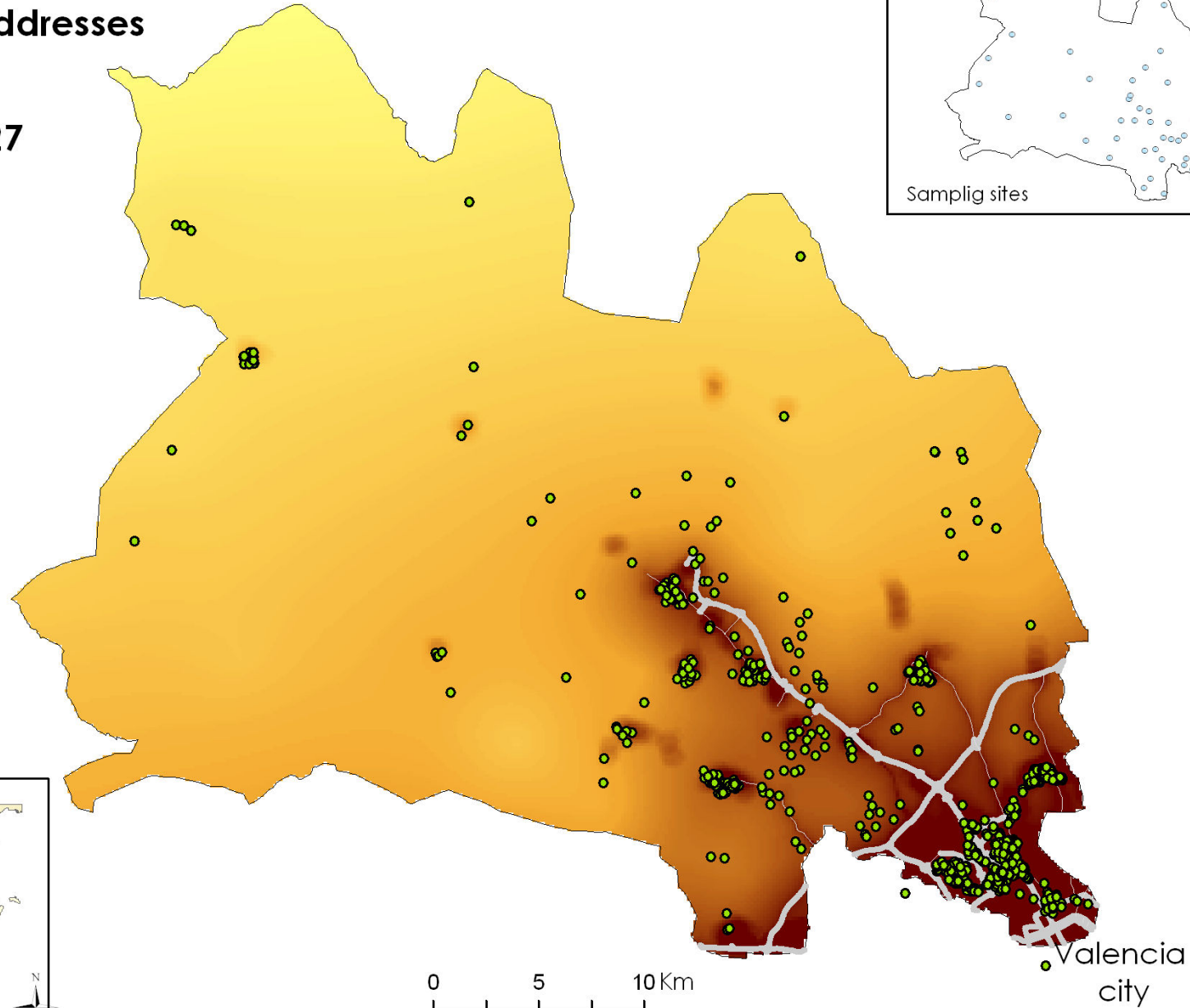
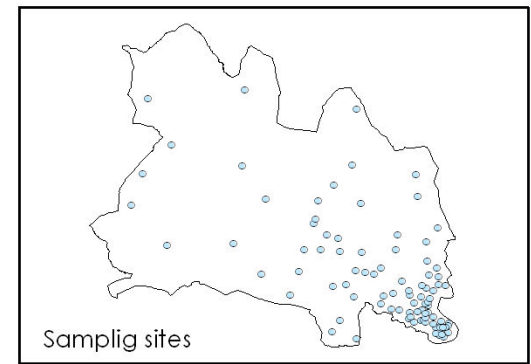
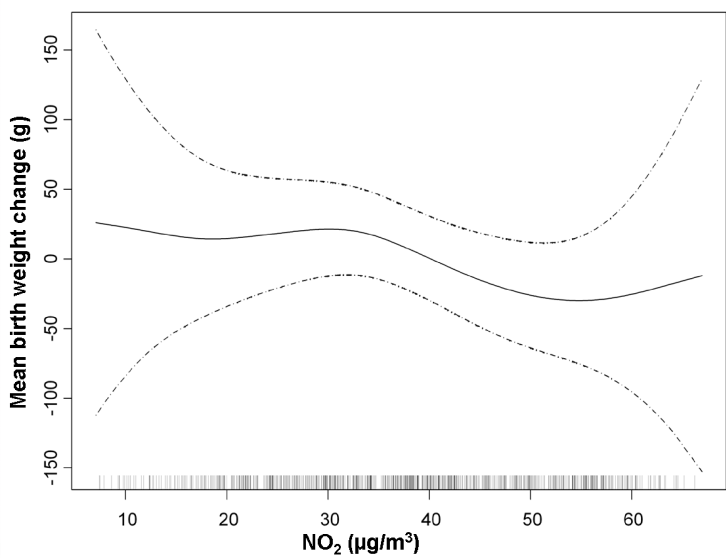
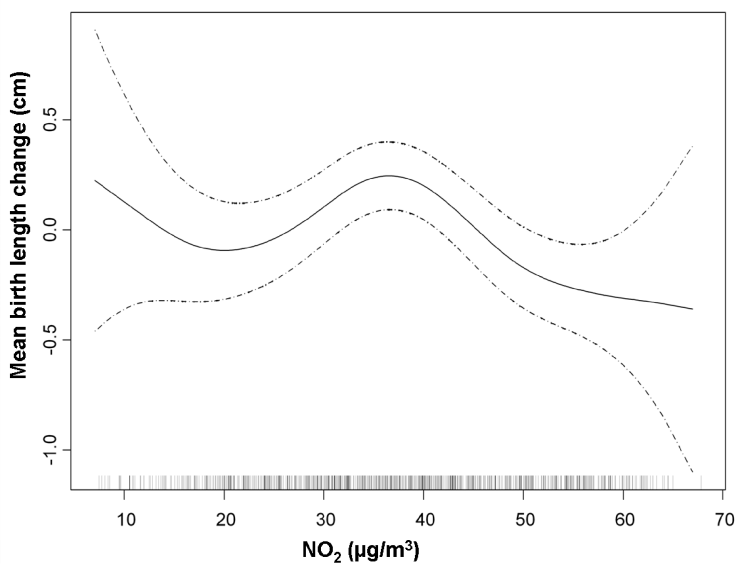


Figure 1

(A)



(B)



(C)

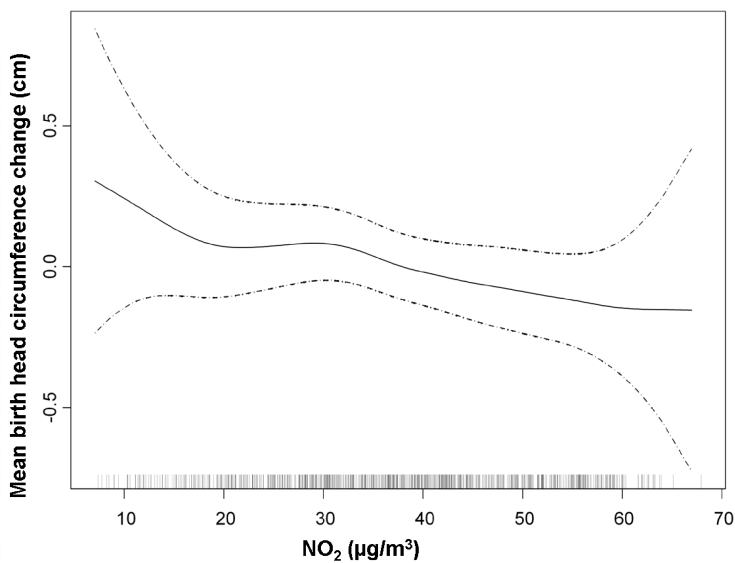
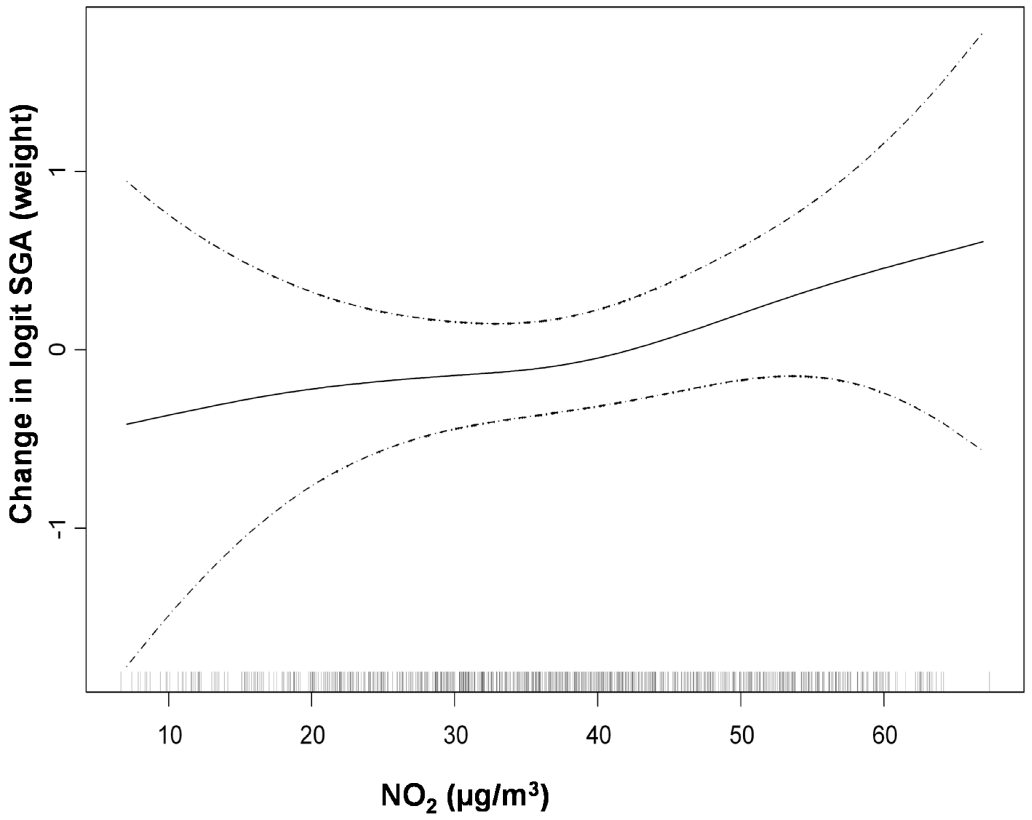


Figure 2

(A)



(B)

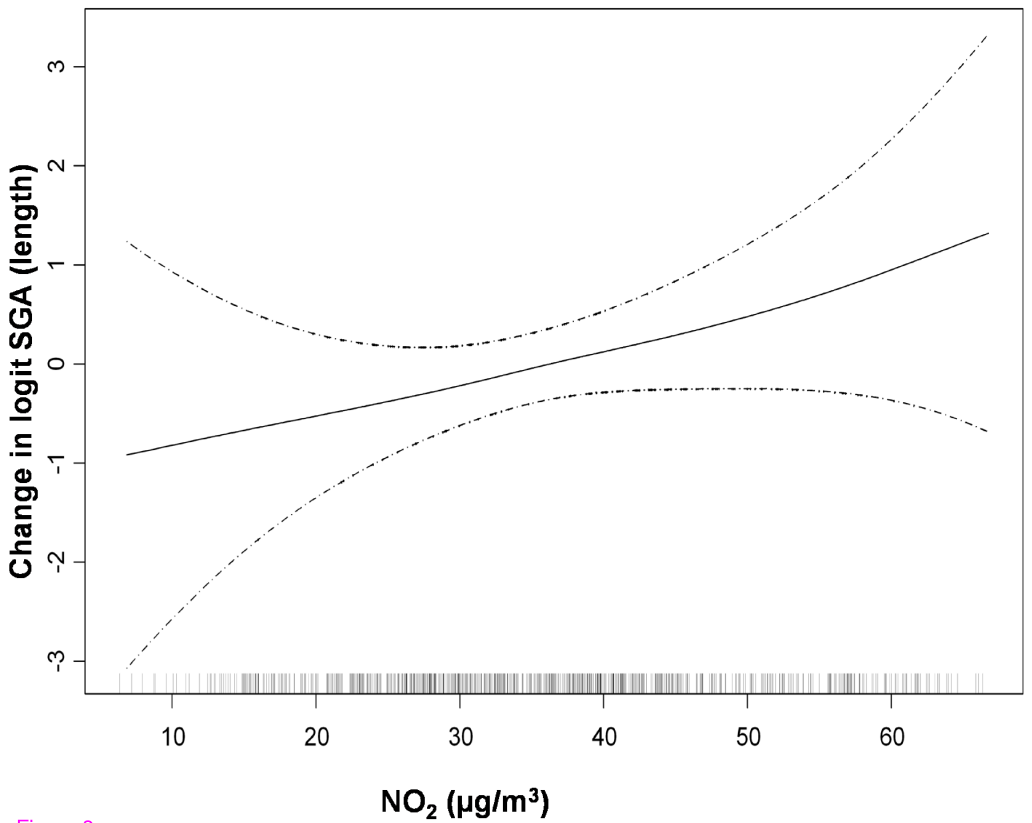


Figure 3