Air pollution exposure during pregnancy and reduced birth size in a mother and child cohort 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: 785 pregnant women and their newborns participated in the study. Ambient nitrogen dioxide (NO_2) was estimated by means of land use regression. NO_2 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), and small for gestational age (SGA). Association between exposure to residential outdoor NO_2 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 suggested a change in slope at NO_2 concentrations of around 40 µg/m^3. NO_2 exposure >40 µg/m^3 during the first trimester was associated with a change in birth length of -0.27 cm (95% confidence interval -0.51 to -0.03); during the second trimester with a change in birth weight of -40.4 grams (-96.3 to 15.6), and during the whole pregnancy with a change in birth HC of -0.17 cm (-0.34 to -0.00). The shape of the relation was seen to be roughly linear for the risk of being SGA. A 10 µg/m^3 increase in NO_2 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 foetal growth. Findings from this study provide further evidence indicating that strategies should be developed to reduce air pollution in order to prevent risks for foetal development.

Keywords: Air pollution; Nitrogen dioxide; Foetal growth; Small for gestational age; Birth weight

Introduction

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] .On the other hand, reduction in foetal growth has been associated with poor neurological development as well as with an increased risk of chronic diseases later in life [5,6].

A cohort study is the design of choice for evaluating the impact of air pollution on foetal 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 included smaller samples but more detailed, primary data [11-13]. Authors of recent methodological reviews [7, 14-16] agree that new prospective studies should allow adequate assessment of air pollution exposure, consider different time windows of exposure, and collect sufficient information on confounding variables.

Nitrogen dioxide (NO_2) 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 the case because outdoor NO_2 levels correlate well with traffic generated pollutants, they may be easily measured using passive samplers, and are routinely measured by air quality networks allowing 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 foetal development and children's health in the general population in Spain [19]. Our objective is to assess the association between residential exposure to outdoor NO_2 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 foetal death, 33 withdrew from the study or were lost to follow up, and 787 delivered a live infant. Exposure to outdoor NO_2 was assessed for 785 of the 787 mother-child pairs in the study, so this was our 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 km^2 including 34 municipalities with a reference population of almost 300,000 inhabitants and a wide 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) and 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 using the residuals method. 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 10^{th} percentile using standard percentile charts for sex and gestational age in the Spanish population [20].We did not classify SGA in terms of head circumference because our measurement procedure was different to that used in those published charts.

Assessment of air pollution exposure

A procedure was designed to assess individual exposure to NO_2 as a marker of outdoor air pollution. Ambient NO_2 concentrations for 93 sampling points covering the study area were obtained using radial symmetry passive samplers (Radiello®, Fondazione Salvatore Maugeri, Padua /Italy) that 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. Universal kriging was used to predict NO_2 levels at unmonitored sites, i.e. women's addresses. 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 by means of land use regression (LUR). Using daily information from seven stations of the monitoring network within 5 km or less of the study area, NO_2 spatial estimations were adjusted to correspond with the pregnancy period for each woman. In order to explore critical exposure windows an air pollution exposure indicator for each trimester of pregnancy was constructed. 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 [21].

Covariates and potential confounders

The mothers completed a detailed questionnaire about socio-demographic characteristics, environmental exposures and life style variables at two time points during their pregnancy (weeks 10-13 and 28-32). The questionnaires were administered at in-person interviews by previously trained interviewers. Potential confounders included maternal variables (see Table1), 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 [22]. 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 NO_2 levels and maternal and pregnancy characteristics. Association between exposure to residential outdoor NO_2 and anthropometric measures was assessed by linear regression for continuous variables and by 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 multivariate analyses because it was highly correlated with NO_2 levels. To assess the shape of the relation between measures at birth and NO_2 levels, we used adjusted GAM models to evaluate the linearity of the relation between NO_2 levels and the reproductive outcomes, comparing models with NO_2 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 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 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 NO_2 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. Mean residential outdoor NO_2 level corresponding to the 785 pregnancy periods was 36.9 µg/m^3 (SD 11.1) (25^{th}, 50^{th}, and 75^{th} percentile: 29.4, 37.9, and 45.6 µg/m^3). During the pregnancy period of 43.2% of the women, the outdoor NO_2 level at their residences was above 40 µg/m^3 - the World Health Organization guideline for annual NO_2 concentration [23].

Individual NO_2 levels for each trimester highly correlated with NO_2 levels for the whole pregnancy. The highest Pearson correlation was found between the average level for the whole pregnancy and the level for the second trimester (r: 0.92), followed by the third trimester (r: 0.83), and the first (r: 0.80). Considering the NO_2 levels for each individual trimester, the correlation between the second trimester and the other two (r: 0.69 with the first; and 0.65 with the third) was higher than between the first and third trimesters (r: 0.34).

Air pollution exposure and anthropometric measures

Simple analysis considering the variables in their continuous form showed a negative relationship between individual exposures to ambient NO_2 and anthropometric measures at birth (Table 2). This relation was statistically significant for first trimester exposure and both birth length and head circumference, and also for second trimester exposure and head circumference. After adjustment for covariates and potential confounders, the same temporal pattern persisted (Table 2). Although 95% confidence intervals yielded results that do not rule out the null hypothesis, birth head circumference and NO_2 exposure in the first trimester were marginally associated. Specifically, an increase of 10 µg/m^3 in NO_2 levels during the first trimester of pregnancy was associated with a decrease of -0.07 cm (95%CI -0.14 to 0.005) in head circumference.

When the shape of the relation between NO_2 exposure and anthropometric measures was assessed a non linear relation was seen. In most cases of multivariate analysis, the best fit was obtained when

NO_2 was introduced as a cubic smoothing spline with 3 or 4 degrees of freedom (Table 2). Graphical examination of the relation between NO_2 exposure during the first trimester and birth weight and length, and between NO_2 exposure during the second trimester and head circumference suggested a change in slope around 40 µg/m^3 (Figure 1). Therefore, the association between NO_2 exposure and weight, length and head circumference at birth was also analyzed considering NO_2 as a categorical variable. i.e. >40 µg/m^3 versus ≤40 µg/m^3 (Table 3). Results from multivariate analysis indicated that NO_2 exposure above 40 µg/m^3 during the first trimester was associated with a reduction in birth length of -0.27 cm (95%CI -0.51 to -0.03). Also a significant reduction in head circumference was found for exposures above 40 µg/m^3 during the whole pregnancy. Birth weight was just marginally associated with NO_2 exposure; i.e. a reduction of -40.4 grams in birth weight (95%CI -96.3 to 15.6) for the same comparison.

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

On 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 NO_2 during pregnancy (Table 4). After adjustment for potential confounders, a clearer association emerged with the second trimester being the most relevant window of exposure. A 10 µg/m^3 increase in NO_2 during the second trimester was associated with 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 only present results for the relation with NO_2 exposure as a continuous variable (Table 4).

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 NO_2 levels increased 10 µg/m^3 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 NO_2 levels above 40 µg/m^3. The first and second trimesters seem to be the relevant window of exposure.

Although particulate matter (PM) [either of diameter < 10 µm -PM_{10}- or < 2.5 µm -$PM_{2.5}$-] and carbon monoxide (CO) have been the two pollutants most frequently examined in studies on air pollution and birth outcomes, the effect of NO_2 has also been assessed. During 2004 and 2005 several reviews summarized the scientific evidence on the effects of air pollution on foetal growth [1, 3, 4], including a review by some of us [2]. In that review we identified six articles reporting associations between NO_x or NO_2 with either birth weight, low birth weight (LBW, measured as birth weight < 2500 g) or SGA. The three articles including 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 NO_2, results from the reviewed literature suggested some association with birth weight but were still not conclusive [8, 24, 25]. In recent years a considerable number of articles have been published in this field. We have identified 12 articles studying the association of NO_2 exposure with birth weight published after our previous review (Table 5) [10, 12, 26-35]. Of the four studies analyzing birth weight, an association was found in three of them, i.e. Bell et al. in Massachusetts and Connecticut (USA) [10], Mannes et al. in Sydney (Australia) [31], and Gouveia and cols in Brazil [28]; but not in the one within the National Children Study [30]. Interestingly, all except one of the articles [35] studying SGA found an association with NO_2, although in that study NO_2 was the only pollutant studied that was associated with head circumference. On the other hand, only three studies found an association between LBW and NO_2 [10, 27, 34]. This discrepancy may be due to the fact that the number of cases of SGA is greater than that of LBW term babies, and so the study has 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 done by simply selecting births that take place after a certain period of gestation (i.e. between weeks 37- 44).

Results for the different air pollutants varied in the different studies. Besides PM and CO, NO_2 appears as one of the pollutants more frequently associated with birth outcomes. For example, in their study in Vancouver, Brauer et al. [34] estimated residential exposures to air pollution using nearest monitor and inverse-distance weighting, and LUR [34]. Of the seven air pollutants studied, the association with

NO_2 was the most robust; an increase of 10 µg/m^3 in NO_2 estimated using inverse-distance weighting was associated with a 14% (95% CI 9% to 18%) increase in risk of SGA. The association was consistent when proximity to traffic was taken into account. Mothers who resided within 50 m of an expressway or highway had a 26% increased risk of an SGA compared with mothers residing >50 m.

Few studies have examined the relation between air pollution exposure during pregnancy and other anthropometric indicators at birth such as birth length or head circumference (HC). Studies in two cohorts of pregnant women have assessed the relationship between prenatal exposure to airborne polycyclic aromatic hydrocarbons (PAH) and foetal growth [36].One of these cohorts was from Cracow (Poland) and the other was made up of predominantly African-American and Dominican women from New York City (US). PAH exposure was related to a reduction in birth weight, length and HC among babies from Cracow, where exposure levels were higher. Among the New Yorkers, results indicated a greater effect on African-American women, with higher reductions in both birth weight and HC, showing some kind of susceptibility to PAH exposure. We found only two references of studies analyzing prenatal NO_2 exposure and birth length or HC, one from a birth-register based study in Australia [35], and another from the French Eden cohort [37]. In the first one, Hansen et al. [35] assessed birth length and HC among 26,617 term births in Brisbane, Australia. Exposures to the four pollutants studied (i.e. PM_{10}, black smoke, ozone and NO_2) were not significantly associated with a reduction in HC. However an interquartile range increase in NO_2 (11.1 µg/m^3), but not in other pollutants, during the third trimester was associated with a reduction in crow-heel length: -0.15 cm (95%CI -0.25 to -0.05) in NO_2. Our results are quite similar since we found a reduction in birth length of -0.07 cm (95%CI -0.15 to 0.02) for a 10 µg/m^3 increase in NO_2 during the first trimester. When we compared exposure above 40 µg/m^3 with exposure equal to or less than 40 µg/m^3, we found a reduction of -0.27 cm in birth length. In the French Eden cohort [37] a reduction of -0.31 cm in HC at birth was found when comparing NO_2 exposure in the highest tertile (>31.4 µg/m^3) to that in the lowest tertile. Our results are also consistent with these findings. We found a reduction of -0.17 (95%CI -0.34 to -0.003) when exposure >40 µg/m^3 during the whole pregnancy was compared with exposure equal to or below this level.

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 clearest relationship was found with exposure in the second trimester. Regarding reduced HC, when exposure was evaluated above vs. below 40 $\mu g/m^3$, exposure during the whole pregnancy was the most clearly related. This may indicate that in the case of growth retardation of HC, exposure during the whole pregnancy plays the most important role.

Most of the studies on the relation of ambient air pollution and adverse birth outcomes are based on birth register data, have a retrospective design and use data from air monitoring networks. In this prospective study we followed a pregnant cohort from early pregnancy and assessed exposure, health outcomes and covariates in detail. NO_2 obtained from LUR models has been used in epidemiological studies as a marker of traffic related air pollution [38]. This approach has also been used for assessing the influence of maternal exposure during pregnancy on foetal development [12]. We developed a protocol combining measurements from NO_2 passive samplers, kriging and LUR to obtain estimates of individual exposure to ambient NO_2 for each woman. We also performed four different campaigns to assess the stability over time of the spatial NO_2 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, 29]. Another strength of our study is the information available about each woman's residence throughout their pregnancy including changes in address during pregnancy.

Very few studies have completely assessed the shape of the relationship between air pollution exposure and reproductive outcomes. Most of them analyzed the relation using air pollution variables in the continuous form or comparing only two levels. Some attempted to examine the shape using tertiles or quartiles and found a relation with increasing risk of LBW at higher quartiles [12, 27]. Regarding NO_2 exposure and birth weight only Ha et al. [24] examined their relationship using GAM models, as we did in this study. In the former study, although the authors did consider the relation relatively linear, a change in the slope may be observed in the figures, with a higher negative gradient after NO_2 values around 32 ppb (60 $\mu g/m^3$). In our study, we found some indication for a threshold around 40 μg/m^3 associated with a reduction in birth length. 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 foetal growth are still not clear. There is some evidence that NO_2 alters foetal growth and so may play a causal role. NO_2 is a potent oxidant and increased lipid peroxidation in the maternal and/or foetal compartment has been found in preterm birth [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 measures of oxidant/antioxidant status. A high percentage of women suffered from pregnancy complications. The most common ones were anaemia (67%), threatened abortion/premature labour (33%), and signs of preeclampsia (23%). Methemoglobin was significantly elevated in all three conditions, compared with normal pregnancies. Reduced:total glutathione, an indicator of maternal antioxidant reserves, decreased, whereas cell-damaging lipid peroxide levels increased. More recently, Mohoroviz 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 the formation methemoglobin, which may lead to hypoxia and hypoxemia in pregnant women and has an important influence on maternal health as well as placental and foetal development.

Our study has some limitations. The number of women participating in the study is small compared with other studies. Subsequently, the power of the study is low and estimates have wide confidence intervals. In addition, we had no information available on other important pollutants like PM_{10}, $PM_{2.5}$, sulphur dioxide (SO_2), and CO that have been shown to play an important role in foetal growth in other studies. Consequently, we can not affirm that NO_2 is the air pollutant associated with birth measurements. Due to the colinearity between pollutants, NO_2 may simply be a proxy for other pollutants. NO_2 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. We did not have information on indoor levels of air pollutants either. However we did have information on environmental tobacco smoke exposure, an important source of indoor air pollution, and we controlled for this.

This study also has several strengths. Most of them have already been discussed: a) its prospective design starting at early pregnancy that made it possible to collect an extensive set of data on potential risk factors for SGA and reduced anthropometry; b) we used a combined LUR approach including spatial and temporal information on NO_2 distribution plus GIS that permitted individual exposure indicators to be estimated for each woman and for various periods of the pregnancy; c) we considered residential mobility during pregnancy avoiding this source of misclassification; d) we performed a meticulous analysis controlling for risks factors and potential confounders; e) and, lastly, a statistical approach using GAM models to examine the shape of the relationship and robust methods to minimize the role of extreme values were employed.

Conclusions

Findings from this mother and birth cohort study in Valencia, Spain, suggest that prenatal exposure to NO_2 affects the anthropometric development of the foetus, 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 NO_2 above 40 µg/m^3 during the first trimester of pregnancy and a reduction in birth weight. For birth length this association was only marginal.

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

Compared with other recent studies, NO_2 levels in the study area occupy an intermediate position, so results are not due to extreme exposure conditions. Taking into account the relation between foetal 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

NO_2: nitrogen dioxide

NO_x : nitrogen oxides

OR: odds ratio

PAH: polycyclic aromatic hydrocarbons

PM: particulate matter

PM_{10} : 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

SO_2 : 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 and conducted data analysis of the association of interest, and helped with manuscript preparation. CI prepared the outcome variables, developed the land use regression analysis and 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.

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Figure legends

Figure 1: Relationship between individual NO_2 exposure during first trimester and anthropometric measures at birth. Graphical estimation of the association and 95 % confidence interval for the non-linear model with lower AIC (degrees of freedom: df).

Figure 1(A). Birth weight (gr) and NO_2 exposure (3 df)

Figure 1(B). Birth length (cm) and NO_2 exposure (4 df).

Figure 1(C). Birth head circumference (cm) and NO_2 exposure (4 df)

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

Figure 2: Relationship between individual NO2 exposure during second trimester and small for gestational age, in birth weight and in birth length in multivariate analysis. Graphical estimation of the association and 95 % confidence interval 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 NO_2 exposure (2 df).

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

Figure 2(B). Logit of small for gestational age in birth length and NO_2 exposure (2 df)

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

Table 1. Characteristics among 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]		
Categorical variables		N[a]	(%)	Mean	(SD)	p[c]	%	p[e]	Mean	(SD)	p[c]	%	p[e]	Mean	(SD)	p[c]
Maternal age	<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
(years)	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	<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
Weight (Kg)	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	Low	286	(37)	3320.2	(390.7)	0.001	9.4	0.011	50.6	1.8	0.045	4.2	0.053	34.3	1.3	0.357
weight gain[f]	Normal	190	(24)	3234.1	(440.6)		18.0		50.3	2.0		9.5		34.2	1.3	
	High	300	(39)	3382.5	(457.3)		9.7		50.7	1.8		5.0		34.4	1.4	
Pre-pregnancy	<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
BMI[f]	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	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 at 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 at 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	
	Europe	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	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

at home	Exposed	366	(47)	3305.8	(444.6)		12.8		50.5	1.8		5.2		34.2	1.2	
Alcohol	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
consumption	0-1	260	(34)	3359.8	(433.5)		10.0		50.6	1.8		5.4		34.5	1.5	
(daily mean in g.)	>=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 at last	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
menstrual period	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 755 in all variables because some missing values. 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/m^2)
[g] Beta coefficient (and standard error) from simple linear regression
[f] Odds ratio (95% confidence interval)

Table 2. Individual exposure to ambient NO_2 in different time periods during pregnancy and anthropometric measures. Estimates are expressed as the change in birth and length size for a 10 µg/m^3 increase in the mean NO_2 levels at each woman residence during the correspondent period. Unadjusted and adjusted models.

	Birth weight (in g)[a] (n:785)			Birth length (in cm)[a] (n:784)			Birth head circumference (in cm)[a] (n:782)		
NO_2 exposure period	**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)

[a] Standardized for gestational age

[b] Shape of the relationship after contrast between model with NO_2 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 at last menstrual period.

-Birth length = maternal age, maternal height, gestational weight gain, parity, maternal education, smoking during pregnancy, working status at 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 at last menstrual period .

Table 3. Individual exposure to ambient NO_2 >40 μg/m^3 in different time periods during pregnancy and anthropometric measures. Estimates are expressed as the change in birth anthropometric measures comparing NO_2 exposure >40 μg/m^3 vs. exposure ≤40 μg/m^3 levels at each woman residence during the correspondent period. Unadjusted and adjusted models.

	Birth weight (in g)[a] (n=785)		Birth length (in cm)[a] (n:784)		Birth head circumference (in cm)[a] (n:782)	
NO_2 exposure period	**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 at last menstrual period.

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

Table 4. Individual exposure to ambient NO_2 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) by a 10 µg/m^3 increase in the mean NO_2 levels at each woman residence during the correspondent period. Unadjusted and adjusted models.

	SGA – weight (n= 785)			SGA – length (n=784)		
NO_2 exposure period	**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 NO_2 in non-linear vs linear form; L: linear; NL: Non-linear (and degrees of freedom of the selected model)

[b]Adjusted 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 at 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 at last menstrual period.

Table 5. Results from studies assessing NO_2 effect on birth weight published 2003-2008

Study	Location (time period)	Design Nº of births	Outcome(s)	Exposure: Assessment: -data source; -individual assignment	Exposure: Mean (SD) NO_2 levels, in µg/m³	Exposure: Pregnancy periods examined	Exposure: NO_2 increase assessed	Results β (95% CI) grams OR (95% CI)	Adjusted for[a]	Other outcomes/ air pollutants studied / comments
This 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 µg/m³ (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 [34]	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 µg/m³ (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 µg/m³ (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 µg/m³ (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 [35]	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 µg/m³ (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 g/m³) third trimester on crow-heel length : -0.15cm (95%CI: -0.25 to -0.05). No effects for PM_{10}, BSP, O_3
Liu et al., 2007 [32]	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/m³ (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 $PM_{2.5}$ where no longer observed. No effects for SO_2 and O_3.
Mannes et al., 2005 [31]	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/m³ (1 ppb) increase among women living <5km 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 [30]	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/m³ (25 ppb)	β for birth weight Entire pregnancy: -7.2 g (-34.7 to 20.4) OR for SGA 1stTrimester : 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	O3 exposure during 2nd and 3rd trimester and CO exposure during 1st trimester were associated with reduced birth weight.
Wilhelm and Ritz, 2005 [29]	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 NO2 are not provided. No association between NO_2 and LBW after adjusting for CO and/or PM10.	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
Gouveia et al., 2004 [28]	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 NO2 monitoring stations in the city	117.9 (51.2)	Trimester	10 µg/m³ (5.3 ppb)	β for birth weight 1st trimester: -7.0 g (-14.3 to 0.3) No association between NO2 and LBW	1,2,7,10,18,23,24	An association between LBW and CO and $PM_{2.5}$ exposure during 1st trimester was found
Lee et al.,2003 [27]	Seul, 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/m³ (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 tor 3rd trimester for all pollutants, and for 1st trimester for SO_2.
Liu et al., 2003 [26]	Vancouver (Canadá) (1986-1998)	Birth register-based study 229085	SGA born between wg 37-44 LBW	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/m³ (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)	1,2,7,18,19	An association between SGA and CO and SO_2 first month exposure was also found

			excluded <500g or <22wg					**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)**		

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: <10^{th} 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 5^{th}. P95th: Percentile 95^{th} ; IQR: Interquartile range.

[a] 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.

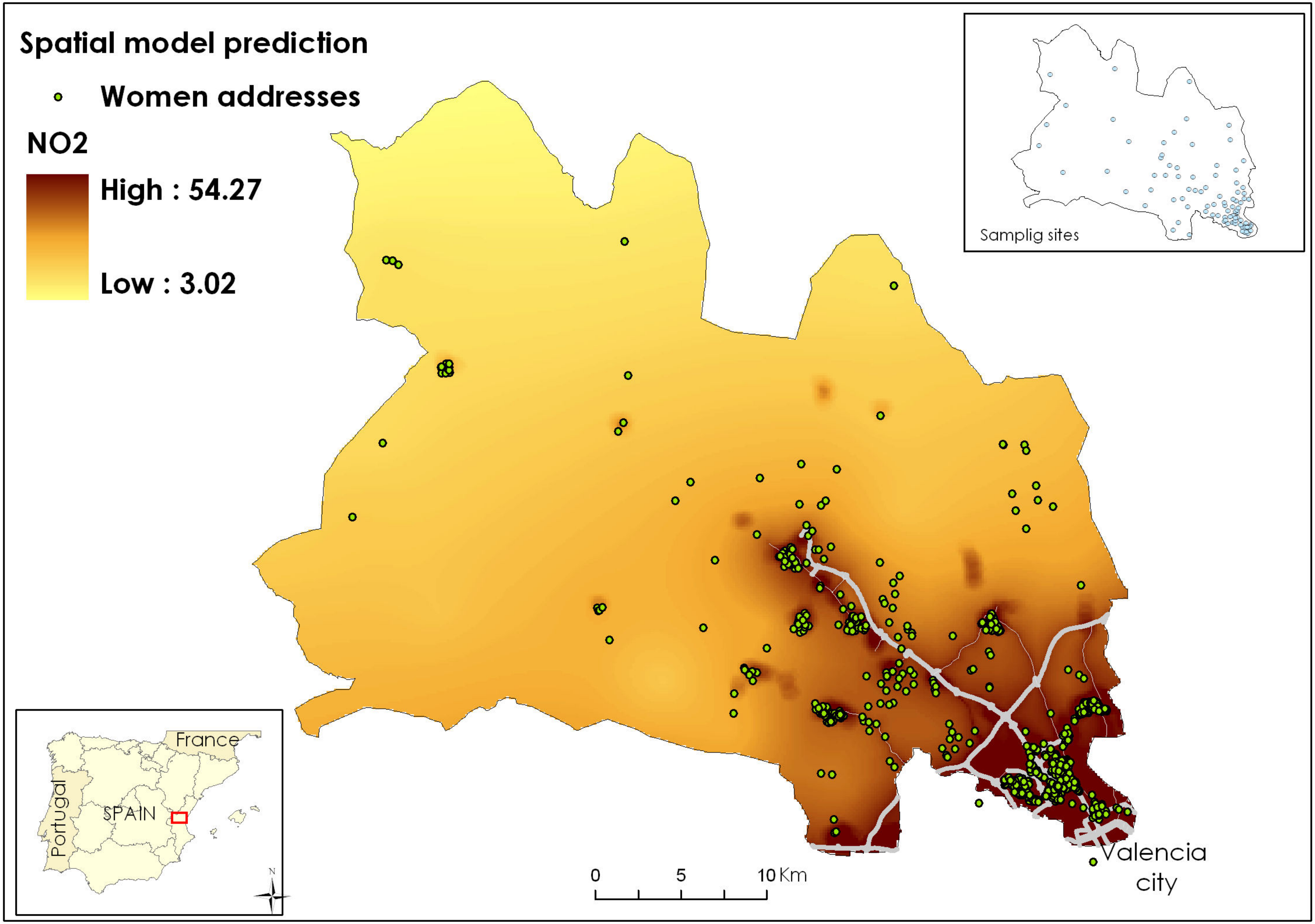
Spatial model prediction
Women addresses
NO2
High : 54.27
Low : 3.02
Samplig sites
France
Portugal
SPAIN
N
0
5
10 Km
Valencia
city

Figure 1

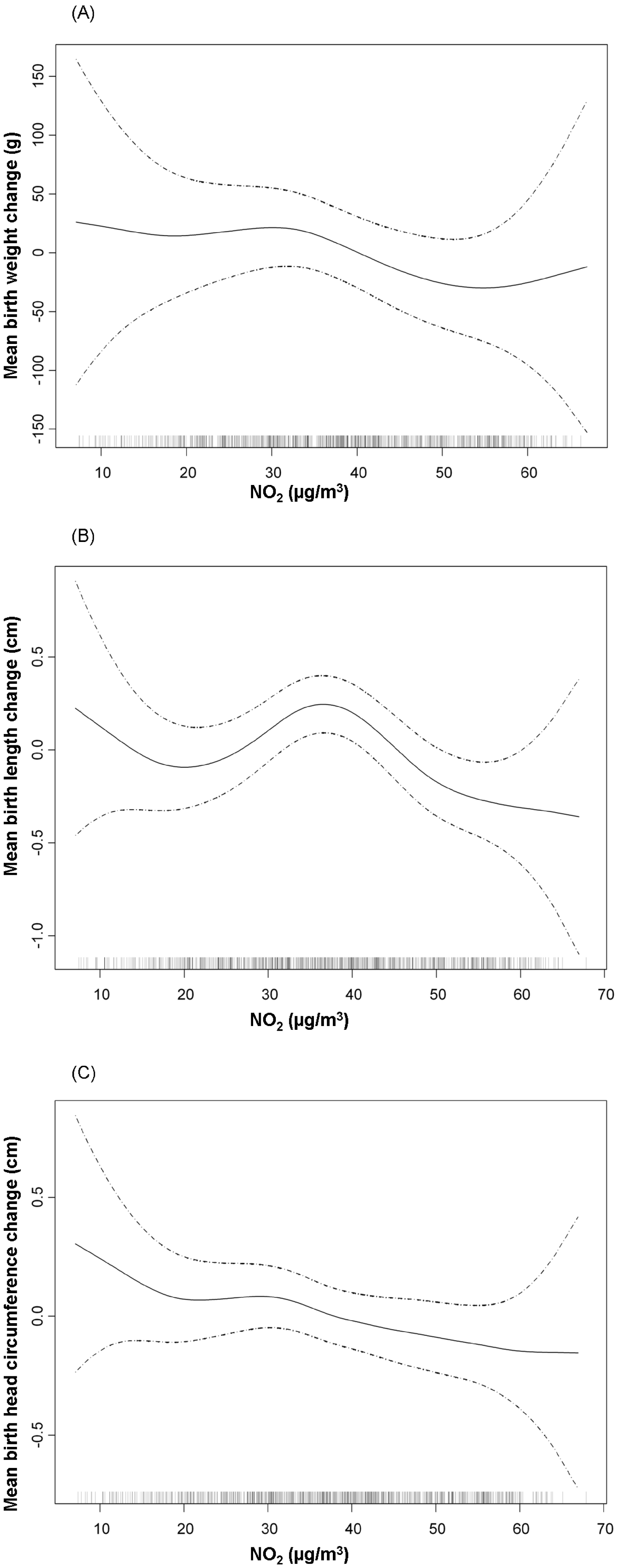
(A)
Mean birth weight change (g)
150
100
50
0
-50
-100
-150
10
20
30
40
50
60
NO2 (µg/m3)
(B)
Mean birth length change (cm)
0.5
0.0
-0.5
-1.0
10
20
30
40
50
60
70
NO2 (µg/m3)
(C)
Mean birth head circumference change (cm)
0.5
0.0
-0.5
10
20
30
40
50
60
70
NO2 (µg/m3)

Figure 2

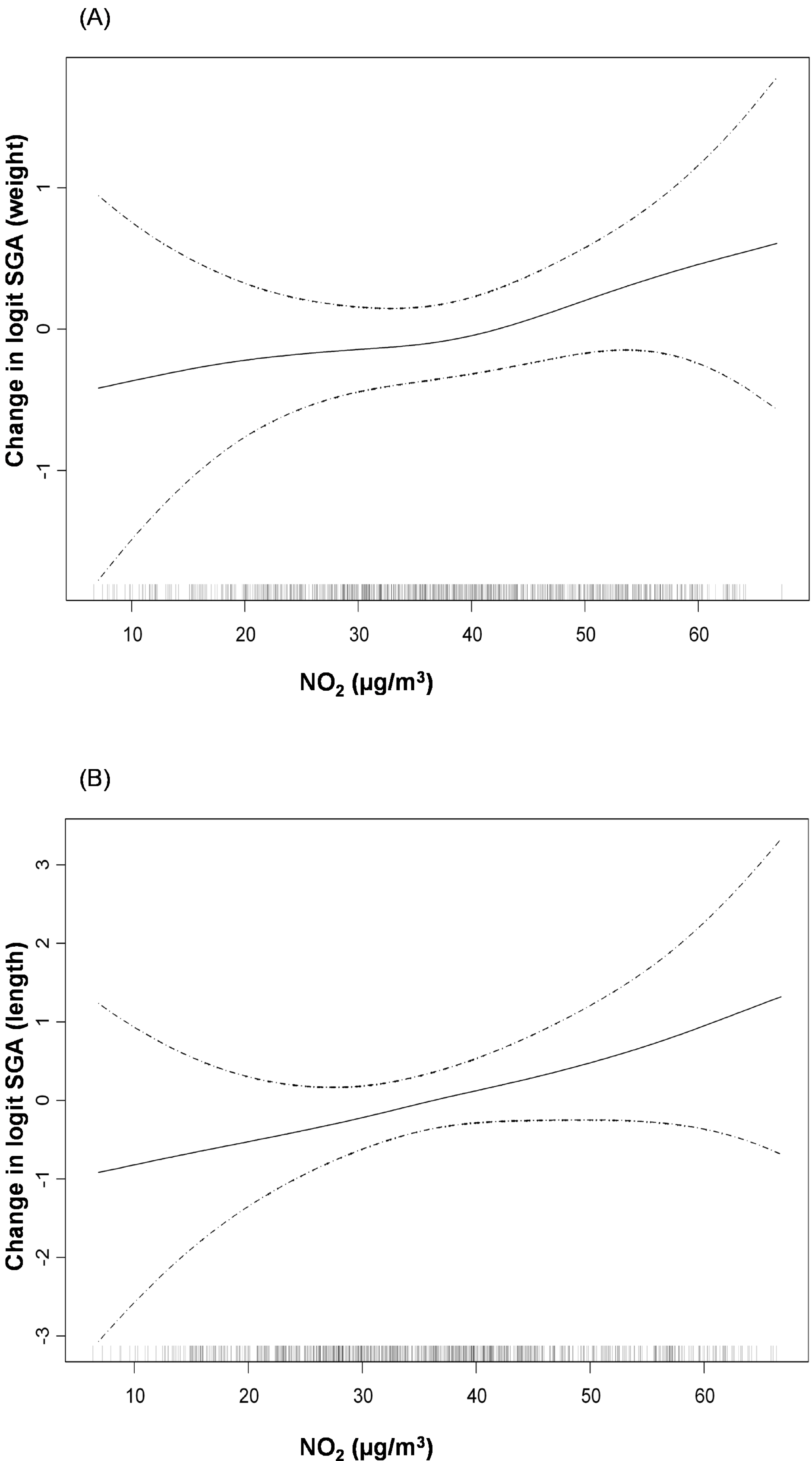
(A)
Change in logit SGA (weight)
1
0
-1
10
20
30
40
50
60
NO2 (µg/m3)
(B)
Change in logit SGA (length)
3
2
1
0
-1
-2
-3
10
20
30
40
50
60
NO2 (µg/m3)

Figure 3