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Maternal Exposure to Nitrogen Dioxide during Pregnancy and Offspring Birthweight: Comparison of Two Exposure Models

Johanna Lepeule[1,2], Fabrice Caïni[3], Sébastien Bottagisi[1,2], Julien Galineau[4], Agnès Hulin[3], Nathalie Marquis[4], Aline Bohet[5,6], Valérie Siroux[2,7], Monique Kaminski[8,9], Marie-Aline Charles [10,11], Rémy Slama[1,2] and the Eden mother-child cohort study group

1: Inserm, Avenir Team "Environmental Epidemiology Applied to Fecundity and Reproduction", Institut Albert Bonniot, U823, Grenoble, France

2: University J. Fourier Grenoble, Grenoble, France.

3: ATMO Poitou-Charentes, Perigny, France.

4: AIRLOR, Vandoeuvre les Nancy, France.

5: Inserm, U1018, CESP Centre de Recherche en Epidémiologie et Santé des populations, Team Epidemiology of reproduction and child development, Le Kremlin-Bicêtre, France.

6: Univ Paris-Sud 11, UMRS 1018, Le Kremlin Bicêtre, France

7: Inserm, Team « Epidemiology of Cancer and Severe Diseases », Institut Albert Bonniot, U823, Grenoble, France

8: UMR S953, IFR 69, Epidemiological Research Unit on Perinatal and Women's and Children's Health, Villejuif, France.

9: UPMC, Paris, France.

10: Inserm, U1018, CESP Centre de Recherche en Epidemiologie et Santé des Populations, Team Epidemiology of obesity, diabetes and renal disease over the life course, Villejuif, France.

11: University Paris-Sud 11, UMRS 1018, Le Kremlin Bicêtre, France

Corresponding author: Johanna Lepeule, johanna.lepeule@ujf-grenoble.fr, Phone: +33 476 54 94 66; Fax: +33 476 54 94 14

Inserm, Team “Environmental Epidemiology applied to Fertility and Human Reproduction”, U823, Institut Albert Bonniot, BP 170, La Tronche, F-38042 Grenoble CEDEX 9, France.

Running title: Comparison of Two Exposure Models to Air Pollutants

Key-words: atmospheric pollution, birthweight, cohort, exposure modeling, geostatistical, measurement error, monitoring station, nitrogen dioxide, spatial variation, temporal variation

Abbreviations:

AQMS	: Air Quality Monitoring Station
CI	: Confidence Interval
LUR	: Land Use Regression
NO_2	: Nitrogen dioxide
TAG model	: Temporally Adjusted Geostatistical model

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Outline of manuscript -section headers

Abstract

Background: Studies of the effects of air pollutants on birthweight often assess exposure with permanent air quality monitoring stations (AQMS) networks; these have a poor spatial resolution.

Objective: We aimed to compare the exposure model based on the nearest AQMS and a temporally adjusted geostatistical (TAG) model with a finer spatial resolution, for use in pregnancy studies.

Methods: The AQMS and TAG exposure models were implemented in two areas surrounding medium-sized cities in which 776 pregnant women were followed as part of the EDEN mother-child cohort. The exposure models were compared in terms of estimated nitrogen dioxide (NO_2) levels and of their association with birthweight.

Results: The correlation between the two estimates of exposure during the first trimester of pregnancy was r=0.67, 0.70, and 0.83 for women living within 5, 2 or 1 km of an AQMS, respectively. Exposure patterns displayed greater spatial than temporal variations. Exposure during the first trimester of pregnancy was most strongly associated with birthweight for women living less than 2 km away from an AQMS: a 10 $\mu g/m^3$ increase in NO_2 exposure was associated with an adjusted difference in birthweight of -37g (95% confidence interval (CI), -75; 1g) for the nearest AQMS model and of -51g (95% CI, -128; 26g) for the TAG model. The association was less strong (higher p-value) for women living within 5 or 1 km of an AQMS.

Conclusions: The two exposure models tended to give consistent in terms of association with birthweight, despite the moderate concordance between exposure estimates.

Introduction

Several epidemiological studies have reported associations between maternal exposure to nitrogen dioxide (NO_2) during pregnancy and fetal growth assessed by birthweight, taking into account gestational duration (e.g., Bell et al. 2007; Liu et al. 2007; Ritz and Wilhelm 2008; Slama et al. 2008; Wilhelm and Ritz 2003). Various approaches may be used to estimate exposure, from the use of biomarkers of exposure to personal dosimeters and environmental models. Most previous studies have been based on measurements from permanent air quality monitoring stations (AQMS), using data from the AQMS closest to the subject's home address, or interpolating data for neighboring monitors, for which measurements are averaged over the entire pregnancy or over each trimester of pregnancy. This approach has the advantage of making use of readily available exposure data, being simple to implement and, because pollutants are assessed on an hourly or at least weekly basis, being highly flexible in terms of the temporal exposure window considered. However, the spatial density of AQMS networks is generally low, and studies have shown that the data provided by permanent AQMS are representative only of air pollution levels in the close vicinity of the station (Lebret et al. 2000). Studies based on AQMS measurements assume that air pollution levels are homogeneous within a buffer of several kilometers around each monitor, or, at least, that exposure misclassification introduces no major bias into the estimated exposure-response relationship. However, studies based on the simultaneous use of several exposure models have demonstrated that the amplitude of the measurement error may be large (Nerriere et al. 2005; Nethery et al. 2008; Sarnat et al. 2005). Moreover, at least for respiratory or cardiovascular outcomes, measurement error may have a large impact on the exposure-response relationship (Miller et al. 2007; Van Roosbroeck et al. 2008). This issue has very little been studied in the context of reproductive outcomes (Brauer et al. 2008).

We aimed to compare the exposure model based on the nearest AQMS and a temporally adjusted geostatistical (TAG) model based on measurement campaigns with a fine spatial resolution and also focusing on background pollution, in the context of a mother-child cohort. These models were compared in terms of estimated NO_2 levels and the estimated association between NO_2 levels and birthweight.

Materials and Methods

Study population and data collection

This study was conducted in a subgroup of the French EDEN (study of pre and early postnatal determinants of the child's development and health) mother-child cohort. Pregnant women at less than 26 weeks of gestation were recruited from the maternity wards of Poitiers and Nancy University Hospitals (France), between September 2003 and January 2006. Gestational age was assessed from the date of the last menstrual period (Slama et al. 2009). Exclusion criteria were a personal history of diabetes, multiple pregnancy, intention to deliver outside the university hospital or to move out of the study region within the next three years and an inability to speak and read French. The birthweight of the infants were extracted from the maternity records. Information on maternal active and passive smoking, height, weight, and educational level were collected by interview between 24 and 28 weeks of gestation, and by questionnaire after birth. The study was approved by the relevant ethical committees (*Comité Consultatif pour la Protection des Personnes dans la Recherche Biomédicale*, Le Kremlin-Bicêtre University Hospital, and *Commission Nationale de l'Informatique et des Libertés*), and all participating women gave informed written consent for their own participation and that of their children. More details of this study can be found elsewhere (Drouillet et al. 2008; Slama et al. 2009; Yazbeck et al. 2009).

Exposure to NO_2

We restricted the cohort to pregnant women living in two areas, one of 165 km^2 around Nancy and the other of 315 km^2 around Poitiers, in which air quality measurement campaigns have been conducted. We then further restricted the study area to the immediate vicinity of an AQMS, focusing on circular buffers with a radius of 5, 2, and 1 km around each AQMS (Figure 1B and D). The detailed addresses of all women were geocoded in Arcgis 9.3 (ESRI, Redlands, CA, USA). For both models, changes of home address between inclusion and delivery were taken into account by calculating time-weighted means of exposure over the relevant time windows (whole pregnancy, and each trimester (92 days per trimester if no delivery) of pregnancy).

Nearest air quality monitoring station model (model 1)

We obtained air pollution data from the AIRLOR (Nancy) and ATMO-PC (Poitiers) AQMS networks. All permanent AQMS measuring NO_2 concentration during the study period and located within 2.5 km of the limits of the study areas were considered (three in the Poitiers area and six in the Nancy area, Figures 1A and C), excluding those labeled as *traffic* (i.e. located <5 m from a road with traffic levels of >10,000 vehicles/day (ADEME 2002)) or *industrial* stations. For each woman *i*, hourly measures of NO_2 concentration by the AQMS *j* closest to her home address were averaged over each time-window Δ_t^i considered (noted Δ_t for convenience), to obtain our exposure estimate $E1_{j,\Delta_t}^i$.

Temporally adjusted geostatistical model (model 2)

NO_2 measurement campaigns with a Palmes diffusive sampler (Palmes et al. 1976) were conducted in the urban and peri-urban areas of both cities. The diffusive samplers were located so as to give measurements of background pollution in each area (61 locations in the Poitiers area, 98 locations in the Nancy area). The campaigns lasted 14 days (Poitiers) or 10 to 15 days (Nancy) and were repeated throughout the year to capture seasonal variations. Nine campaigns were performed in 2005 in the Poitiers area and 10 were performed in 2002 in the Nancy area (AIRLOR 2004; ATMO-PC 2007). In each area, for each passive sampler, the AQMS giving the measurements most strongly correlated with the measurements of the passive sampler during campaigns was used to estimate mean annual concentration at each measurement location. These estimated annual concentrations were smoothed over the whole area with kriging techniques (Chilès and Delfiner 1999) on a 50x50 meter grid, with Isatis Software (Géovariances, Fontainebleau; Figure 1B and D). This corresponded to our estimate of C^i_{yearly}, the mean NO_2 concentration at the home address, for the year 2005 in Poitiers and 2002 in Nancy (spatial component of the model).

The estimated annual NO_2 concentrations were then combined with time-specific measurements from the permanent AQMS to capture temporal variations in concentrations. This approach has previously been used in the context of LUR models (Slama et al. 2007). The hourly NO_2 measures of all AQMS from the area were averaged over each time-window Δ_t considered ($S^i_{all, \Delta t}$) and also over the year in which the measurement campaign was performed ($S_{all, yearly}$). The ratio $S^i_{all, \Delta t} / S_{all, yearly}$ was the temporal component of the model. The temporally adjusted estimate of NO_2 exposure $E2^i_{\Delta t}$ for woman *i* was the product of the spatial and temporal components, or

$$E2^i_{\Delta t} = C^i_{yearly} \times \left(\frac{S^i_{all,\ \Delta t}}{S_{all,\ yearly}}\right). \qquad [1]$$

Statistical analyses

Spatial and temporal variations in exposure

For each model, the relative contribution of spatial (or temporal) variations in exposure contrasts was assessed by Pearson's correlation coefficient between the exposure estimate and its spatial (or temporal) component. We also carried out variance decomposition. The nearest AQMS model could be broken down as follows

$$E1^{i}_{j,\Delta_t} = \overline{E1_{\Delta t}} + \left(S^{i}_{j} - \overline{E1_{\Delta t}}\right) + \left(E1^{i}_{j,\Delta_t} - S^{i}_{j}\right), \qquad [2]$$

With $\overline{E1_{\Delta t}}$ being the mean level of exposure of all women during the time-window Δ_t, and S^i_j the NO_2 concentration at AQMS *j* averaged over the entire study period, so as to obtain a spatial component $\left(S^{i}_{j} - \overline{E1_{\Delta t}}\right)$ dependent solely on the address of the woman. This corresponded to our estimate of the spatial component of the AQMS model; $(E1^i_{j,\Delta t} - S^i_j)$ corresponded to our estimate of the temporal component of the model. The TAG model was log-transformed and expressed as

$$\log\left(E2^{i}_{\Delta t}\right) = \log\left(C^{i}_{yearly}\right) + \log\left(\frac{S^{i}_{all,\ \Delta_t}}{S_{all,\ yearly}}\right) \qquad [3]$$

for the variance analysis. These analyses were restricted to women who did not change address during pregnancy.

Comparison of the exposure estimates generated by each model

Exposure estimates for the two models were compared by Kruskal-Wallis rank tests and by calculating correlation coefficients (r). The distributions of the exposures estimated by the nearest AQMS model and by the TAG model were plotted either as a function of the AQMS closest to woman's home address, then excluding the AQMS located in the city-center. We also assessed the concordance between the estimates generated by the two models, classified into tertiles, by determining percentage concordance and the kappa coefficient (K). Bland-Altman plots were used to estimate the magnitude of the systematic error between the two exposure models (Bland and Altman 1986).

Exposure-response relationship

We studied the relationship between birthweight and NO_2 exposure during each exposure window in linear regression models taking into account gestational age and adjustment factors. Linear trend tests were performed with a categorical variable, the value of which corresponded to the category-specific median NO_2 concentration. The adjustment factors were selected on the basis of *a priori* knowledge (Rothman et al. 2008). We adjusted for active and passive smoking during the second trimester of pregnancy, because these factors were more strongly associated with birthweight than exposures during the first trimester, the third trimester or any of the three trimesters. We also adjusted for sex of the newborn, maternal height (as a continuous variable), pre-pregnancy weight (broken stick model with a knot at 60 kg), birth order, maternal age at end of education, center, and trimester of pregnancy. Statistical analyses were carried out with STATA statistical software (Stata SE 10.1, Stata Corp, College Station, TX). Analyses were repeated for the three buffers considered (less than 5, 2 or 1 km from an AQMS).

Results

Population

Of the 1893 women from the cohort with a known offspring birthweight, 776 lived in the study area, less than 5 km from an AQMS, during at least one trimester of pregnancy (431 and 158 women lived within 2 and 1 km of an AQMS, respectively). Mean birthweight was 3284 g (25, 50, 75th percentiles, 3005, 3310, 3620 g). The characteristics of the study population are described in Table 1.

Exposure to air pollutants

Estimates of exposure to NO_2 were higher in Nancy than in Poitiers, whatever the exposure model and exposure window considered (Figure 1, Tables 1 and 2). The nearest AQMS model estimate during pregnancy was more strongly correlated with the spatial component of the TAG model (r=0.61, 0.68, 0.84, for the 5, 2, 1 km buffers, respectively) than with its temporal component (r=0.35, 0.35, 0.45, respectively). For both models, exposure estimates throughout pregnancy were subject to strong spatial variation (accounting for >90% of the variance of exposure, Table 3). Temporal variations made a greater contribution to total variation when we considered trimester-specific windows, but remained smaller than spatial variations for the nearest AQMS model (72-84% for spatial variation and 20-25% for temporal variation), whereas the contributions of the spatial and temporal variation components were similar for the TAG model (43-61% for spatial variation and 44-57% for temporal variation, Table 3). The buffer around the AQMS studied had no major effect on the relative contributions of spatial and temporal components of variation.

The levels and range of NO_2 concentrations estimated by the nearest AQMS model were greater than those estimated by the TAG model (Table 2). Bland and Altman plots (See Supplemental Material, Figure 1) showed that the difference between the two models increased with mean exposure estimates. This pattern was principally due to between-model differences for women living in the city-centers (mean NO_2 concentrations estimated by the nearest AQMS model were higher and ranges were narrower than for the TAG model), rather than in the peri-urban areas. Indeed, the exposure distributions for the two models became more similar when city-center AQMS measurements were not taken into account (Figure 2). All this indicates that the overestimation of NO_2 exposure levels by the AQMS model with respect to the TAG model mainly concerned the women who were also the most exposed with the TAG model.

The correlation and concordance (K) between the two exposure models were fair (0.40 -0.74) when we considered all the women living within 5 km of an AQMS (Table 2 and Supplemental Material, Figure 2), but were stronger if we restricted the study population to women living within 2 (0.37 -0.79) or 1 km (0.59 -0.87) of an AQMS. The correlation and concordance between the two exposure models also differed between the areas (Nancy/Poitiers) and between the city center and suburban areas (See Supplemental Material, Figure 2).

Associations between air pollutants and fetal growth

The patterns of association with birthweight identified were similar for the two exposure models, in terms of estimates of adjusted effects and confidence intervals (CI), although these associations were stronger for the nearest AQMS model (Figure 3, and see Supplemental Material, Table 1). The first and third trimesters of pregnancy corresponded to the exposure windows most clearly associated with effects on birthweight, for both exposure models. For women living less than 2 km from an AQMS, an increase of 10 $\mu g/m^3$ in NO_2 concentration during the first trimester of pregnancy was associated with an adjusted change in mean birthweight of -37 g (95% CI, -75; 1 g) for the nearest AQMS model and of -51 g (95% CI, -

128; 26 g) for the TAG model. Qualitatively similar results were obtained when exposure was coded in tertiles (See Supplemental Material, Table 1). For the AQMS model, the parameter quantifying the association between NO_2 exposure and birthweight approached 0 as buffer size increased. Similar results were obtained if no adjustment was made for the center (results not shown).

Discussion

Our study is one of the first to describe associations between NO_2 exposure assessed with a TAG model and birthweight, and to compare this model with the more commonly used approach based on permanent AQMS. Models were compared in terms of both exposure estimates and association with birthweight. The nearest AQMS model was influenced by the location of monitors. Variations in exposure were mostly due to spatial rather than temporal variations in both models, with temporal variation making a larger overall contribution to total variation in the TAG model than in the nearest AQMS model. The concordance between NO_2 exposures estimates with the two models was fair when the 5 km buffer was considered. This concordance was stronger if the analysis was restricted to women living closer (<2 km, and more clearly, <1 km) to an AQMS. When exposure was coded as a continuous term, associations with birthweight for the TAG model were consistent with those obtained in analyses based on exposure estimated from the nearest AQMS model, for the various buffers around AQMS and exposure windows.

The TAG model is thought to have a better spatial resolution than the nearest AQMS model, due to the use of data from fine measurement campaigns, with no loss of temporal resolution, because TAG exposure estimates were seasonalized on the basis of AQMS measurements. The stronger contribution of the spatial component in the nearest AQMS model than in the TAG model may at first glance appear counterintuitive, as the AQMS model could be considered to be essentially based on temporal variations. However, this finding may be accounted for by the considerable variation of the concentrations obtained with different AQMS, some of which (in the city center) were influenced by traffic, despite meeting the criteria for background stations. This illustrates the extent to which the nearest AQMS estimates depend on the location of the monitors, and the need for exposure models with a finer spatial resolution in studies with medium- or long-term exposure windows (3 to 9 months in our study). As passive samplers were located at background sites less affected by traffic, the TAG approach led to a more purely background model than the AQMS approach. The higher concentrations estimated by the nearest AQMS model than by the TAG model (Table 2) may be accounted for by this feature. The TAG model may also smooth extreme exposure values, leading to an underestimation of the role of spatial variation.

One possible limitation of the TAG model stems from the approach used to *seasonalize* this model, in which we assumed that spatial differences in exposure remained constant over time. This assumption was found to be reasonable for an LUR model developed in Rome (Porta et al. 2009), but may not hold in other areas with different characteristics.

Several studies have evaluated the performance of AQMS for estimating exposure to air pollutants (Marshall et al. 2008; Nerriere et al. 2005; Nethery et al. 2008; Sarnat et al. 2005). The last three of these studies reported poor concordance between AQMS estimates and personal monitoring data, which is not surprising because personal exposure is not expected to strictly correspond to background levels of air pollution at the home address. Marshall et al. (2008) reported correlations and Kappa coefficients for estimates from the nearest AQMS model (within 10 km) and estimates stemming from either an LUR (r=0.61, K=0.42) or a dispersion model (r=0.37, K=0.22). The concordance obtained with the LUR model was similar to that observed in our study with the TAG model for a 5 km buffer around the AQMS. However, Marshall's study is not directly comparable with ours, because they used a larger buffer zone (10 km) and because the LUR and dispersion models incorporate all local sources of pollution, whereas our TAG model does not.

In this study, we focused on women living less than 5 km from an AQMS, whereas previous studies on the effects of air pollution on birthweight have included women living more than 8 km (5 miles) from a monitor (Basu et al. 2004; Brauer et al. 2008; Parker et al. 2005). Our results indicate that the size of buffer around monitors considered has a major effect on the concordance between models and the estimated association between NO_2 concentration and birthweight. Higher levels of concordance between the models were obtained if we focused on women living within 2 km of a monitor, with concordance levels even higher if we limited the analysis to women living within 1 km of a monitor. Associations between NO_2 levels and birthweight, although not statistically significant at the 5% level, tended to be stronger for the 2 km buffer around the AQMS than for the 5 km buffer (Figure 3). The findings were sometimes less clear for women living within 1 km of an AQMS, and the confidence intervals were slightly larger than for the 2 km buffer, probably because of the small number of subjects. Previous studies (Hansen et al. 2008; Wilhelm and Ritz 2005) with buffers of different sizes gave results similar to ours: the authors found stronger negative associations between fetal growth and levels of exposure to carbon monoxide, PM_{10}, SO_2 and O_3 during pregnancy, as estimated from data from the nearest AQMS, for women living within 2 km of a station than for those living up to 14 km away. The choice of the buffer size can probably be seen as a trade-off between bias and variance: the use of smaller buffers decreases sample size (increasing variance) but also probably decreases exposure misclassification (assuming that exposure is generally less well assessed for subjects living further away from an AQMS). However, selection bias may also contribute to the increase in the absolute value of the regression parameter quantifying the association between exposure and birthweight when smaller buffers are considered. Indeed, for associations with third-trimester exposure (but less clearly for first-trimester exposure), the absolute value of the regression parameter also tended to increase as buffer size decreased for the TAG model. This is unlikely to be due to variations in exposure misclassification and might instead be attributed to differences in the selection effects associated with buffers of different sizes.

Most previous studies considering the effects of NO_2, have reported larger decreases in birthweight for exposure in the first and third trimesters of pregnancy (Bell et al. 2007; Gouveia et al. 2004; Ha et al. 2001; Liu et al. 2007; Mannes et al. 2005; Salam et al. 2005) than for exposure in the second trimester or over the entire pregnancy (Ha et al. 2001; Lee et al. 2003; Mannes et al. 2005). A similar pattern was observed in our study. A discussion of the biological relevance of the exposure window or the underlying mechanisms is beyond the scope of this article. Several potential mechanisms by which air pollution may affect fetal growth have been proposed (Kannan et al. 2006; Ritz and Wilhelm 2008; Slama et al. 2008), but none of these mechanisms has been validated.

It is generally difficult to predict the impact of an error in an exposure variable in terms of the potential for bias in the exposure-response relationship (Jurek et al. 2008). However, in the specific case of a Berkson-type error, the power of the study is reduced and confidence intervals are widened, but no bias in linear regression coefficients is expected (Armstrong 2008; Zeger et al. 2000). Berkson-type error (Armstrong 2008) may occur when the exposure is measured at the population level and individual exposures levels vary because of differences in the time windows of exposure or time-activity patterns. The measurement error for the nearest AQMS approach would be expected to have a Berkson-type component, because the same proxy exposure is used for all women living in a circular area around a given monitor. The observation that exposure estimates for the nearest AQMS model were at least as strongly associated with birthweight as those for the TAG model is consistent with the nearest AQMS model being subject principally to Berkson-type error. Therefore, assuming that the observed association with birthweight was real, exposure misclassification seemed to have little impact on the dose-response relationship. If we accept that the TAG model cannot be seen as a gold standard, exposure mismeasurement seemed to affect both models in similar ways. In a study in Vancouver, Brauer et al. (2008) found significant negative associations between NO_2 exposure and fetal growth when they used an AQMS-based approach, but no association when they used a LUR model. They considered women living up to 10 km away from an AQMS, and the AQMS-based model corresponded to an inverse-distance weighting index, taking into account the three closest stations within 50 km.

Conclusion

Our study indicates that models of exposure to background NO_2 concentrations based on data from the nearest AQMS may entail large errors in estimated exposure, but that in some instances these errors have little impact on the exposure-birthweight relationship. The amplitude of exposure misclassification in AQMS-based models and of the resulting bias may be limited by restricting the size of the study area around each AQMS considered. Full quantification of the exposure error for each model would require a consideration of the temporal and spatial activities of each subject. Our study cannot be interpreted as providing clear evidence that the nearest AQMS approach yields unbiased estimates of the association between NO_2 concentrations and fetal growth. This question requires further consideration in other cohorts and in other countries, in which the sitting of permanent monitors may follow different rules.

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TABLES

Table 1: Characteristics of the participants and their association with NO_2 levels averaged during pregnancy (n=776 women living less than 5 km away from an air quality monitoring station (AQMS)).

Characteristic	n (%)	Mean (median) NO_2 level, µg/m^3			
		Nearest AQMS model	p[a]	TAG model	p[a]
Sex of offspring			0.97		0.28
Male	395 (51)	28.6 (32.3)		23.6 (23.8)	
Female	381 (49)	28.6 (32.5)		23.9 (23.9)	
Gestational duration (weeks)			0.37		0.17
30-36	48 (6)	30.2 (33.4)		24.7 (23.1)	
37-38	151 (20)	29.1 (32.6)		24.3 (24.1)	
39-40	407 (52)	28.1 (32.2)		23.4 (23.6)	
≥ 41	170 (22)	29.2 (32.8)		23.8 (24.3)	
Birth order			0.71		0.14
First birth	367 (47)	28.8 (33.4)		23.9 (23.9)	
Second birth	263 (34)	28.7 (31.7)		23.9 (24.0)	
Third birth or more	145 (19)	28.0 (32.2)		23.0 (23.1)	
Missing value	1				
Trimester of conception of the child			$<10^{-4}$		$<10^{-4}$
January-March	167 (21)	25.7 (25.3)		21.5 (21.9)	
April-June	184 (24)	29.1 (33.6)		23.5 (24.0)	
July-September	226 (29)	31.2 (35.2)		25.9 (25.7)	
October-December	199 (26)	27.7 (31.3)		23.3 (23.5)	
Maternal age at conception			$<10^{-2}$		$<10^{-2}$
<25 years	187 (24)	26.7 (26.3)		22.8 (22.7)	
25-29 years	289 (37)	30.0 (33.8)		24.3 (24.3)	
30-34 years	203 (26)	28.7 (32.1)		24.2 (24.0)	
≥ 35 years	97 (13)	27.9 (32.3)		22.9 (23.4)	
Maternal height			0.64		0.44
<160 cm	188 (24)	28.3 (32.0)		23.4 (24.0)	
160-169 cm	460 (60)	28.6 (32.7)		23.8 (23.8)	
≥ 170 cm	121 (16)	29.4 (33.1)		24.2 (24.2)	
Missing value	7				
Maternal pre-pregnancy weight			0.33		0.46
<50 kg	83 (11)	27.7 (28.8)		24.3 (24.1)	
50-59 kg	333 (43)	28.6 (32.3)		23.8 (23.8)	
60-69 kg	211 (27)	29.4 (33.5)		23.8 (24.0)	
70-79 kg	87 (11)	29.0 (33.0)		23.6 (23.8)	
≥ 80 kg	60 (8)	26.6 (25.9)		22.7 (22.0)	
Missing value	2				
Body mass index before pregnancy			0.39		0.07
<18.5 kg/m²	82 (11)	29.6 (34.3)		25.0 (24.7)	
18.5 to 24.9 kg/m²	512 (67)	28.5 (32.1)		23.8 (23.9)	
25 to 29.9 kg/m²	111 (14)	29.4 (33.7)		23.3 (23.4)	

≥30 kg/m²	62 (8)	27.1 (30.6)		23.0 (22.4)	
Missing value	9				
Center			$<10^{-4}$		$<10^{-4}$
Poitiers	316 (41)	24.9 (18.8)		20.3 (19.2)	
Nancy	460 (59)	31.2 (34.4)		26.1 (25.7)	
Maternal age at end of education			0.02		$<10^{-3}$
≤16 years	52 (7)	29.6 (33.1)		24.0 (23.6)	
17-18 years	104 (13)	27.0 (29.6)		22.2 (21.9)	
19-20 years	124 (16)	27.1 (29.1)		23.2 (23.0)	
21-22 years	165 (21)	27.9 (30.0)		23.3 (23.5)	
23-24 years	174 (22)	29.3 (33.1)		24.5 (24.6)	
≥ 25 years	157 (20)	30.6 (34.5)		24.7 (24.6)	
Maternal active smoking (2nd trimester)			0.45		0.30
No	641 (83)	28.8 (32.7)		23.8 (24.0)	
Yes	133 (17)	28.1 (32.0)		23.3 (22.8)	
Missing value	2				
Maternal passive smoking (2nd trimester)			0.48		0.53
No	507 (66)	28.5 (32.1)		23.7 (23.9)	
Yes	264 (34)	29.0 (33.3)		23.9 (23.6)	
Missing value	5				

AQMS: Air Quality Monitoring Station, TAG: Temporally adjusted geostatistical model
[a] p-value comparing model specific exposure estimates between categories (Student test for dichotomous variables) or among categories (Fischer's analysis of variance for variables with >2 categories). Tests were performed without including missing data as a separate category.

Table 2: Maternal exposure to NO_2 (µg/m^3) and concordance between NO_2 levels (mean ± standard deviation (5th, 50th, 95th percentiles)) estimated by the nearest air quality monitoring station (AQMS) model and the temporally adjusted geostatistical (TAG) model, for various exposure windows and buffer sizes considered around AQMS.

Area exposure window	Nearest AQMS model (5km buffer)		TAG model (5km buffer)			Between-model agreement											
						Distance [a] <5km				Distance [a] <2km				Distance [a] <1km			
	n	NO_2 levels	n	NO_2 levels	p[b]	n	r	c	K	n	r	c	K	n	r	c	K
Both areas																	
1st trimester	770	28.8 ± 10.8 (11.3, 30.1, 43.6)	773	23.7 ± 6.2 (13.6, 23.0, 34.6)	10^{-4}	767	0.67	61	0.41	429	0.70	62	0.43	158	0.83	75	0.63
2nd trimester	771	29.0 ± 10.9 (11.5, 30.0, 43.9)	770	24.1 ± 6.5 (13.6, 23.6, 34.4)	10^{-4}	766	0.69	60	0.40	426	0.72	58	0.37	156	0.82	73	0.60
3rd trimester	770	28.1 ± 11.1 (10.4, 29.4, 44.2)	772	23.3 ± 6.8 (12.5, 22.8, 34.7)	10^{-4}	767	0.74	63	0.44	428	0.79	68	0.52	155	0.87	79	0.68
Whole pregnancy	776	28.6 ± 10.0 (13.3, 32.4, 41.8)	770	23.7 ± 5.0 (16.1, 23.8, 32.3)	10^{-4}	770	0.65	63	0.44	428	0.70	64	0.46	157	0.85	73	0.59
Poitiers area																	
1st trimester	310	25.6 ± 11.9 (9.3, 21.6, 43.0)	316	20.9 ± 6.3 (12.0, 20.4, 35.8)	$<10^{-3}$	310	0.61	59	0.38	181	0.65	57	0.36	75	0.89	83	0.74
2nd trimester	311	25.2 ± 11.6 (10.1, 22.2, 42.7)	315	20.4 ± 6.1 (11.8, 19.9, 32.0)	10^{-4}	311	0.61	56	0.34	179	0.65	57	0.36	74	0.83	63	0.45
3rd trimester	310	23.9 ± 11.3 (8.5, 21.7, 42.0)	315	19.5 ± 6.3 (11.5, 19.0, 30.8)	10^{-4}	310	0.66	62	0.43	179	0.72	67	0.51	73	0.86	78	0.67
Whole pregnancy	316	24.9 ± 10.6 (12.4, 18.8, 40.5)	316	20.3 ± 4.7 (14.7, 19.2, 30.0)	0.12	316	0.55	56	0.34	181	0.62	58	0.37	75	0.87	68	0.52
Nancy area																	
1st trimester	460	31.0 ± 9.5 (13.6, 31.3, 44.1)	457	25.7 ± 5.2 (17.9, 25.5, 34.6)	10^{-4}	457	0.67	55	0.32	248	0.69	58	0.36	83	0.72	59	0.39
2nd trimester	460	31.6 ± 9.6 (14.1, 32.0, 44.4)	455	26.7 ± 5.5 (18.5, 26.6, 35.6)	10^{-4}	455	0.70	58	0.37	247	0.73	65	0.48	82	0.74	66	0.49
3rd trimester	460	30.9 ± 10.0 (13.5, 31.4, 45.0)	457	26.0 ± 5.8 (17.5, 25.7, 36.2)	10^{-4}	457	0.74	61	0.41	249	0.78	67	0.51	82	0.82	76	0.63
Whole pregnancy	460	31.2 ± 8.7 (16.9, 34.4, 42.4)	454	26.1 ± 3.7 (20.8, 25.7, 32.8)	10^{-4}	454	0.66	64	0.46	247	0.69	64	0.47	82	0.66	71	0.56

r: Pearson correlation coefficient, c: concordance percentage (based on NO_2 levels categorized in tertiles), K: Kappa coefficient (based on NO_2 levels categorized in tertiles).

[a]: Maximal distance between home address and the nearest AQMS (buffer size).

[b]: p-value of Kruskal-Wallis rank test comparing the exposure levels from the two models.

Table 3: Variance component (%) of NO_2 exposure levels estimated by the nearest air quality monitoring station (AQMS) model and by the temporally adjusted geostatistical (TAG) model for various exposure windows and buffer sizes considered around AQMS.

Exposure window	Distance <5km (n=681)				Distance <2km (n=383)				Distance <1km (n=146)			
	Nearest AQMS model		TAG model		Nearest AQMS model		TAG model		Nearest AQMS model		TAG model	
	Spatial	Temporal	Spatial	Temporal	Spatial	Temporal	Spatial	Temporal	Spatial	Temporal	Spatial	Temporal
1st trimester	82	21	61	52	79	22	55	57	84	25	56	49
2nd trimester	82	20	55	46	79	21	53	52	83	21	58	44
3rd trimester	78	21	47	46	76	21	43	52	80	24	52	48
Pregnancy	95	7	92	14	91	8	92	17	97	9	92	13

The sum of variance components is more than 100% because the data are not balanced as in experimental plans (i.e. the covariance is not null).

Figure legends

Figure 1: Mean annual NO_2 levels estimated by the nearest air quality monitoring station (AQMS) model in Poitiers (A) and Nancy areas (C), and by the temporally adjusted geostatistical (TAG) model in Poitiers (B) and Nancy areas (D)

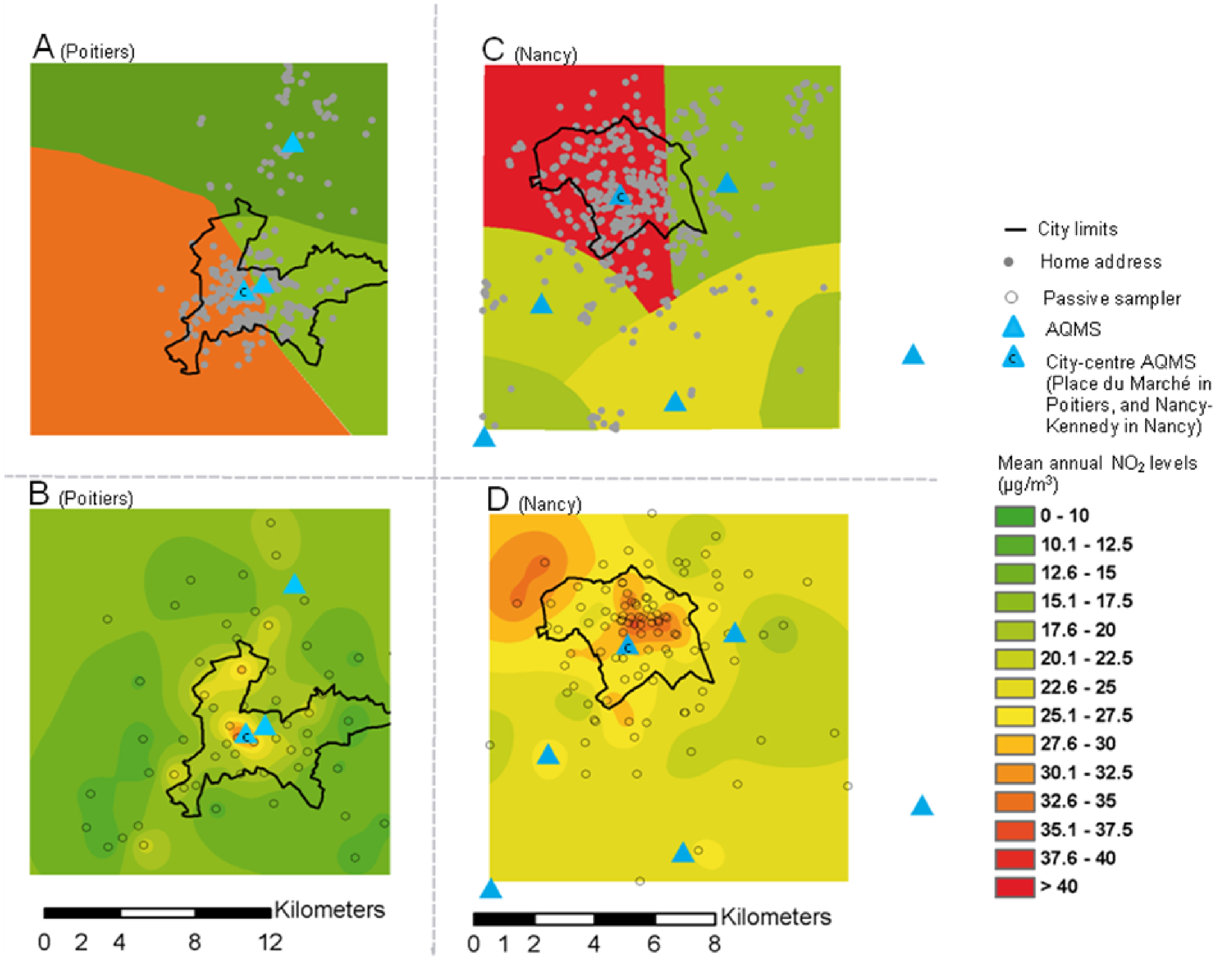
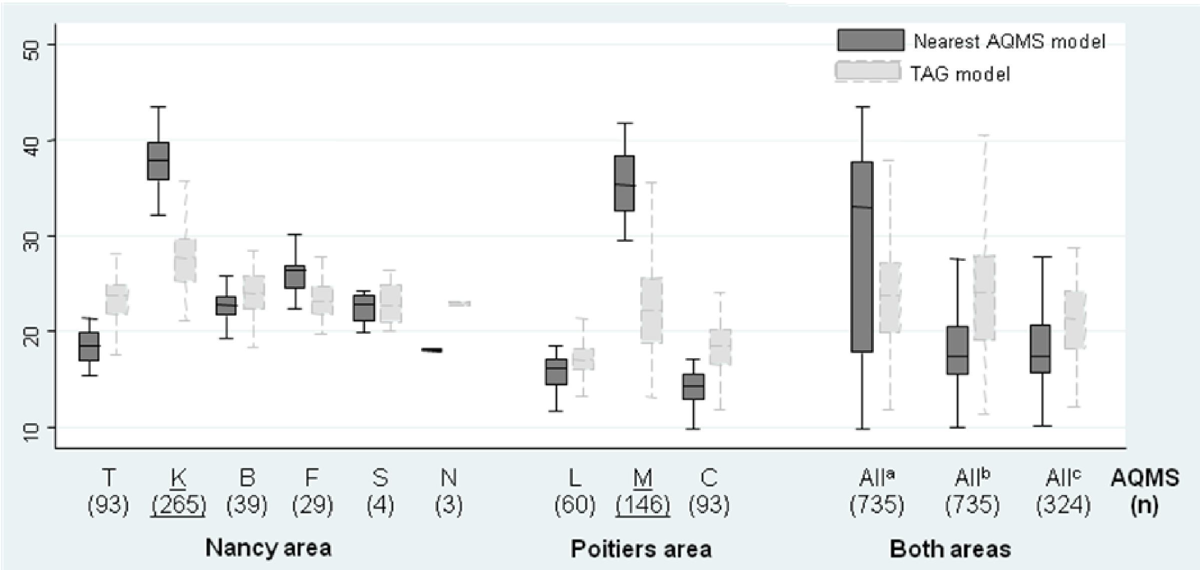
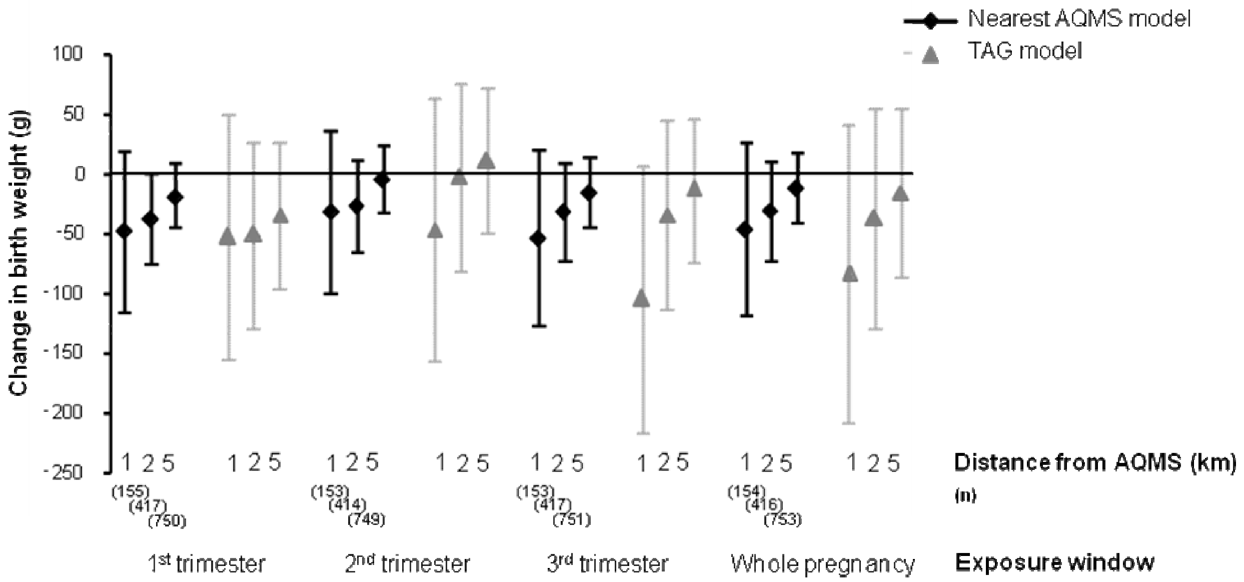


Figure 2: Box plot (25th, 50th and 75th percentiles) of NO_2 exposure levels during the whole pregnancy as estimated by the nearest air quality monitoring station (AQMS) model and by the temporally adjusted geostatistical (TAG) model, according to the AQMS closest to the residential address. Population restricted to 735 women living less than 5 km away from an AQMS without change of assigned station during pregnancy.



[a]: Exposures were estimated taking into account all AQMS.
[b]: Exposures were estimated taking into account all AQMS except K and M (city-center stations); for subjects initially assigned to one of these stations, the closest station has been replaced by the second AQMS nearest to the home address located outside the city center and less than 5 km away from the home address, if any.
[c]: Exposures were estimated taking into account all AQMS except K and M; all women for whom K or M is the closest station have been excluded from the analysis.
T: Tomblaine, K: Nancy-Kennedy, B: Nancy-Brabois, F: Fléville, S: St Nicolas de Port, N: Neuves-Maison, L: Les couronneries, M: Place du marché, C: Chasseneuil. Stations located in the peri-urban area. Letters identifying stations located in the city center are underlined.

Figure 3: Adjusted[a] change in mean birthweight (g) for an increase by 10 $\mu g/m^3$ in NO_2 during pregnancy, as a function of the size of the buffer considered around each air quality monitoring station (AQMS). The error bars indicate the 95% CIs.



[a] adjusted for maternal age at conception, gestational age at delivery (linear and quadratic terms), sex of newborn, maternal height (continuous variable), pre-pregnancy weight (broken stick model with a knot at 60 kg), birth order, center, trimester of conception, maternal age at end of education, active smoking during the second trimester of pregnancy (binary variable), passive smoking during the second trimester of pregnancy.