Fetal growth is an important indicator of the health of newborns and infants that may influence the health status in the adulthood (Sinclair et al. 2007). In recent years, a growing body of research has associated prenatal exposure to air pollution with adverse pregnancy outcomes, including intrauterine growth restriction (IUGR), low birth weight (LBW), preterm birth (PTB), and intrauterine mortality. Detailed reviews of these studies have concluded that the strength of the evidence differs among air pollutants, birth outcomes, and exposure periods, although differences in study design, exposure assessment, and definition of outcomes make comparability of results difficult (Glinianaia et al. 2004; Lacasťa et al. 2005; Šrám et al. 2005; Wang and Pinkerton 2007).

To advance in this emerging and fast-growing field, some key methodologic issues have been highlighted (Gilliland et al. 2005; Ritz and Wilhelm 2008; Slama et al. 2008a). Because most studies have linked birth outcomes and covariates from birth certificate records with routinely measured air pollutants, one priority is to develop prospective cohort studies that are able to obtain high-quality individual data on outcomes, covariates, and exposure estimates. Because pregnancy is a well-defined and relatively narrow period of exposure, identification of windows of greater susceptibility to air pollution is also a key issue, but is difficult because of the lack of biological knowledge and the correlations among trimester- or month-specific exposures. Furthermore, exposure assessment can be improved by using approaches based on geographic information systems (GIS) that take into account small-area variations in vehicle exhaust pollutants, such as land-use regression (LUR). Because LUR models have mainly been used for estimating annual average exposures, being able to accurately incorporate temporal variability in the LUR models is key for studies of birth outcomes, where shorter-term exposures are of interest. Improving exposure assessment also requires consideration of women’s residential mobility (Fell et al. 2004) and time–activity patterns during pregnancy (Nethery et al. 2009).

In this study we assessed the relationship between GIS-based exposure to traffic-related air pollution during pregnancy and birth weight in an urban cohort from the Spanish INMA (Environment and Childhood) Study. We also examined the influence of time–activity patterns during pregnancy in the association between air pollution and birth weight.

Methods

Cohort. The study area is Sabadell, a city of nearly 200,000 inhabitants situated in the metropolitan area of Barcelona, Spain. Women who visited the public health center of Sabadell in the 12th week of pregnancy and fulfilled the inclusion criteria were eligible to participate in the study (Ribas-Fitó et al. 2006). Main exclusion criteria were being < 16 years of age, nonsingleton pregnancy, not planning to deliver at the Hospital of Sabadell, and having followed an assisted reproduction program. Women were interviewed in the 12th and 32nd weeks of pregnancy and answered several questionnaires on sociodemographic characteristics, health status, use of drugs, occupational data, environmental exposures, time–activity patterns, and a food-frequency questionnaire. The protocol of the INMA study, including a detailed description of data collection and assessment of determinants and outcomes, has been published elsewhere (Ribas-Fitó et al. 2006). The study was approved by the Ethical Committees of the Municipal Institute of Medical Research and the Hospital of Sabadell, and all subjects gave written informed consent before participating.

Address correspondence to I. Aguilera, Centre for Research in Environmental Epidemiology, Barcelona Biomedical Research Park, Doctor Aiguader 88, 08003 Barcelona, Spain. Telephone: 34-93-2147300. Fax: 34-93-2147301. E-mail: iaguilera@creal.cat

We thank K. Meliefste (Institute for Risk Assessment Sciences, Utrecht University, the Netherlands) and R. Fernández-Patier, A. Aguirre, T. Bomboi, and D. Herce (National Centre for Environmental Health, Madrid, Spain) for the laboratory analysis of passive samplers.

The INMA (Environment and Childhood) study has the financial support of the “Carlos III Health Institute, Spanish Ministry of Health” (G03/176), Red de Centros de Investigación en Epidemiología y Salud Pública (C03/09), and Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública. The authors declare they have no competing financial interests.

Received 6 October 2008; accepted 13 April 2009.
A total of 657 women were enrolled in the study between June 2004 and July 2006. This sample was representative of the target population in terms of women’s attendance at prenatal care in the public health system (used by 85% of the pregnant women in Sabadell), but the educational level of our sample was higher than the target population average. From the initial sample, we followed 619 (94%) women until the child’s birth. We excluded 44 children from the analysis because their mothers did not live in Sabadell during pregnancy but in nearby cities covered by the health service of the municipal hospital. We also excluded three children with no recorded birth weight and two with gestational duration of 28 and 32 weeks, respectively, because of missing data in the covariates obtained in the 32nd week interview. Finally, 570 (87%) children were included in the analysis.

**Air pollution exposure model.** We used LUR modeling in the study area to estimate individual exposure to nitrogen dioxide and BTEX (benzene, toluene, ethylbenzene, m/p-xylene, and o-xylene) as markers of motor vehicle exhaust pollution. A complete description of the methodology on exposure modeling has been reported previously (Aguilera et al. 2008). Briefly, we measured NO2 and BTEX with passive samplers in four and three sampling campaigns of 1 week, respectively, between April 2005 and March 2006, conducted simultaneously at 57 sampling sites (29 urban background and 28 traffic sites) representing the gradient of exposure in the study population. For each pollutant, we calculated average concentrations of all the sampling campaigns, assuming that they are representative of annual mean levels of NO2 and BTEX (Lebret et al. 2000), and fitted linear regression models using five groups of geographic data (land coverage, topography, population density, roads, and distance to local sources of pollution) as predictor variables. Geographic variables were stored and derived in ArcGIS, version 9.1 (ESRI, Redlands, CA, USA). The final model for NO2 ($R^2 = 0.75$) included altitude, road type (major, secondary, or minor road), and a land cover factor within a 500-m buffer as predictor variables. Geographic variables included in the final BTEX model ($R^2 = 0.74$) were altitude and three source-proximity variables (distance to nearest major road, secondary road, and parking lot). We used two cross-validation procedures to evaluate the precision of the regression models.

We then applied models to predict outdoor air pollution levels at the cohort addresses. For women who changed their home address during pregnancy ($n = 25, 4%$), exposure was calculated using the estimated concentrations at both the old and new home address, weighted by the percentage of the pregnancy period spent in each of them.

We adjusted models for temporal variations to calculate term-specific individual exposures, as it has been done in other studies relying on LUR exposure models (Brauer et al. 2008; Slama et al. 2007). To obtain an average exposure for the whole pregnancy period and for each trimester, we used temporal variations of air pollution measured in the only fixed monitoring station operating in Sabadell. The station is located on a traffic island in the middle of a main road, in a relatively open area with unobstructed air flow. Daily measurements of air pollution conducted simultaneously in this traffic site and in an urban background location during 1 month showed similar temporal variations in NO2 levels between the two sites, with a correlation coefficient of 0.96 (Rivas-Lara 2008).

We averaged daily means of NO2 measured at the fixed station over the pregnancy period for each woman. The resulting value was divided by the average NO2 concentration corresponding to the whole sampling period (from April 2005 to March 2006) and multiplied by the predicted value obtained in the LUR model. We applied the same procedure to estimate trimester-specific exposures for each woman. We defined the first trimester of pregnancy as weeks 1–13, the second trimester as weeks 14–26, and the third trimester as the period from week 27 until birth.

Regarding BTEX, the fixed monitoring station measures daily mean levels of benzene and toluene, but the high percentage of missing data (65% of the sampling period) did not allow us to “seasonalize” the BTEX model with them. Because NO2 showed higher correlation with benzene and toluene in the fixed monitoring station than with other traffic-related pollutants such as carbon monoxide or particulate matter (PM), and given the high correlation between NO2 and BTEX levels measured with the passive samplers ($r = 0.80$ for the whole sampling period), we used NO2 daily levels to make the temporal adjustment, assuming that the temporal variations in both pollutants were similar.

**Birth weight and gestational age.** Birth weight was recorded by specially trained midwives at delivery. We calculated gestational age from the date of the last menstrual period (LMP) reported at recruitment and confirmed using estimates based on ultrasound examination in the 12th week of gestation. When the difference between the LMP reported at recruitment and estimated from the ultrasound was $\geq 7$ days ($n = 91; 16%$), we estimated LMP using a quadratic regression formula defined by Westerway et al. (2000).

**Statistical analysis.** We examined the association between birth weight and prenatal exposure to NO2 and BTEX by simple and multiple linear regression models. Other reproductive outcomes such as LBW or small for gestational age were not considered for analysis because of the relatively low sample size. Given the high correlation among the five BTEX compounds ($r > 0.75$) and because the relative fetal toxicity of each of them is not well known (Agency for Toxic Substances and Disease Registry 2004), we used the LUR estimate of the sum of the five compounds to assess the relationship between BTEX exposure and birth weight.

We chose covariates included in the analysis based on previous knowledge on their influence on birth weight. We collected some through questionnaire in the two interviews carried out during pregnancy for each woman: Maternal age, maternal education, maternal ethnicity, parity, maternal height and prepregnancy weight, and paternal height and weight were obtained in the 12th-week interview; tobacco use and passive smoking information were collected in the 32nd-week interview. Birth date and child sex were collected from the child’s neonatal anthropometry record filled in by the midwives. We calculated season of conception using date of LMP. Because season of birth is influenced by the duration of pregnancy, we used season of conception in the analysis rather than season of birth.

With linear regression models, we estimated the change in birth weight for an interquartile range (IQR) increase in NO2 and BTEX exposure (micrograms per cubic meter), for each trimester and for the entire pregnancy. We retained as adjustment factors only those covariates that modified the association between air pollution and birth weight by $> 10%$. Because fetal weight gain per week is not constant throughout pregnancy, we examined the association between birth weight and gestational age by using fractional polynomial models to identify the best-fit transformation of gestational age and allow polynomial terms for gestational age in the linear regression models (Blair et al. 2005).

We performed a sensitivity analysis considering time–activity patterns during pregnancy. In the 32nd-week interview, women answered the following question for a typical weekday and for a typical weekend: “Since you have gotten pregnant, how much time have you typically spent daily in these environments?” The answer options were (a) home indoors, (b) work indoors, (c) in other people’s houses, (d) in other indoor environments, (e) home outdoors, (f) work outdoors, (g) in other outdoor environments, and (h) in means of transportation. The question was designed to obtain a 24-hr sum. We weighted the data to account for weekdays (5 of 7) and weekends (2 of 7) and then calculated time spent at home (answers a + e) and time spent in nonresidential outdoor environments (answers f + g). We used the median (rounded to the nearest whole number) as a cutoff value to...
restrict our analysis to two subsets: a) women who spent more time at home and b) women who spent less time in nonresidential outdoor environments. Because we based LUR estimates on the women's residential addresses, we assumed that these two subsets suffered less from exposure misclassification and that misclassification was nondifferential.

We performed statistical analyses using Stata 8.2 (StataCorp., College Station, TX, USA).

**Results**

Mean birth weight of included births was 3,247 g (10th, 50th, and 90th percentiles: 2,721, 3,288, and 3,760 g), and mean maternal age was 31.4 years (minimum and maximum, 18.2 and 43 years, respectively). Table 1 shows other characteristics of the study population and mean birth weight for each categorized variable. Birth weight was associated ($p < 0.10$) with child’s sex, season of conception, parity, tobacco smoking, maternal ethnicity, gestational age, maternal height and prepregnancy weight, and paternal height and weight.

We examined whether air pollution exposure was associated with maternal education as a surrogate of socioeconomic status (SES). We found a small but statistically significant association between LUR estimates of BTEX levels and maternal education ($p = 0.02$). Predicted annual mean levels of BTEX were 17.6, 16.0, and 16.1 µg/m³ for women with a university degree, secondary education, and primary education, respectively. The corresponding NO₂ values for the three categories were 37.4, 35.7, and 35.7 µg/m³ ($p = 0.14$).

Tables 2 and 3 provide the distribution of 9-month and trimester-specific exposures to NO₂ and BTEX and the correlation coefficients among them, respectively. We found only slight differences between mean exposure levels by trimester and 9-month exposures, although the range of exposure was wider for the three trimester exposures than for the whole pregnancy period. According to these estimates, 14% of the women had an average NO₂ exposure > 40 µg/m³ for the entire pregnancy period, which is the European Union limit value to come into force in 2010 (European Commission 1999).

Correlation coefficients among the three trimesters ranged from 0.45 to 0.50 for NO₂ and from 0.72 to 0.74 for BTEX, reflecting small seasonal variation in exposure.

Table 4 shows time–activity patterns reported in the 32nd-week interview and referring to the entire pregnancy. Differences between weekdays and weekends were statistically significant for all the activities. During weekdays, women who did not work during pregnancy or worked only during part of it ($n = 350$) spent more time at home and in nonresidential outdoor environments, and less time in means of transportation, compared with women who worked during the entire pregnancy ($n = 210$) (Mann–Whitney test, $p < 0.05$). We found no differences in total time spent in indoor environments between the two groups.

Table 5 presents the effect of air pollution exposure during pregnancy and during each trimester on birth weight. Neither NO₂ nor BTEX exposure was significantly associated with the outcome in any of the exposure periods. Associations for BTEX were more pronounced in the subset of women who spent ≥ 15 hr/day at home ($n = 276$), but they were also not statistically significant. However, when considering only women who spent < 2 hr/day in nonresidential outdoor environments ($n = 259$), BTEX exposure during pregnancy and the second trimester showed a statistically significant negative effect on birth weight. Estimated reductions in birth weight for an IQR increase of BTEX exposure were 76.6 g and 101.9 g during pregnancy and the second trimester, respectively. The negative effect of NO₂ exposure variables in this subset of women was less clear but showed some stronger effects during the second trimester of pregnancy ($p = 0.09$).

Because the three trimester exposures of both pollutants (particularly BTEX) were

### Table 1. Characteristics of the study population ($n = 570$).

| Variable                          | Birth weight (g) | P-Value* |
|-----------------------------------|-----------------|----------|
| Categorized variable              |                 |          |
| Child's sex                       |                 | < 0.001  |
| Male                              | 3,316           |          |
| Female                            | 3,177           |          |
| Season of conception              |                 | 0.04     |
| Spring                            | 3,217           |          |
| Summer                            | 3,248           |          |
| Fall                              | 3,252           |          |
| Winter                            | 3,198           |          |
| Tobacco smoking during pregnancy  |                 | < 0.001  |
| 0                                 | 3,277           |          |
| 1–5 cigarettes/day                | 3,200           |          |
| > 5 cigarettes/day                | 3,023           |          |
| Passive smoking during pregnancy  |                 | 0.03     |
| Yes                               | 3,207           |          |
| No                                | 3,285           |          |
| Maternal parity                   |                 | 0.09     |
| 0                                 | 3,221           |          |
| ≥ 1                               | 3,283           |          |
| Maternal education                |                 | 0.11     |
| Primary education                 | 3,197           |          |
| Secondary education               | 3,258           |          |
| University degree                 | 3,274           |          |
| Maternal race/ethnicity           |                 | 0.01     |
| White/Caucasian                   | 3,238           |          |
| Latin American                    | 3,595           |          |
| Black                             | 3,136           |          |
| Continuous variables              |                 |          |
| Maternal age (years)              | 31.1            | 0.43     |
| Gestational age (weeks)           | 39.9 ± 1.9      | < 0.001  |
| Maternal height (cm)              | 162 ± 8.3       | 0.01     |
| Maternal prepregnancy weight (kg) | 60 ± 14         | < 0.001  |
| Paternal height (cm)              | 175 ± 8         | 0.02     |
| Paternal weight (kg)              | 79 ± 15         | 0.01     |

*p-Values for comparing means by t-test or analysis of variance. *p-Values for Pearson correlation coefficients between each continuous variable and birth weight.

### Table 2. Distribution of 9-month and trimester exposures to NO₂ and BTEX (µg/m³).

| Pollutant (period) | Mean ± SD | Minimum | 25th Percentile | Median | 75th Percentile | Maximum |
|--------------------|-----------|---------|-----------------|--------|-----------------|---------|
| NO₂                |           |         |                 |        |                 |         |
| 9 months           | 32.17 ± 8.89 | 17.37   | 26.40           | 30.77  | 35.91           | 68.45   |
| First trimester    | 32.66 ± 10.56 | 9.59    | 25.83           | 31.81  | 36.10           | 74.30   |
| Second trimester   | 31.86 ± 10.57 | 10.33   | 24.98           | 30.97  | 36.98           | 77.47   |
| Third trimester    | 32.87 ± 10.90 | 10.18   | 25.19           | 31.81  | 37.66           | 74.37   |
| BTEX               |           |         |                 |        |                 |         |
| 9 months           | 14.65 ± 5.52 | 3.95    | 10.25           | 14.65  | 18.67           | 27.63   |
| First trimester    | 14.91 ± 6.21 | 2.44    | 9.78            | 14.68  | 19.57           | 29.51   |
| Second trimester   | 14.49 ± 6.05 | 2.69    | 9.42            | 13.82  | 19.46           | 31.30   |
| Third trimester    | 14.88 ± 6.24 | 2.62    | 9.86            | 14.03  | 19.58           | 31.69   |

### Table 3. Spearman correlation coefficients between estimated air pollutant’s concentrations by 9-month and trimester exposures.

| Exposure          | NO₂ | BTEX |
|-------------------|-----|------|
| 9 Months          |     |      |
| First trimester   | 0.79|      |
| Second trimester  | 0.79| 1    |
| Third trimester   | 0.80| 0.46 |
| BTEX              |     |      |
| 9 months          | 0.77| 1    |
| First trimester   | 0.69| 0.60 |
| Second trimester  | 0.71| 0.89 |
| Third trimester   | 0.72| 0.72 |

All correlation coefficients are significantly different from 0 ($p < 0.01$).
correlated, we also adjusted models for trimester-specific exposures (Table 5). Associations found for BTEX and NO$_2$ exposures in the second trimester were more pronounced in the whole cohort and in the two subsets, but only statistically significant among women who spent < 2 hr/day in nonresidential outdoor environments. Variance inflation factor values ranged from 1.76 to 1.96 for NO$_2$ and from 2.53 to 2.89 for BTEX, indicating acceptable levels of collinearity in the multi-trimester models.

### Discussion

We found an effect of exposure to BTEX, and to a lesser extent NO$_2$, during the second trimester of pregnancy on birth weight among a subset of women who spent < 2 hr/day in outdoor environments during pregnancy, after controlling for exposure to the same pollutant during the other two trimesters. Exposure to BTEX during the whole pregnancy period was also significantly associated with birth weight for the same subset. The magnitude of the association was higher for BTEX in all the exposure periods. Overall, exposure during the second trimester appeared to be the most harmful, and the association became larger after adjusting for trimester-specific exposures.

Identifying critical exposure windows is a research need but a difficult task because of differences in mixture of pollutants across space and time, as well as possible different effects of specific pollutants during specific exposure periods (Slama et al. 2008a). In addition, there is currently a lack of toxicologic information to help guide selection of relevant exposure periods for most fetal growth end points (Ritz and Wilhelm 2008).

To our knowledge, this is the first study assessing the relationship between prenatal exposure to ambient BTEX and birth weight, so we cannot compare our results with those of other studies. Regarding NO$_2$, the evidence of a susceptible window of exposure is unclear. Some studies found an adverse effect of NO$_2$ on birth weight in the second trimester of pregnancy. Some other studies found no association between NO$_2$ and birth weight.

### Table 5. Change (coefficient) in birth weight (g) for an IQR increase (µg/m$^3$) in exposure to NO$_2$ and BTEX at the entire pregnancy period and each trimester in 570 newborns from INMA-Sabadell.

| Activity | All women (n = 570) | Women who spent ≥ 15 hr/day at home (n = 278) | Women who spent < 2 hr/day in nonresidential outdoor environments (n = 259) |
|----------|---------------------|-----------------------------------------------|-------------------------------------------------------------|
| BTEX     |                      |                                               |                                                             |
| 9 Months |                     |                                               |                                                             |
| First trimester | –24.5 (–57.2 to 8.2) | –20.4 (–62.1 to 17.2) | –23.3 (–65.6 to 9.0) |
| Second trimester | –24.5 (–57.2 to 8.2) | –20.4 (–62.1 to 17.2) | –23.3 (–65.6 to 9.0) |
| Third trimester | 5.6 (–28.2 to 39.4)  | 4.1 (–26.7 to 34.9)  | 5.0 (–27.1 to 37.1) |
| NO$_2$   |                      |                                               |                                                             |
| 9 Months |                     |                                               |                                                             |
| First trimester | 18.5 (–9.2 to 56.2)  | 16.0 (–7.2 to 49.4)  | 17.5 (–8.7 to 53.7) |
| Second trimester | 18.5 (–9.2 to 56.2)  | 16.0 (–7.2 to 49.4)  | 17.5 (–8.7 to 53.7) |
| Third trimester | 18.5 (–9.2 to 56.2)  | 16.0 (–7.2 to 49.4)  | 17.5 (–8.7 to 53.7) |

*Adjusted for child’s sex, gestational age, season of conception, parity, maternal educational level, maternal smoking during pregnancy, maternal height and prepregnancy weight, and paternal height. *Adjusted for above variables and exposures to the same pollutant during the other two trimesters. *p < 0.05.

### Table 4. Hours/day in specific activities/locations during pregnancy (reported in the 32nd week of pregnancy).

| Activity          | Mean ± SD | 10th Percentile | Median | 90th Percentile | Mean ± SD | 10th Percentile | Median | 90th Percentile |
|-------------------|-----------|-----------------|--------|----------------|-----------|-----------------|--------|----------------|
| Indoor            |           |                 |        |                |           |                 |        |                |
| a. Home           | 15.1 ± 3.3| 11.2            | 14.5   | 19.6           | 16.0 ± 3.1| 12.0            | 16.0   | 20.0           |
| b. Work           | 4.4 ± 3.8 | 0.0             | 5.0    | 9.0            | 0.2 ± 1.2 | 0.0             | 0.0    | 0.0            |
| c. Other people’s houses | 1.0 ± 1.4 | 0.0             | 0.5    | 3.0            | 2.3 ± 1.9 | 0.0             | 2.0    | 4.0            |
| d. Other indoor environments | 1.0 ± 0.8 | 0.0             | 1.0    | 2.0            | 1.6 ± 1.3 | 0.0             | 2.0    | 3.0            |
| Outdoor           |           |                 |        |                |           |                 |        |                |
| a. Home           | 0.1 ± 0.4 | 0.0             | 0.0    | 0.0            | 0.2 ± 1.0 | 0.0             | 0.0    | 0.3            |
| b. Work           | 0.2 ± 0.8 | 0.0             | 0.0    | 0.0            | 0.0 ± 0.5 | 0.0             | 0.0    | 0.0            |
| c. Other outdoor environments | 1.4 ± 1.1 | 0.3             | 1.0    | 3.0            | 2.7 ± 1.8 | 1.0             | 2.0    | 5.0            |
| Walking$^b$       | 0.9 ± 0.9 | 0.3             | 0.8    | 0.2            | 1.3 ± 1.1 | 0.5             | 1.0    | 2.0            |
| Means of transportation$^a$ | 0.8 ± 0.8 | 0.0             | 0.5    | 2.0            | 1.0 ± 0.7 | 0.0             | 1.0    | 2.0            |
| Car               | 0.6 ± 0.8 | 0.0             | 0.5    | 1.5            | 0.9 ± 0.7 | 0.0             | 1.0    | 2.0            |
| Bus               | 0.2 ± 0.9 | 0.0             | 0.0    | 0.5            | 0.0 ± 0.1 | 0.0             | 0.0    | 0.0            |
| Metro/train       | 0.1 ± 0.3 | 0.0             | 0.0    | 0.0            | 0.0 ± 0.1 | 0.0             | 0.0    | 0.0            |
| Total in nonresidential outdoor environments$^d$ | 1.6 ± 1.3 | 0.3             | 1.0    | 3.0            | 2.7 ± 1.8 | 1.0             | 2.0    | 5.0            |
| Total at home     |           |                 |        |                |           |                 |        |                |
| (a + e)           | 15.1 ± 3.4| 11.5            | 14.5   | 20.0           | 16.2 ± 3.0| 12.5            | 16.4   | 20.0           |
| Total in indoor environments | 21.5 ± 1.6 | 20.0            | 22.0   | 23.0           | 20.1 ± 2.2 | 17.0            | 20.5   | 22.5           |

See "Materials and Methods" for time–activity questions (a–h).

$^a$Differences between weekdays and weekends are statistically significant for all the activities (Wilcoxon signed rank test, p < 0.05). $^b$Women reported specifically the amount of time spent walking as part of the time spent in other outdoor environments. $^d$Mean, 10th percentile, median, and 90th percentile values for bicycle and motorcycle categories were 0. $^e$This activity refers to time spent in outdoor environments other than at the home address.
pregnancy (Lee et al. 2003; Mannes et al. 2005), whereas others identified first trimester of exposure to NO2 as the only period influencing fetal growth, measured as continu-
ous birth weight, LBW, or IUGR (Bell et al. 2007; Ha et al. 2001; Salam et al. 2005). Two studies found an association between NO2 and birth weight for the whole pregnancy but did not identify any specific harm exposure period (Brauer et al. 2008; Liu et al. 2007). Finally, other studies did not observe any sig-
nificant association between NO2 and fetal growth (Gouveia et al. 2004; Hansen et al. 2007; Liu et al. 2003; Slama et al. 2007). However, between-study comparisons are lim-
ited by differences in study design, exposure assessment, and different outcome definitions (IUGR or birth weight treated as continuous or dichotomous variable).

We found reductions in birth weight with increases in BTEX concentrations only among women who spent < 2 hr/day in nonresi-
dential outdoor locations. This could poten-
tially be due to less exposure misclassification (assumed nondifferential) in residence-based LUR estimates for this subset. Although rep-
resenting a small portion of total daily activ-
ity, time spent outdoors can signify direct exposure to traffic-related pollutants. Thus, women who spent a considerable amount of time (≥ 2 hr/day) in nonresidential out-
door environments could have been exposed to a high variability of traffic-related NO2 and BTEX levels, very different than those reflected by the LUR estimates based on the residential address. This hypothesis is sup-
ported by results obtained for a subset of 53 women of this cohort in their third trimester of pregnancy, selected to represent the geo-
graphic distribution of the cohort addresses, and for which personal levels of NO2 were measured with passive samplers during 48 hr. In this subset, women who spent ≥ 2 hr/ day in nonresidential outdoor environments (reported for the 48-hr measurement period) showed higher personal levels of NO2 (β = 14.4 µg/m3; 95% confidence interval, 4.6–24.3 µg/m3), compared with the reference group (< 2 hr/day) (Valero N, Aguilera I, Llop S, Esplugues A, de Nazelle A, Ballester F, et al., unpublished observations). A study con-
ducted in Athens also found that time spent outdoors in the city center was a major con-
tributor to personal exposure to toluene and xylenes (Alexopoulou et al. 2006). Nethery et al. (2008) found a better correlation (r = 0.72) between 48-hr personal exposure to nitric oxide and LUR-estimates based on home address in a subset of pregnant women who spent > 65% of sampling time at home, compared with those who spent ≤ 65% (r = 0.31). Although not statistically significant, effect estimates for BTEX in our cohort were also more pronounced among women who spent more time at home, compared with the whole cohort. Overall, results reinforce the need of considering time–activity patterns during pregnancy to better characterize the exposure (Ritz and Wilhelm 2008).

The inclusion of LUR estimates based on work addresses also could improve exposure assessment among employed women (Nethery et al. 2008). In our study, we were unable to account for work-based LUR estimates for the whole subset of employed women because approximately 25% of them worked outside the area covered by our LUR models and 16% reported imprecise work addresses that we were unable to geocode. We did not con-
duct a sensitivity analysis by working status because 37% (n = 160) of the 437 women who were employed at the beginning of the study changed their working status during the 12th- and 32nd-week interviews, making the trimester-specific classification of working status in this subset prone to error, par-
icularly for the second trimester of pregnancy. Instead, we investigated differences in time–activity patterns by working status during the whole pregnancy and found that women who worked during the entire pregnancy spent less time in nonresidential outdoor environments. This suggests that this time–activity variable, although reported mainly as a walking activ-
ity, is not an indicator of commuting but of a wider variety of transit activities.

Several studies have reported seasonal pat-
terns both in air pollution levels and in birth weight (Hazenkamp-von Arx et al. 2004; Murray et al. 2000). In Sabadell, daily mean levels of NO2, benzene, and toluene (measured at the fixed monitoring station) were higher in winter and lower in summer during the study period, probably due to seasonal differences in meteorologic conditions and traffic intensity. We also have found a seasonal pattern in birth weight, with lowest birth weights seen in infants conceived in winter. This effect is larger than that observed in other studies (Jedrychowski et al. 2004; Slama et al. 2007; Wilhelm and Ritz 2005) and independent from the air pollu-
tion effects (p for interaction > 0.10), suggesting that seasonal effects on birth weight could be related to seasonal factors other than air pollu-
tion, such as ambient temperature and sunlight (Murray et al. 2000; Tustin et al. 2004).

LUR estimates of NO2 and BTEX lev-
els were higher among women with higher educational level, compared with women with secondary or primary education. This could be explained by the higher percentage of women with university degree living in the city center, which is one of the districts with higher air pollu-
tion levels because of its higher road density and economic activity (Aguilera et al. 2008). O’Neill et al. (2003) found that people with lower SES tend to live in areas with higher levels of air pollution in North America. This
evidence is more limited in Europe, with some studies suggesting that the inverse association may occur (Forastiere et al. 2007; Hoek et al. 2002). Differences between European and North American cities in their structure and social class distribution could explain these dis-
crepancies. Within Europe, southern European cities have a more dense structure of roads and buildings, and thus higher traffic emissions, particularly in central districts (Muñoz 2003). Although preliminary, our results support the hypothesis that higher SES can be associated with living in more polluted areas in southern European cities.

One of the strengths of our study is esti-
mation of individual exposure to traffic-related air pollutants based on temporally adjusted LUR models applied to geocoded home addresses, whereas most studies assess expo-
sure by using routinely measured air pollution levels and community-level residence (cen-
sus data or postal codes). To date, only two studies have also applied temporally adjusted LUR models in Munich, Germany, and Vancouve, Canada (Brauer et al. 2008; Slama et al. 2007), although they did not take into account time–activity patterns as potential factors affecting exposure misclassification. In addition, we accounted for residential mobility during pregnancy when assigning exposures, and we were able to control for a considerable number of potential confounders not always available in studies relying on data from birth certificates, such as quantitative measures of maternal smoking, passive smoking, or mater-
nal and paternal weight and height.

Because we used ultrasound measurements to correct reported LMP dates that differed in ≥ 7 days from the ultrasound-based estimates, corrected gestational age could be biased if air pollution exposure shows an early effect on fetal growth (Slama et al. 2008b). However, analysis of gestational age (both corrected and noncorrected) by exposure categories during the first trimester indicated that the correc-
tion of gestational age was not biased by air pollution effects.

A limitation of this study was the relatively small sample size, which limited our ability to investigate other birth outcomes (i.e., PTB or IUGR) and evaluate interactions between air pollution exposure and potential effect modi-
fiers such as maternal nutrition (Kannan et al. 2006). In addition, because we used daily mean levels of NO2 to temporally adjust the BTEX exposure model, identification of the second trimester as the most susceptible to BTEX exposure needs careful interpretation. Because NO2 and BTEX were highly correlated in space and time and both originate mainly from vehicle emissions in the study area, it remains unclear whether the more pronounced effect found for BTEX was independent of other traffic-related pollutants. Considering that
Traffic-related air pollution and birth weight

NO₂ is mainly a secondary pollutant (formed from the oxidation of NO primary emissions) and that LUR estimates of BTEX capture the influence of additional traffic emission sources such as parking lots, our results suggest that BTEX could be a more specific marker for exhaust toxins of concern for pregnancy in studies conducted within urban areas.

Conclusions

We found an effect of exposure to traffic-related air pollutants (BTEX and, to a lesser extent, NO₂) on birth weight among pregnant women who live in an urban area and spent <2 hr/day in nonresidential outdoor locations. Although the magnitude of the association was higher for BTEX, the independent effect of different air pollutants with common emission sources remains to be determined.

When possible, time-activity patterns during pregnancy should be considered to examine whether they may affect exposure misclassification. Overall, our findings add to a growing body of research linking intraurban variations of vehicle exhaust pollutants and reduced birth weight. Even being small, adverse reproductive effects of air pollution may have a considerable public health impact at the population level given the ubiquity of air pollution exposure (Slama et al. 2008a). This study reinforces the importance of developing strategies for air pollution prevention in a context of urban planning and management.

References

Agency for Toxic Substances and Disease Registry. 2004. Interaction Profile for Benzene, Toluene, Ethylbenzene, and Xylenes (BTEX). Atlanta, GA:Agency for Toxic Substances and Disease Registry. Available: http://www.atsdr.cdc.gov/interactionprofiles/IP-BTEX/ip005.pdf [accessed 10 September 2008].

Aguilera I, Sunyer J, Fernandez-Patier R, Hoek G, Aguirre-Alfaro A, Meulstee K, et al. 2008. Estimation of outdoor NO₃, NO₂, and BTEX exposure in a cohort of pregnant women using land use regression modeling. Environ Sci Technol 42:815–821.

Alexopoulos EC, Chatzi C, Linos A. 2006. An analysis of factors that influence personal exposure to toluene and xylene in residents of Athens, Greece. BMC Public Health 6:50; doi:10.1186/1471-2458-6-50 [Online 28 February 2006].

Bell ML, Ebisu K, Belanger K. 2007. Ambient air pollution and low birth weight in Connecticut and Massachusetts. Environ Health Perspect 115:1118–1124.

Blair EM, Liu Y, de Klerk NH, Lawrence DM. 2005. Optimal fetal growth for the Caucasian singleton and assessment of appropriateness of fetal growth: an analysis of a total population perinatal database. BMC Pediatr 5:13; doi:10.1186/1471-2431-5-13 [Online 24 May 2005].

Brauer M, Lencar C, Tamburic L, Koehoorn M, Demers P, Kerr D. 2008. A cohort study of traffic-related air pollution impacts on birth outcomes. Environ Health Perspect 116:680–686.

European Commission. 1999. Council Directive 1999/30/EC of 22 April 1999 Relating to Limit Values for Sulphur Dioxide, Nitrogen Dioxide and Oxides of Nitrogen, Particulate Matter and Lead in Ambient Air. Available: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1999:163:00410053:EN:PDF [accessed 15 September 2008].

Fell DB, Dodds L KG. 2004. Residential mobility during pregnancy. Paediatric Perinatal Epidemiol 18:408–414.

Forastiere F, Stefoglia M, Tasco C, Piccotto S, Agabiti N, Cesaroni G, et al. 2007. Socioeconomic status, particulate air pollution, and daily mortality: differential exposure or differential susceptibility. Am J Ind Med 50:208–216.

Gilliland F, Avol E, Kinney P, Jerrett M, Dvorch T, Lurmann F, et al. 2005. Air pollution exposure assessment for epidemiologic studies of pregnant women and children: lessons learned from the Centers for Children’s Environmental Health and Disease Prevention Research. Environ Health Perspect 113:1447–1454.

Giniana EV, Rankin J, Bell R, Pless-Mulloli T, Hovell D. 2004. Particulate air pollution and fetal health: a systematic review of the epidemiologic evidence. Epidemiology 15:36–45.

Gouveia N, Bremner SA, Novaes HM. 2004. Association between ambient air pollution and birth weight in Sao Paulo, Brazil. J Epidemiol Community Health 58:11–17.

Ha EH, Hong YC, Lee BE, Woo BH, Schwartz J, Christiani DC. 2001. Is air pollution a risk factor for low birth weight in Southw Orleans? J Epidemiol Community Health 55:1643–1648.

Hansen C, Neller A, Williams G, Simpson R. 2007. Low levels of ambient air pollution during pregnancy and fetal growth among term neonates in Brisbane, Australia. Environ Res 103:838–840.

Hazen-kvon-arx ME, Gitsch T, Ackerman-Liebrich U, Boro N, Burney P, Cyrys J, et al. 2004. PM₁₀ and NO₂ assessment in 21 European study centres of ECRHS II: annual means and seasonal differences. Atmos Environ 38:1943–1953.

Hoek G, Brunekreef B, Goldobin S, Fischer P, van den Brandt PA. 2002. Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. Lancet 360:1203–1209.

Jedrychowski W, Bendkowski I, Flak E, Penar A, Jacek R, Kaim I, et al. 2004. Estimated risk for altered fetal growth resulting from exposure to fine particles during pregnancy: an epidemiologic prospective cohort study in Poland. Environ Health Perspect 112:1398–1402.

Kannan S, Misra DP, Dvorch JT, Krishnakumar A. 2006. Exposures to airborne particulate matter and adverse perinatal outcomes: a biologically plausible mechanistic framework for exploring potential effect modification by nutrition. Environ Health Perspect 114:1636–1642.

Lacasas E, Exploules A, Ballester F. 2005. Exposure to ambient air pollution in prenatal and early childhood health effects. Eur J Epidemiol 20:183–199.

Lebret E, Briggs D, Van Reeuwijk H, Fischer P, Smallbone K, Hansen C, Neller A, Williams G, Simpson R. 2007. Low levels of ambient air pollution during pregnancy and fetal growth among term neonates in Brisbane, Australia. Environ Res 103:838–840.

Murray LJ, O’Reilly DP, Betts N, Patterson CC, Davey SG, Evans AE. 2000. Seasonal and outdoor ambient temperature: effects on birth weight. Obstet Gynecol 96:689–695.

Nethery E, Brauer M, Janssen P. 2009. Time-activity patterns of pregnant women and changes during the course of pregnancy. J Expo Sci Environ Epidemiol 19:317–324.

Nethery E, Leckie SE, Teschke K, Brauer M. 2008. From measures to models: an evaluation of air pollution exposure assessment for epidemiologic studies of pregnant women. Occup Environ Med 65:579–589.

O’Neill MS, Jerrett M, Kawachi I, Levy JI, Cohen AJ, Gouveia N, et al. 2003. Health, wealth, and air pollution: advancing the theory and methods. Environ Health Perspect 111:1861–1870.

Rivas-Fité N, Ramón R, Ballester F, Grimalt J, Marco A, Olea N, et al. 2006. Child health and the environment: the INMA Spanish Study. Paediatric Perinatal Epidemiol 20:403–410.

Ritz B, Wilhelm M. 2008. Ambient air pollution and adverse birth outcomes: methodologic issues in an emerging field. Basic Clin Pharmacol Toxicol 102:182–190.

Rivas-Lara I. 2008. Variabilidad temporal y geográfica y caracterización quimica de la contaminación atmosférica particulada a Sabadell [in Catalan] [MSc thesis]. Barcelona, Spain:Autonomous University of Barcelona. Available: http://www.recercat.net/bitstream/2072/12571/1/PECoIaoRivas.pdf [accessed 15 December 2008].

Salm MT, Millstein J, Li FY, Lurmann FW, Margolis HG, Green G. 2006. Estimated risk for altered fetal growth attributable to ozone, carbon monoxide, and particulate matter: results from the Children’s Health Study. Environ Health Perspect 113:1638–1644.

Sinclair KD, Lee BS, Pees WD, Young LE. 2007. The developmental origins of health and disease: current theories and epidemiologic mechanisms. Soc Reprod Fertil 46(suppl):425–443.

Slama R, Darrow L, Parker J, Woodruff TJ, Strickland M, Nieuwbehuisen M, et al. 2008a. Meeting report: atmospheric pollution and human reproduction. Environ Health Perspect 116:791–798.

Slama R, Khooshnood B, Kaminski M. 2008b. How to control for gestational age in studies involving environmental effects on fetal growth [Letter]. Environ Health Perspect 116:2248.

Slama R, Morgenstern V, Cyrys J, Zutavern A, Herbarth O, Wichmann HE, et al. 2007. Traffic-related atmospheric pollutants levels during pregnancy and offspring’s term birth weight: a study relying on a land-use regression exposure model. Environ Health Perspect 115:1283–1292.

Šram RJ, Binková B, Dejmek J, Bobak M. 2005. Ambient air pollution and pregnancy outcomes: a review of the literature. Environ Health Perspect 113:375–382.

Tustin K, Gross J, Hayne H. 2004. Maternal exposure to first-trimester sunshine is associated with increased birth weight in human infants. Dev Psychobiol 45:221–230.

Wang L, Pinkerton KE. 2007. Air pollutant effects on fetal and early postnatal development. Birth Defects Res C Embryo Today 81:144–154.

Westercat SC, Davison A, Cowell S. 2000. Ultrasonic fetal measurements: new Australian standards for the new millennium. Aust N Z J Obstet Gynaecol 40:297–302.

Wilhelm M, Ritz B. 2005. Local variations in CO and particulate air pollution. Clin Pharmacol Toxicol 102:182–190.

Corbett S. 2005. Impact of ambient air pollution on birth weight and pregnancy outcome. Environ Epidemiol 17:426–432.