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Sex-specific differences in fetal growth in newborns exposed prenatally to traffic-related air pollution in the PELAGIE mother–child cohort (Brittany, France)

Mélanie Bertin [a,b,c], Cécile Chevrier [a,b], Tania Serrano [a,b,c], Christine Monfort [a,b], Sylvaine Cordier [a,b], Jean-François Viel [a,b,d,*]

[a] INSERM U1085-IRSET, France
[b] University of Rennes 1, Rennes, France
[c] EHESP School of Public Health, Sorbone Paris Cité, Rennes, France
[d] Department of Epidemiology and Public Health, University Hospital, 2 rue Henri Le Guilloux, 35033 Rennes, France

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ABSTRACT

Background: Numerous studies have linked prenatal traffic-related air pollution exposure to fetal growth. Recently, several studies have suggested exploring this association independently among boys and girls because of potential sex-specific biological vulnerability to air pollution. Residence-based factors can also influence fetal growth by enhancing susceptibility to the toxic effects of air pollution and must also be considered in these relations.
Objective: We examined sex-specific associations between prenatal air pollution exposure and fetal growth and explored whether they differed by the urban–rural status of maternal residence.
Methods: This study relied on the PELAGIE mother–child cohort (2521 women, Brittany, France, 2002–2006). Fetal growth was assessed through birth weight, head circumference and small weight (SGA) and small head circumference (SHC) for gestational age. Nitrogen dioxide (NO_2) concentrations at mothers' homes were estimated by using a land use regression model taking into account temporal variation during pregnancy. Associations between estimated NO_2 concentrations and fetal growth were assessed with linear regression or logistic regression models, depending on the outcome investigated.
Results: An interquartile range (8.8 $\mu g\, m^{-3}$) increase in NO_2 exposure estimates was associated with a 27.4 g (95% CI 0.8 to 55.6) increase in birth weight and a 0.09 cm (95% CI 0.00–0.17) significant increase in head circumference, among newborn boys only. Their risks of SGA and SHC were reduced (OR 0.70, 95% CI 0.53–0.92, OR 0.76, 95% CI 0.56–1.03, respectively, for an increase of 8.8 $\mu g\, m^{-3}$). No statistically significant trends were observed among girls. Urban–rural status modified the effect of air pollution only for SHC and again only for newborn boys.
Conclusion: Findings from this study confirm the need to consider sex-specific associations between air pollution and fetal growth and to investigate possible mechanisms by which traffic-related air pollution may increase anthropometric parameters at birth.

1. Introduction

Ambient air pollution is one of the most ubiquitous and hazardous environmental substances or combination of substances to which fetuses are exposed during their development and early postnatal life (Wang and Pinkerton, 2007). Growing concerns about the adverse effects of air pollution on human health have progressively led researchers to investigate its effects on fetuses and newborns, who are especially vulnerable to environmental toxicants because of their physiological immaturity (Perera et al., 1999) and may accordingly be subjected to lifelong health consequences (Barker, 1995). Over the past decade, numerous authors have examined the evidence of the relation between air pollution and birth outcomes and more particularly fetal growth (Stieb et al., 2012).

Birth weight is commonly used as a proxy for fetal growth, and metrics based on it have been used to identify suboptimal growth.

* Corresponding author at: INSERM-IRSET, Department of Epidemiology and Public Health, University Hospital, 2 rue Henri Le Guilloux, 35033 Rennes, France. Fax: +33 299 289 766.
E-mail address: jean-francois.viel@univ-rennes1.fr (J.-F. Viel).

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Although pooled estimates of effects generally indicate associations between prenatal exposure to several air toxicants and low birth weight, heterogeneity between studies is considerable (Stieb et al., 2012). Several possible mechanisms, not mutually exclusive, have been suggested in the literature to explain the effects of ambient air pollutants on low birth weight (LBW) or small weight for gestational age (SGA). These pathways include oxidative stress, maternal and placental inflammation, blood coagulation, endothelial dysfunction, hypertension, and possible endocrine disruption. These mechanisms may disrupt placenta growth, transplacental oxygen, and nutrient transport; they may also foster placental/fetal epigenetic changes or enhance maternal susceptibility to infections that can also affect fetal growth (Slama et al., 2008; Kannan et al., 2006). Furthermore, growing evidence suggests these mechanisms may differ according to the fetus's sex (Bolton et al., 2014). Sex-linked traits (e.g., hormonal status and body size) influence both biological responses to exposure to environmental toxicants and the biological transport of these environmentally derived chemicals (Clougherty, 2010), and male newborns are suggested to be more vulnerable to prenatal exposure to air pollution (Jedrychowski et al., 2009; Ghosh et al., 2007; Lakshmanan et al., 2015). Because these biological differences in toxicology begin at the embryo stage, it appears necessary to assess sex-specific air pollution effects on fetal growth.

Head circumference has been used in the literature as a marker of fetal growth less often than birth weight and still more rarely as a marker of cerebral development or impairment, despite growing evidence that air pollution has neurotoxic effects (Calderón-Garcidueñas et al., 2012; Block and Calderón-Garcidueñas, 2009; Genc et al., 2012). Similarly, some studies (Slama et al., 2009; Hansen et al., 2008; Pedersen et al., 2013; Van den Hooven et al., 2012) have reported adverse effects of prenatal exposure to ambient air pollution on head circumference, while others have not (Estarlich et al., 2011; Hansen et al., 2007; Ritz et al., 2014).

Moreover, researchers have underlined the need to take place-based factors as well as individual characteristics into account to elucidate the pathways by which air pollution might influence fetal growth (Morello-Frosch and Shenassa, 2006). Neighborhood socioeconomic status, the extent of natural spaces, and traffic road nuisances — all previously shown to be associated with outdoor air pollutant concentrations and fetal growth (Hystad et al., 2014; Gehring et al., 2014; Vrijheid et al., 2012) — must therefore be considered to be potential confounding factors of the relation between air pollution and fetal growth. Urban–rural status may also influence the relation between air pollution and fetal growth because it may increase exposure contrasts and pollutant mixtures but also because characteristics of populations may vary substantially from urban to rural settings; these differences, which may include health behaviors as well as time spent both outdoors and commuting, may increase confounding or mediating biases (Malmqvist et al., 2011). However, to our knowledge, only one previous study has explored the influence of air pollution on fetal growth according to urban–rural status (Vinikoor-Imler et al., 2014).

In this study of the PELAGIE mother–child cohort, our aim was to examine the sex-specific effects on fetal growth, assessed at birth, of prenatal exposure to nitrogen dioxide (NO_2), used as a marker of traffic-related air pollution. We also explored the extent to which the urban or rural status of the mother's home may modulate the influence of traffic-related air pollution on fetal growth.

2. Methods

2.1. Study population

The PELAGIE cohort included 3421 pregnant women living in the Brittany region (France) from 2002 to 2006. They were recruited during prenatal care visits to gynecologists, obstetricians, or ultrasonographers before the 19th week of gestation and enrolled after providing written informed consent. They were asked to complete a self-administered questionnaire at home concerning family, social, and demographic characteristics, diet, and lifestyle. This analysis is restricted to the 3226 women who gave birth to singleton liveborn infants without any major congenital malformation. The home address of each woman included in the PELAGIE cohort was geocoded. To exploit the fine resolution of the exposure data, we excluded women whose address could not be geocoded or who lived outside Brittany (n=44) and those who reported only their municipality of residence (n=661); this process left us with 2521 women. The study was approved by all relevant ethics committees, and all participating women gave informed content for their own participation and that of their children.

2.2. Assessment of fetal growth

A midwife or obstetrician at the maternity unit of delivery assessed the infant's birth weight (BW) and head circumference (HC) at birth. Each infant's expected birth weight was estimated from his/her gestational age (third-degree polynomial) and sex, parity (third-degree polynomial), and maternal prepregnancy weight (third-degree polynomial), height, and age (second-degree polynomial), according to the model of Mamelle et al. (2001). Model parameters were estimated from all live singleton births without congenital malformations. Babies with a birth weight below the tenth percentile of the expected birth weight distribution were classified as small for gestational age (SGA). Small head circumference for gestational age (SHC) at birth was defined by a head circumference below the tenth percentile of the head circumference distribution for a given gestational age and sex, according to French reference curves (AUDIPOG, 2008).

2.3. Traffic-related air pollution exposure assessment

Annual ambient 3-year average NO_2 concentrations were estimated from a land-use regression (LUR) model on a 100-m grid across Western Europe for the years 2005–2007, as previously described elsewhere (Vienneau et al., 2013). Briefly, LUR predictor variables included land coverage (Corine total built up land and seminatural land), length of minor roads and major roads in zones from 0.1 km to 10 km, and satellite-derived estimates of ground-level NO_2 concentrations from the Ozone Monitoring Instrument onboard the NASA Aura satellite. This NO_2 LUR model has been evaluated against an independent subset of 20% sites reserved for this purpose. Overall, it explained 60% of the variation in log-transformed annual mean NO_2 at independent sites distributed across Europe.

To validate the extrapolation of the modeled NO_2 concentrations (2005–2007) to the four preceding years (for n=2061 women with pregnancies between 2002 and 2004), we calculated a Pearson correlation coefficient between the NO_2 concentrations at their homes according to the 100-m grid over the 2005–2007 period and the annual NO_2 concentrations from two other datasets: the nationwide French NO_2 concentrations at a 4-km grid, established in 2000 (Jeannée et al., 2006), and Europe-wide NO_2 concentrations at a 1-km grid established in 2001 (European APMoSPHERE project) (Beelen et al., 2009). The latter are described