Environmental Research 148 (2016) 39–45

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Small for gestational age and exposure to particulate air pollution in the early-life environment of twins

Esmée M. Bijnens [a,b], Catherine Derom [c,d], Marij Gielen [b], Ellen Winckelmans [a], Frans Fierens [e], Robert Vlietinck [c], Maurice P. Zeegers [b], Tim S. Nawrot [a,f,*]

[a] Centre for Environmental Sciences, Hasselt University, Agoralaan Building D, 3590 Diepenbeek, Belgium
[b] Department of Complex Genetics, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre, P.O. Box 616, 6200 MD Maastricht, The Netherlands
[c] Centre of Human Genetics, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium
[d] Department of Obstetrics and Gynaecology, Ghent University Hospitals, 9000, Ghent, Belgium
[e] Belgian Interregional Environment Agency, Kunstlaan 10-12, 1210 Brussel, Belgium
[f] Department of Public Health, Leuven University (KU Leuven), Kapucijnenvoer 35, 3000 Leuven, Belgium

ARTICLE INFO

Article history:
Received 25 August 2015
Received in revised form
2 March 2016
Accepted 3 March 2016

Keywords:
Air pollution
Particulate matter
Pregnancy
Birth weight
Small for gestational age
Twin

ABSTRACT

Several studies in singletons have shown that maternal exposure to ambient air pollutants is associated with restricted fetal growth. About half of twins have low birth weight compared with six percent in singletons. So far, no studies have investigated maternal air pollution exposure in association with birth weight and small for gestational age in twins.

We examined 4760 twins of the East Flanders Prospective Twins Survey (2002–2013), to study the association between *in utero* exposure to air pollution with birth weight and small for gestational age. Maternal particulate air pollution (PM_{10}) and nitric dioxide (NO_2) exposure was estimated using a spatial temporal interpolation method over various time windows during pregnancy.

In the total group of twins, we observed that higher PM_{10} and NO_2 exposure during the third trimester was significantly associated with a lower birth weight and higher risk of small for gestational age. However, the association was driven by moderate to late preterm twins (32–36 weeks of gestation). In these twins born between 32 and 36 weeks of gestation, birth weight decreased by 40.2 g (95% CI: −69.0 to −11.3; $p=0.006$) and by 27.3 g (95% CI: −52.9 to −1.7; p=0.04) in association for each 10 μg/m³ increment in PM_{10} and NO_2 concentration during the third trimester. The corresponding odds ratio for small for gestational age were 1.68 (95% CI: 1.27–2.33; $p=0.0003$) and 1.51 (95% CI: 1.18–1.95; $p=0.001$) for PM_{10} or NO_2, respectively. No associations between air pollution and birth weight or small for gestational age were observed among term born twins. Finally, in all twins, we found that for each 10 μg/m³ increase in PM_{10} during the last month of pregnancy the within-pair birth weight difference increased by 19.6 g (95% CI: 3.7–35.4; $p=0.02$).

Assuming causality, an achievement of a 10 μg/m³ decrease of particulate air pollution may account for a reduction by 40% in small for gestational age, in twins born moderate to late preterm.

1. Introduction

Low birth weight and small for gestational age are associated with increased neonatal morbidity and mortality (Behrman and Butler, 2007; McIntire et al., 1999). The consequences of low birth weight and being born small for gestational age occur not only in the neonatal period but also in adulthood. These newborns are possibly at increased risk for developing heart and metabolic disease later in life according to the 'Barker hypothesis' (Levy-Marchal and Jaquet, 2004; Osmond and Barker, 2000).

Several studies have shown that maternal exposure to ambient air pollutants during pregnancy is associated with restricted fetal growth in singletons (Dadvand et al., 2013; Pedersen et al., 2013; Sapkota et al., 2012; Stieb et al., 2012). Heterogeneity of study designs, exposure period and exposure assessment exits, but meta-analyses have shown that particulate matter with an aerodynamic diameter of less than 10 μm (PM_{10}) is negatively associated with term birth weight (Dadvand et al., 2013; Stieb et al., 2012). In addition, a European multi cohort study found that PM_{10} and NO_2 are associated with increased risk of low birth weight at

* Corresponding author at: Centre for Environmental Sciences, Hasselt University, Agoralaan Building D, 3590 Diepenbeek, Belgium.
E-mail address: tim.nawrot@uhasselt.be (T.S. Nawrot).

http://dx.doi.org/10.1016/j.envres.2016.03.006
0013-9351/

term (Pedersen et al., 2013). Besides birth weight, small for gestational age (SGA) has been found to be associated with ambient air pollution (Le et al., 2012; Liu et al., 2007; Mannes et al., 2005; van den Hooven et al., 2012). A population-based cohort study in the Netherlands demonstrated an association between small for gestational age and PM_{10} exposure (van den Hooven et al., 2012). Based on ultra sound measurements they suggest that maternal PM_{10} exposure is inversely associated with fetal growth during the second and third trimester (van den Hooven et al., 2012). Large studies in Detroit and Sydney show similar observations for PM_{10} (Le et al., 2012; Mannes et al., 2005). In addition, adverse effects of NO_2 on fetal growth restriction among singleton births were noted in Canadian cities (Liu et al., 2007).

However to the best of our knowledge, no studies have investigated the association of air pollution with birth weight and small for gestational age in twins. The growth of a twin fetus differs from a singleton after 32 weeks of gestation probably due to the restricted capability of the *uterine* environment to nurture more than one fetus at a time (Blickstein, 1995). This finally results in decreased birth weight and increased odds of perinatal mortality (Hack et al., 2008). Therefore, twins could have potentially increased vulnerability to *in utero* exposure to air pollution.

2. Methods

2.1. Subjects

The East Flanders Prospective Twin Survey (EFPTS) is a population based register of multiple births in the province of East-Flanders (Belgium) (Derom et al., 2013). The twins are ascertained at birth. We geocoded the addresses of 5190 twin born between 2001 and 2013. We excluded still-born twins (n=56) or twins suffering from major congenital malformation (n=70). We excluded twins with missing data; birth weight (n=20), gestational age (n=20), zygosity (n=240), maternal age (n=6), parity (n=18). This resulted in a final study population of 4760 persons.

2.2. Tissue sampling and zygosity determination and tissue sampling

A trained midwife examined the placentas within 24 hours after delivery following a standardized protocol (Derom et al., 1995). Fetal membranes were dissected, and after removing the membranes and blood clots, the fresh unfixed placentas were weighed, and their length and thickness were measured. Zygosity was determined by sequential analysis based on sex, chorion type, blood group determined on umbilical cord blood, DNA fingerprints (Vlietinck, 1986). After DNA-fingerprinting, a zygosity probability of 0.999 was reached.

2.3. Data collection

Data recorded by the obstetrician at birth included gestational age, newborns birth weight, sex of the twins, birth date, maternal age, parity, mode of delivery and mode of conception, and live born versus stillborn. Gestational age was based on the last menstruation or on a first trimester ultrasound investigation and was calculated as the number of completed weeks of pregnancy. We classified births as small for gestational age when birth weight was below the 10th percentile of the birth weight for a given gestational age and gender according to cut-off values based on data from twin births in Flanders from the Study Centre for Perinatal Epidemiology (SPE) in the period 2001–2010 (Cox et al., 2013). We gathered information on neighbourhood socio economic status. All mothers were assigned to statistical sectors (average area=1.55 km^2), the smallest administrative entity for which statistical data are produced by the Belgian National Institute of Statistics (NIS), based on their home address. Belgian census data (FOD Economie/DG Statistiek) derived from the NIS were used to define neighbourhood socio economic status based on annual household income (2005).

2.4. Exposure assessment

Regional background levels of PM_{10} for each mother's residential address were estimated using a spatial temporal interpolation method (Kriging) that uses land cover data obtained from satellite images (Corine land cover data set) in combination with monitoring stations (n=19, 44 for PM_{10} and NO_2 in 2002) (Janssen et al., 2008). This model provides interpolated daily PM_{10} values in 4×4 km grids from the Belgian telemetric air quality networks.

Individual mean PM_{10} concentrations (micrograms per cubic meter) were calculated for various periods: last month and week of pregnancy and each of the three trimesters of pregnancy, with trimesters being defined as: 1–13 weeks (trimester 1), 14–26 weeks (trimester 2) and 27 weeks to delivery (trimester 3). This provides the opportunity to explore potentially critical exposure periods during pregnancy. Additionally, NO_2 exposure was interpolated using the same methods as PM_{10} exposure.

2.5. Statistical analysis

For data management and statistical analyses, we used SAS software, version 9.3 (SAS Institute, Cary, NC). All reported p-Values are two-sided and were considered statistically significant when $p < 0.05$. The normal distribution of all quantitative variables was visually inspected in QQ-plots.

Mixed modeling was performed to investigate the association between birth weight and air pollution exposure. The twins were analyzed as individuals in a multilevel regression analysis. To account for relatedness between twin members a random intercept was added to the model. The variance-covariance structure was allowed to differ between the three zygosity-chorionicity groups. Potential confounders and covariates were selected a priori including newborn's sex, birth order, parity, gestational age (linear and quadratic), season of birth, birth year, zygosity and chorionicity, maternal age and neighbourhood household income.

A generalized linear mixed model was used to investigate the association between the binary outcome small for gestational age and air pollution exposure. In this model similar covariates were used, with exception of newborn's sex and gestational age.

In addition, we formally tested the air pollution by zygosity interaction on birth weight.

Based on previous evidence between air pollution and birth weight in singleton births (Pereira et al., 2012; Winckelmans et al., 2015) and differences in growth patterns of twins over gestational age compared with singletons, (Gielen et al., 2008a; Loos et al., 2005; Odibo et al., 2013) we stratified the analysis *a priori* in term (> 36 weeks), moderate to late preterm (32–36 weeks) and very preterm (< 32 weeks).

2.6. Within-pair analysis

We calculated the difference in birth weight within each pair. We analyzed the association between air pollution and the within-pair difference in birth weight by the use of a multiple regression model adjusted for sex of the twin pair, birth order, parity, gestational age, season of birth, birth year, zygosity and chorionicity, maternal age and neighbourhood household income. In addition, we stratified the analysis in dizygotic, monozygotic-dichorionic, monozygotic-monochorionic twin pairs. We tested the interaction between zygosity-chorionicity group and air pollution exposure on the intra-pair difference in birth weight.