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The association of air pollution with congenital anomalies: An exploratory study in the northern Netherlands

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ABSTRACT

Background: There are a growing number of reports on the association between air pollution and the risk of congenital anomalies. However, the results are inconsistent and most studies have only focused on the association of air pollution with congenital heart defects and orofacial clefts.

Objectives: Using an exploratory study design, we aimed to identify congenital anomalies that may be sensitive to maternal exposure to specific air pollutants during the periconceptional period.

Methods: We conducted a case-control study of 7426 subjects born in the 15 years between 1999 and 2014 and registered in the European Registration of Congenital Anomalies and Twins Northern Netherlands (EUROCAT NNL). Concentrations of various air pollutants (PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, NO_2, NO_X, absorbance) were obtained using land use regression models from the European Study of Cohorts for Air Pollution Effects (ESCAPE). We linked these data to every subject in the EUROCAT NNL registry via their full postal code. Cases were classified as children or fetuses born in the 15-year period with a major congenital anomaly that was not associated with a known monogenic or chromosomal anomaly. Cases were divided into anomaly subgroups and compared with two different control groups: control group 1 comprised children or fetuses with a known monogenic or chromosomal anomaly, while control group 2 comprised all other non-monogenic and non-chromosomal registrations.

Results: Using control group 1 (n = 1618) for analysis, we did not find any significant associations, but when we used control group 2 (ranges between n = 4299 and n = 5771) there were consistent positive associations between several air pollutants (NO_2, $PM_{2.5}$, $PM_{10-2.5}$, absorbance) and the genital anomalies subgroup.

Conclusion: We examined various congenital anomalies and their possible associations with a number of air pollutants in order to generate hypotheses for future research. We found that air pollution exposure was positively associated with genital anomalies, mainly driven by hypospadias. These results broaden the evidence of associations between air pollution exposure during gestation and congenital anomalies in the child. They warrant further research, which should also focus on possible underlying mechanisms.

1. Introduction

Congenital anomalies are one of the main causes of perinatal mortality (Linhart et al., 2000). Worldwide, an estimated 10% of under five-year-olds die due to congenital anomalies (World Health Statistics, 2013). Therefore, congenital anomalies are a major public health issue, especially because of the lack of information on prevention. There is growing evidence that fetal development is particularly vulnerable to air pollution. Several studies have shown an association between pregnant women being exposed to air pollutants and an increased risk of fetal growth restriction (Pedersen et al., 2013), low birth weight (Pedersen et al., 2013), preterm birth and neonatal mortality (Effects of Air Pollution on Children's Health and Development, 2005). In addition, several studies have shown that maternal exposure to several air pollutants is possibly associated with congenital anomalies. Farhi et al. described the increased risk for congenital anomalies, specifically in the

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circulatory system and genital organs, when mothers were exposed to higher levels of particulate matter (PM_{10}) and nitrogen oxide (NO_X) (Farhi et al., 2014). Liang et al. showed an association between maternal exposure to PM_{10} and the risk of congenital anomalies (Liang et al., 2014).

There is substantial evidence that oxidative stress and inflammation are involved in the mechanisms underlying the effects of air pollutants which can contribute to epigenetic changes, including alteration of DNA methylation (Baccarelli and Bollati, 2009; Mazzoli-Rocha et al., 2010). Such epigenetic modifications during pregnancy could impair normal embryo development and lead to congenital anomalies.

Despite this evidence, there remain inconsistencies and uncertainties about the effects of specific air pollutants. Most studies have focused on congenital heart defects or orofacial clefts. We hypothesize that other anomalies may also be sensitive to air pollution. Therefore, using an exploratory study design, we set out to identify congenital anomalies that may be sensitive to maternal exposure to specific air pollutants during the periconceptional period.

2. Material and methods

2.1. Study design and population

We performed an exploratory case-malformed control study on congenital anomalies and air pollution using data from EUROCAT (European Registration of Congenital Anomalies and Twins) Northern Netherlands (NNL). The air pollution data was obtained from ESCAPE (European Study of Cohorts for Air Pollution Effects).

EUROCAT NNL is a population-based registry of children and fetuses with congenital malformations in the three northern provinces of the Netherlands. The methods of case ascertainment have been described elsewhere (http://www.eurocat-network.eu/content/Reg-Des-North-Netherlands.pdf). The registry is based on multiple sources of information such as hospital records, and post mortem examinations, and includes information about live births (LB), spontaneous abortions, fetal deaths (FD) with a gestational age greater than 24 weeks, and terminations of pregnancy after prenatal diagnosis of a fetal anomaly (TOPFA). All major structural malformations are registered and coded according to ICD9 or ICD10 with BPA (British Pediatric Association) extension and the EUROCAT guidelines (www.eurocat-network.eu). Approximately 15,000 children born between 1981 and 2014 have been registered in the database of EUROCAT NNL. Registration is voluntary and requires parental consent. Information on associated risk factors, such as maternal medication use, parents' professions, family history of congenital anomalies, use of alcohol and cigarettes, prenatal screening and diagnostic procedures performed during pregnancy is collected through a parental questionnaire and supplemented with information from medical files and local pharmacies. The EUROCAT NNL registry records a full postal code for the maternal residence at time of birth. EUROCAT NNL does not collect data on non-malformed children.

2.2. Definition of cases and controls

In this study, we classified cases as children or fetuses born between 1999 and 2014 with a major congenital anomaly that was not associated with a known monogenic or chromosomal anomaly. The congenital anomalies were divided into anomaly subgroups, according to organ system.

Anomaly subgroups with 30 cases or more were the primary outcome of the analysis (30 cases was set as a cutoff to perform meaningful analyses). These subgroups included anomalies of the nervous system, eye, heart, respiratory tract, digestive system, urinary tract, limb, genital tract, abdominal wall defects, and orofacial clefts. The cases in these anomaly groups all had isolated birth defects, i.e. they had an isolated anomaly or only anomalies in one organ system. A separate subgroup was created consisting of multiple congenital anomalies (cases diagnosed with multiple, unrelated anomalies in more than one organ system).

We excluded any subjects without a full postal code (needed to link EUROCAT NNL data with air pollution data from ESCAPE), or if no data was available on air pollution for their specific postal code.

In absence of a non-malformed control group, we used two malformed control groups in the exploratory analyses to identify anomaly groups sensitive to air pollution (Spinder et al., 2017):

Control group 1 comprised children or fetuses born or with an end–of-pregnancy date between 1999 and 2014 with a known monogenic or chromosomal anomaly (including microdeletions). This control group was used since a relationship between the genetic disorder and air pollution was not expected.

Control group 2 differed per anomaly subgroup and comprised all the other non-monogenic and non-chromosomal cases. For example, when the orofacial clefts subgroup was analyzed, control group 2 consisted of all the other non-monogenic and non-chromosomal cases that did not have an orofacial cleft.

2.3. Maternal characteristics

Maternal BMI was calculated using self-reported pre-pregnancy weight and height, and grouped using the WHO classification: underweight (BMI $< 18.5\,kg/m^2$), normal weight (BMI 18.5–25.0 kg/m^2), overweight (BMI $> 25.0\,kg/m^2$). Maternal education was assigned in three categories: 1. Lower education (including lower general secondary education and lower vocational education); 2. Medium education (including higher general secondary education and intermediate vocational education); and 3. Higher education (defined as higher vocational education, university and further tertiary college). Maternal age was divided into seven categories: 15–19 years, 20–24 years, 25–29 years, 30–34 years, 35–39 years, 40–44 years and > 44 years. Use of folic acid was divided into two categories: 'use' (400 or 500 μg per day in the periconceptional period of four weeks prior to conception to two months after conception) and 'no use or incorrect use' (use in wrong period or wrong dose (< 400 μg)). Maternal smoking was divided into 'smoking' or 'non-smoking' during pregnancy. 'Smoking during pregnancy' was defined by 'mother smoked during pregnancy or stopped smoking when she knew she was pregnant'. Maternal alcohol use was divided into 'alcohol use' (defined as 'mother drank alcohol during all or a part of pregnancy') or 'no alcohol use' during pregnancy (defined as 'mother stopped drinking alcohol before conception or did not drink alcohol at all'). Pregnancy outcome was divided into live birth, stillbirth (after 24 weeks of gestation), spontaneous abortion (until 24 weeks of gestation), and termination of pregnancy after prenatal diagnosis of a fetal anomaly (TOPFA, up to 24 weeks of gestation). Season of conception was calculated by subtracting the gestation period (in days) from the child's date of birth, which gave a date of conception. Then season of conception was divided into winter (December–February), spring (March–May), summer (June–August) and fall (September–November). For all subjects, their area-level socio-economic status (SES) score was based on the social status of their neighborhood retrieved from the Netherlands Institute of Social Research (*Sociaal Cultureel Planbureau*). This was determined for the postal code areas (first four digits) based on educational level, income and labor market position of the residents in the area (Knol, 1998) (https://www.scp.nl/Onderzoek/Lopend_onderzoek/A_Z_alle_lopende_onderzoeken/Statusscores). The area-level SES-score was divided into three groups based on the rankings: low, intermediate, and high.

2.4. Exposure assessment

The maternal exposure to nitrogen dioxide and nitrogen oxides (NO_2, NO_X), particulate matter with aerodynamic diameter ≤ 10 μm (PM_{10}), ≤ 2.5 μm ($PM_{2.5}$), the coarse fraction of particulate matter ($PM_{10\text{-}2.5}$), and absorbance (soot) were obtained from land use