International Journal of Hygiene and Environmental Health 221 (2018) 1061–1067

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

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

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

N. Salavati[a,*], M. Strak[b], J.G.M. Burgerhof[c], H.E.K. de Walle[d], J.J.H.M. Erwich[a], M.K. Bakker[a,d]

[a] Department of Obstetrics and Gynecology, University Medical Centre of Groningen, University of Groningen, Groningen, the Netherlands
[b] Institute for Risk Assessment Sciences (IRAS), Utrecht University, Utrecht, the Netherlands
[c] Department of Epidemiology, University Medical Centre of Groningen, University of Groningen, Groningen, the Netherlands
[d] Department of Genetics, EUROCAT Registration Northern Netherlands, University Medical Centre of Groningen, University of Groningen, Groningen, the Netherlands

ARTICLE INFO

Keywords:
Air pollution
Congenital anomalies
Land use regression model
Particulate matter pregnancy outcome

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

* Corresponding author. Department of Obstetrics and Gynecology CB21, University Medical Centre of Groningen, PO Box 30 001, 9700 RB, Groningen, the Netherlands.
E-mail addresses: n.salavati@umcg.nl (N. Salavati), m.m.strak@uu.nl (M. Strak), j.g.m.burgerhof@umcg.nl (J.G.M. Burgerhof), h.e.k.de.walle@umcg.nl (H.E.K. de Walle), j.j.h.m.erwich@umcg.nl (J.J.H.M. Erwich), m.k.bakker@umcg.nl (M.K. Bakker).

https://doi.org/10.1016/j.ijheh.2018.07.008
Received 4 January 2018; Received in revised form 9 July 2018; Accepted 17 July 2018

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

regression (LUR) models developed in the European Study of Cohorts for Air Pollution Effects (ESCAPE) (Eeftens et al., 2012; Beelen et al., 2013). Briefly, all the air pollutants included in the study were measured in three two-week periods in the cold, warm and intermediate seasons. The annual average concentration was calculated for each measurement, with adjustment for temporal variation using year-round measurement data from central reference sites. The air pollution concentration obtained from the measurements were then used as outcome variables for a LUR model. Variables derived from geographic information systems (e.g. distance to nearest road, traffic intensity, built-up land, population density, altitude) were used as predictor variables to explain the concentrations measured. The concentrations of all the air pollutants for all addresses in the Netherlands were modeled by using LUR models in the PCRaster environmental software, using 5 × 5 m grids (Karssenberg et al., 2010). In our analysis, we used the median concentration for each specific full postal code of the mother's address at time of birth. On average, there are 19.4 addresses per full postal code in the Netherlands. The LUR models are based on 2009 measurement campaigns. Since spatial distribution of air pollution is generally stable over periods of 10–15 years (Eeftens et al., 2011; Gulliver et al., 2011), our study population contains cases and controls over a 15-year period (birth years 1999–2014).

2.5. Statistical analyses

Since the air pollution data in our study population was skewed, we compared the distribution of values for specific air pollutants between cases and controls using the Wilcoxon ranksum test. The association between maternal characteristics and outcome (cases vs. controls) was examined using the Pearson chi square test for categorical variables or the Student's T-test for independent groups for continuous and reasonably normally distributed maternal characteristics.

Univariable logistic regression was used to determine association between exposure to specific air pollutants and different congenital anomaly subgroups. Multivariable logistic regression complete case analysis was performed to estimate the adjusted odds ratio (OR) and the 95% confidence interval (CI). The explanatory variables were the median concentrations of specific air pollutants and the outcome variables were the congenital anomaly subgroups.

Maternal smoking, level of education, age of mother, sex of child, season of conception, folic acid use, and area-level SES-score were included as covariates in multivariable analysis, based on information from the literature (Chen et al., 2014; Gilboa et al., 2005; Schembari et al., 2014).

The adjusted OR, 95% CI and p-values were reported. A p-value < 0.05 was considered statistically significant. Analyses were performed using SPSS 23.0 for Windows (IBM SPSS Statistics, Armonk, New York, USA).

3. Results

During the 15-year study period 294,421 births were monitored in the northern Netherlands and 7787 children or fetuses were registered in the EUROCAT NNL database with a major congenital anomaly and a full postal code that could be linked to air pollution data. This resulted in a total prevalence of 2.6%. After excluding two anomaly subgroups 'ear, face & neck' (n = 15, 0.2%) and 'endocrine organs' (n = 8, 0.1%), since they had fewer than 30 cases, and excluding those cases that could not be attributed to one specific anomaly subgroup (n = 338, 4.3%), we had 7426 (95.4%) subjects eligible for analysis. Of these, 5808 (78.2%) were cases with a major congenital anomaly attributed to one of the subgroups and 1618 (21.8%) were controls (control group 1) diagnosed with a known monogenic or chromosomal anomaly (including microdeletions). Limb anomalies were the most common subgroup (1509 cases), followed by congenital heart defects (1360 cases), and urinary anomalies (550 cases). Control group 1 was comprised mainly of chromosomal anomalies (n = 952): the main groups were Down Syndrome (trisomy 21, n = 464), Edwards syndrome (trisomy 18, n = 175), Turner syndrome (n = 77) and Patau syndrome (trisomy 13,

Table 1
Maternal and infant characteristics of cases and controls.

Characteristic	Cases[a]		Control group 1[b]		p-value
	N = 5808	(100%)	N = 1618	(100%)	
Age at delivery (years) (mean (sd))	30.4	(4.7)	32.3	(5.2)	< 0.001
Missing	77		9		
Age at delivery					< 0.001
15-19	58	(1.0)	14	(0.9)	
20-24	563	(9.8)	102	(6.3)	
25-29	1809	(31.6)	396	(24.6)	
30-34	2220	(38.7)	540	(33.6)	
35-39	940	(16.4)	406	(25.2)	
40-44	135	(2.4)	141	(8.8)	
> 44	6	(0.1)	10	(0.6)	
BMI (kg/m^2)					0.34
low (< 18.5)	133	(2.8)	35	(2.7)	
medium (18.5–25)	2910	(62.2)	840	(64.4)	
high (> 25)	1639	(35.0)	430	(33.0)	
Missing	1126		313		
Level of education					0.21
Low	678	14.4)	192	(14.7)	
Medium	2302	(49.0)	605	(46.4)	
High	1715	(36.5)	508	(38.9)	
Missing	1113		313		
Sex					< 0.001
Male	3218	(55.4)	802	(49.6)	
Female	2590	(44.6)	816	(50.4)	
Missing		0	0		
Season of conception					0.38
Winter	1380	(25.8)	385	(24.6)	
Spring	1372	(25.6)	434	(27.7)	
Summer	1283	(23.9)	362	(23.1)	
Autumn	1324	(24.7)	383	(24.5)	
Missing	449		54		
Folic acid use					0.30
Use	3653	(80.2)	994	(78.9)	
No use or incorrect use	901	(19.8)	266	(21.1)	
Missing	1254		358		
Smoking during pregnancy					0.02
Yes	1123	(22.8)	274	(19.8)	
No	3796	(77.2)	1108	(80.2)	
Missing	889		236		
Alcohol consumption during pregnancy					0.08
Yes	1051	(21.6)	326	(23.8)	
No	3823	(78.4)	1044	(76.2)	
Missing	934		248		
Area-level SES[c]-score				0.71	
Low	1514	(26.8)	418	(26.4)	
Intermediate	3870	(68.6)	1098	(69.4)	
High	259	(4.6)	66	(4.2)	
Missing		165	36		
Pregnancy outcome					< 0.001
Live birth	5467	(94.1)	1052	(65.0)	
Stillbirth	63	(1.1)	67	(4.1)	
Spontaneous abortion	30	(0.5)	59	(3.6)	
TOPFA[d]	248	(4.3)	440	(27.2)	
Gestation period (weeks) (mean (sd))	37.6	(5.0)	31.3	(10.3)	< 0.001
Missing	449		54		

[a] Infants or fetuses born between 1997 and 2014 with a non-chromosomal and non-monogenic birth defect including anomalies of the nervous system, eye, heart, respiratory tract, digestive system, urinary tract, limb, genital tract, abdominal wall defects and oro-facial clefts.

[b] Infants or fetuses born between 1997 and 2014 diagnosed with a known monogenic anomaly or a chromosomal anomaly (including microdeletions).

[c] SES denotes socio-economic status.

[d] TOPFA denotes termination of pregnancy for fetal anomaly.

n = 49). There were 538 malformed controls diagnosed with a monogenic anomaly and 128 with microdeletions. Maternal and infant characteristics of the cases and control group 1 are shown in Table 1.

The distribution of median air pollution concentrations and their range in the congenital anomaly subgroups and control group 1 are shown in Table 2.

Both univariable logistic regression analyses (Supplementary Tables 1 and 2) and multivariable logistic regression analyses were performed (both with control group 1 and control group 2). These were adjusted for age of mother, sex of child, level of education, season of conception, smoking, folic acid use, and area-level SES-score (Tables 3 and 4).

Univariable logistic regression analyses, using control group 1, showed mostly inconsistent significant negative associations, apart from the significant negative association of cases with anomalies of the digestive system with several air pollutants (NO_2, NO_x, PM_{10}, Absorbance) (Supplementary Table 1). In the multivariable logistic regression analyses, using control group 1, we found no more consistent associations (Table 3).

With univariable logistic regression analyses, using control group 2 (all other non-monogenic and non-chromosomal malformations), we found that cases with a genital anomaly had consistent significant positive associations with all the air pollutants compared to the controls (Supplementary Table 2). In the multivariable logistic regression analyses, using control group 2, the significant positive association of cases with a genital anomaly with several air pollutants (NO_2, $PM_{2.5}$, $PM_{10\text{-}2.5}$, Absorbance) remained (Table 4).

Since the genital anomalies subgroup mainly consists of hypospadias, we performed extra analyses in which we only included cases with hypospadias[1] and male controls. As shown in Table 4, in the analysis for the complete subgroup of genital anomalies, the association between air pollution and cases with hypospadias remained significant for NO_2 and $PM_{10\text{-}2.5}$.

4. Discussion

We performed an exploratory case-control study with malformed controls to extend the knowledge on possible associations between maternal exposure to air pollution and congenital anomalies in the offspring.

When we used other non-chromosomal, non-monogenic anomalies as a control group (control group 2), we found a significant positive association between air pollution with the subgroup of genital anomalies (NO_2, $PM_{2.5}$, $PM_{10\text{-}2.5}$, absorbance). Additional analyses showed this association was mainly driven by hypospadias. To the best of our knowledge, there is only one other study that reports on the association between hypospadias as a separate anomaly subgroup and air pollutants (NO_2, NO, CO, PM_{10}, $PM_{2.5}$ and O_3) (Padula et al., 2013). However, they did not find any significant relations between hypospadias and air pollutants. This could be due to their smaller sample size of hypospadias (n = 69) than in our study (n = 446). In addition, our results are in line with a study that reported an increased risk of hypospadias with the mother living near a landfill site (Elliott et al., 2001). Although this study did not include measurements of air pollutants, it is known that emissions from landfill can contribute to a higher concentration of air pollutants in the local vicinity (UK government, 2011) (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/334356/RCE-18_for_website_with_security.pdf).

In addition to the consistent associations between maternal air pollution exposure and genital anomalies, we found a few isolated associations between some air pollutants and either the cases or controls in our analyses using control groups 1 or 2. One of these associations is a protective association between cases with limb anomalies and PM2.5, an association in unexpected direction. This significant protective association appeared in both analyses with control group 1 as with control group 2. Given the lack of any clear, consistent patterns, it is possible that these results are due to the number of tests performed. We did not correct for multiple testing, given the exploratory nature of this study. In addition, limb anomalies is a heterogeneous subgroup, including polydactyly, club foot and hip dislocation and/or dysplasia. Further research should be performed within this anomaly subgroup to investigate the association found in this study.

Several studies have shown that the risk of having a child with a congenital anomaly is associated with maternal exposure to several harmful air pollutants. However, the findings are inconsistent. Several studies found a significant association between NO_2 and congenital heart defects (Dadvand et al., 2011; Schembari et al., 2014), while others found no significant association between air pollutants (e.g. NO_2) and congenital heart defects (Agay-Shay et al., 2013; Padula et al., 2013). Apart from the other inconsistencies in the literature, most studies reporting on air pollution and congenital anomalies have focused on cardiac anomalies or orofacial clefts (Chen et al., 2014). A recent literature review recommended that studies with sufficient statistical power should also focus on other anomalies that may have an environmental etiology (Vrijheid et al., 2011). The reason for the inconsistent findings in different studies can possible be attributable to the different assessment methods of the air pollutants. In addition, the classification of congenital anomalies and inclusion criteria for databases are different among the different studies. For example, the EUROCAT NNL database includes all type of births, which is not the case for most studies.

4.1. Strengths and limitations

One of the strong features of our study is the use of EUROCAT NNL, a large database of major structural malformations and chromosomal anomalies in all types of births, whereas most studies only had live births available in the registries used for their analyses. Excluding TOPFA may also lead to an underestimation of the association between maternal exposure to air pollutants and congenital anomalies. In addition, compared to other studies, we have used a wide range of major congenital anomaly subgroups, which was recommended by a recent literature review (Vrijheid et al., 2011).

Another strength of our study is that the ESCAPE LUR models are stable and explain a large proportion of the spatial variance seen in measured annual averages of PM_{10}, $PM_{2.5}$, $PM_{2.5\text{-}10}$, absorbance, NO_2 and NO_X (Beelen et al., 2013; Eeftens et al., 2012). Applying these models allows for a robust estimation of outdoor concentrations of a range of air pollutants at the mother's residential address. Furthermore, incorporation of site specific variables (e.g. traffic, topography and other geographic variables) into the LUR models, detects small area variations more effectively than other methods.

In the absence of a healthy control group for our analysis, we used two different control groups, a previously used methodology (Spinder et al., 2017). The use of malformed controls may create selection bias if the exposure also causes other malformations. Control group 1 was used since a relationship of chromosomal anomalies with air pollution was not expected. Although several animal studies have shown an association of maternal exposure to ambient air pollutants and genotoxic effects in the fetuses (Somers et al., 2002), this cannot be directly translated to humans and no studies with humans have demonstrated such an association so far. In our study, subjects in control group 1 were significantly older than the cases (all anomaly subgroups together) ($p < 0.001$). This is due to the fact that chromosomal disorders are associated with advanced maternal age. In addition, there were more male infants in the cases than in the control groups ($p < 0.001$), possibly because congenital anomalies are more prevalent among male infants. The pregnancy outcomes 'stillbirth', 'spontaneous abortion' and 'TOPFA' were higher in control group 1 than in the cases. This can be

[1] A congenital anomaly of the urethra in which the opening is not on the head of the penis.

Table 2
Distribution of air pollution concentration (in μg/m3) per ZIP code by congenital anomaly subgroups and control group 1 and 2.

	N	NO_2	NOx	PM_{10}	$PM_{2.5}$	$PM_{10-2.5}$	Absorbance
All cases[a]	5808	15.66 (9.22; 47.37)	21.80 (16.79; 71.99)	23.89 (23.73; 29.02)	15.45 (15.12; 18.39)	7.74 (7.60; 9.55)	0.93 (0.85; 2.14)
Control group 1 [b]	1618	15.84 (8.93; 29.73)	22.01 (16.79; 57.87)	23.93 (23.73; 27.71)	15.45 (15.16; 18.01)	7.75 (7.60; 9.62)	0.95 (0.85; 1.61)
Anomalies of the nervous system	282	15.73 (10.69; 28.45)	21.83 (17.56; 49.87)	23.95 (23.73; 26.88)	15.46 (15.14; 16.92)	7.74 (7.60; 9.34)	0.95 (0.85; 1.47)
Control group 2[c]	*5526*	*15.66 (9.22;47.37)*	*21.79 (16.79;71.99)*	*23.89 (23.73;29.02)*	*15.45 (15.12;18.39)*	*7.74 (7.60;9.55)*	*0.93 (0.85;2.14)*
Eye anomalies	107	15.32 (11.38; 26.74)	21.78 (17.75; 42.99)	23.91 (23.73; 26.90)	15.45 (15.26; 16.72)	7.76 (7.60; 8.92)	0.93 (0.85; 1.38)
Control group 2[c]	*5701*	*15.66 (9.22;47.37)*	*21.80 (16.79;71.99)*	*23.89 (23.73;29.02)*	*15.45 (15.12;18.39)*	*7.74 (7.60;9.55)*	*0.93 (0.85;2.14)*
Heart defects	1360	15.64 (10.02; 47.37)	21.81 (16.83; 71.99)	23.91 (23.73; 29.02)	15.45 (15.15; 18.39)	7.74 (7.60; 9.41)	0.94 (0.85; 2.14)
Control group 2[c]	*4448*	*15.67 (9.22;32.32)*	*21.79 (16.79;54.49)*	*23.88 (23.73;27.90)*	*15.45 (15.12;18.26)*	*7.74 (7.60;9.55)*	*0.93 (0.85;1.82)*
Anomalies of the respiratory tract	37	15.08 (11.93; 27.60)	20.76 (17.88; 49.70)	23.84 (23.73; 26.66)	15.44 (15.16; 16.56)	7.73 (7.60; 9.17)	0.92 (0.85; 1.35)
Control group 2[c]	*5771*	*15.66 (9.22;47.37)*	*21.81 (16.79;71.99)*	*23.89 (23.73;29.02)*	*15.45 (15.12;18.39)*	*7.74 (7.60;9.55)*	*0.93 (0.85;2.14)*
Oro-facial clefts	427	15.34 (9.41; 27.37)	21.63 (16.85; 46.10)	23.87 (23.73; 26.80)	15.44 (15.12; 16.87)	7.73 (7.60; 9.36)	0.93 (0.85; 1.68)
Control group 2[c]	*5381*	*15.69 (9.22;47.37)*	*21.82 (16.79;71.99)*	*23.89 (23.73;29.02)*	*15.45 (15.13;18.39)*	*7.74 (7.60;9.55)*	*0.93 (0.85;2.14)*
Anomalies of the digestive system	535	15.41 (9.35; 28.34)	21.58 (16.85; 52.05)	23.87 (23.73; 27.00)	15.45 (15.14; 17.08)	7.73 (7.60; 9.45)	0.93 (0.85; 1.53)
Control group 2[c]	*5273*	*15.68 (9.22;47.37)*	*21.82 (16.79;71.99)*	*23.89 (23.73;29.02)*	*15.45 (15.12;18.39)*	*7.74 (7.60;9.55)*	*0.93 (0.85;2.14)*
Anomalies of the urinary tract	550	15.69 (9.64; 32.32)	21.95 (16.90; 45.46)	23.91 (23.73; 26.87)	15.45 (15.17; 17.39)	7.74 (7.60; 9.41)	0.94 (0.85; 1.67)
Control group 2[c]	*5258*	*15.66 (9.22;47.37)*	*21.78 (16.79;71.99)*	*23.89 (23.72;29.02)*	*15.45 (15.12;18.39)*	*7.74 (7.60;9.55)*	*0.93 (0.85;2.14)*
Limb anomalies	1509	15.77 (9.22; 32.10)	21.84 (16.79; 54.49)	23.87 (23.73; 27.90)	15.44 (15.13; 18.26)	7.73 (7.60; 9.55)	0.92 (0.85; 1.76)
Control group 2[c]	*4299*	*15.62 (9.35;47.37)*	*21.77 (16.83;71.99)*	*23.90 (23.73;29.02)*	*15.45 (15.12;18.39)*	*7.74 (7.60;9.54)*	*0.94 (0.85;2.14)*
Abdominal wall defects	52	17.30 (11.27; 24.61)	23.42 (17.68; 34.77)	24.10 (23.73; 25.38)	15.51 (15.22; 16.72)	7.84 (7.60; 8.33)	0.98 (0.87; 1.17)
Control group 2[c]	*5756*	*15.65 (9.22;47.37)*	*21.77 (16.79;71.99)*	*23.89 (23.73;29.02)*	*15.45 (15.12;18.39)*	*7.74 (7.60;9.55)*	*0.93 (0.85;2.14)*
Genital anomalies	482	16.20 (10.10; 27.23)	22.05 (17.29; 47.61)	23.93 (23.73; 27.38)	15.46 (15.17; 17.83)	7.77 (7.60; 9.54)	0.94 (0.85; 1.82)
Control group 2[c]	*5326*	*15.62 (9.22;47.37)*	*21.77 (16.79;71.99)*	*23.89 (23.73;29.02)*	*15.45 (15.12;18.39)*	*7.74 (7.60;9.55)*	*0.93 (0.85;2.14)*
Multiple congenital anomalies	467	15.35 (9.96; 31.99)	21.50 (17.14; 45.61)	23.88 (23.73; 26.66)	15.46 (15.17; 16.98)	7.74 (7.60; 9.49)	0.93 (0.85; 1.65)
Control group 2[c]	*5341*	*15.67 (9.22;47.37)*	*21.83 (16.79;71.99)*	*23.89 (23.73;29.02)*	*15.45 (15.12;18.39)*	*7.74 (7.60;9.55)*	*0.93 (0.85;2.14)*

Values are median (range).

[a] Infants or fetuses born between 1997 and 2014 with a non-chromosomal and non-monogenic birth defect including anomalies of the nervous system, eye, heart, respiratory tract, digestive system, urinary tract, limb, genital tract, abdominal wall defects and oro-facial clefts.

[b] Infants or fetuses born between 1997 and 2014 diagnosed with a known chromosomal anomaly or monogenic anomaly.

[c] Infants or fetuses born between 1997 and 2014 with a non-chromosomal and non-monogenic anomaly, excluding the anomaly of interest in the subgroup.

explained by the fact that chromosomal abnormalities are less compatible with life and couples more often choose for 'TOPFA'. Consequently, the gestational period was significantly shorter in control group 1, which is related to the variable pregnancy outcomes of more terminations and stillbirths seen in control group 1.

In control group 2 specific effects of air pollution are diluted by the heterogeneity of the malformations in the control group. The exploratory nature of our study using two malformed control groups, limits the translation of our results to the general population. The odds ratios we determined indicate which congenital anomaly subgroups are most sensitive to air pollution.

Another limitation of this study is its reliance on measurements of air pollution at the location of the birth, which was not necessarily the mother's address during early pregnancy. However, we postulated that behavior in moving houses would be randomly distributed between the cases and control groups and the resulting exposure misclassification is likely non-differential. Furthermore, since congenital anomalies are a heterogeneous group of many quite rare conditions, there is still a lot of heterogeneity even within the anomaly subgroups used in our analyses. Therefore, in future research with larger datasets, it might well be worth looking at more specific anomalies rather than the larger anomaly subgroups. Another limitation in our analysis may be that the concentration level of air pollutants was based on the median concentration of air pollution for each full postal code area. The actual exposure for any individual could be higher or lower in their specific residential area. In addition, the ranges of the air pollutants as described in Table 2 are very narrow which can be seen as a limitation regarding investigating possible associations. However, this is a result of the decay of the modeled air pollutant in the LUR model, which is for example lower for PM10 and PM2.5 than it is for NO2, resulting in more narrow ranges.

Finally, we used a single estimate of average annual exposure rather than exposure specifically in the periconceptional period capturing seasonal exposure variation. However, we have adjusted for season of conception, which would consequently be the season of the periconceptional period.

5. Conclusions

We examined various congenital anomalies and their possible associations with a number of air pollutants in order to generate hypotheses for further research. We found that exposure to air pollutants was positively associated with genital anomalies, mainly driven by hypospadias. This broadens the evidence of associations between air

Table 3
Results of the multivariable logistic regression analysis, with control group 1 as reference (adjusted for age of the mother, sex of the child, level of education, season of conception, smoking, folic acid use and area-level SES-score).

	Air pollutants (median) (OR (CI))						
	N	NO_2	NO_x	PM_{10}	$PM_{2.5}$	$PM_{10-2.5}$	Absorbance
Control group 1[a]	1573	Reference	Reference	Reference	Reference	Reference	Reference
All cases[b]	5560	0.99 (0.98–1.01)	1.00 (0.98–1.01)	0.96 (0.87–1.06)	0.97 (0.80–1.17)	0.90 (0.74–1.09)	0.76 (0.47–1.24)
Anomalies of the nervous system	266	0.98 (0.94–1.02)	0.99 (0.96–1.02)	1.06 (0.84–1.35)	1.22 (0.78–1.92)	0.99 (0.64–1.55)	1.40 (0.42–4.69)
Eye anomalies	103	0.99 (0.93–1.05)	0.98 (0.94–1.02)	0.87 (0.59–1.28)	0.94 (0.46–1.94)	0.66 (0.31–1.42)	0.35 (0.05–2.61)
Heart defects	1309	0.98 (0.96–1.00)	0.99 (0.98–1.01)	0.96 (0.84–1.09)	1.10 (0.86–1.41)	0.82 (0.63–1.07)	0.76 (0.39–1.50)
Anomalies of the respiratory tract	36	0.97 (0.87–1.07)	0.99 (0.92–1.06)	0.92 (0.49–1.73)	0.77 (0.20–2.99)	0.58 (0.16–2.13)	0.71 (0.03–16.57)
Oro-facial clefts	412	**0.96 (0.93–1.00)***	0.98 (0.96–1.00)	0.84 (0.68–1.05)	0.79 (0.51–1.21)	0.87 (0.59–1.27)	0.43 (0.15–1.29)
Anomalies of the digestive system	504	0.97 (0.94–1.00)	0.99 (0.96–1.01)	0.89 (0.74–1.09)	0.83 (0.55–1.24)	0.78 (0.54–1.12)	0.40 (0.14–1.12)
Anomalies of the urinary tract	532	0.97 (0.94–1.00)	**0.98 (0.96–1.00)***	0.92 (0.76–1.11)	1.11 (0.79–1.57)	**0.70 (0.48–0.99)**	0.83 (0.33–2.13)
Limb anomalies	1435	1.01 (0.98–1.03)	1.00 (0.99–1.02)	0.94 (0.83–1.07)	**0.76 (0.58–0.98)**	0.91 (0.70–1.17)	0.56 (0.29–1.08)
Abdominal wall defects	52	1.05 (0.97–1.14)	1.02 (0.96–1.07)	1.36 (0.87–2.14)	1.43 (0.61–3.38)	1.30 (0.54–3.15)	5.08 (0.49–52.53)
Genital anomalies	457	1.01 (0.97–1.04)	1.00 (0.97–1.02)	1.01 (0.82–1.23)	1.31 (0.89–1.94)	0.96 (0.66–1.41)	1.18 (0.43–3.28)
Hypospadias[c]	0: 775 1: 446	1.00 (0.97–1.04)	0.99 (0.97–1.02)	0.99 (0.80–1.21)	1.24 (0.83–1.86)	0.96 (0.66–1.41)	1.02 (0.36–2.88)
Multiple congenital anomalies	454	0.98 (0.95–1.01)	0.99 (0.96–1.01)	0.90 (0.74–1.10)	0.92 (0.62–1.38)	0.87 (0.60–1.25)	0.71 (0.26–1.95)

Associations in bold are significant at $p < 0.05$. * The upper limit of the CI was smaller than 1, but due to rounding given as 1.00.

[a] Infants or fetuses born between 1997 and 2014 with a non-chromosomal and non-monogenic birth defect including anomalies of the nervous system, eye, heart, respiratory tract, digestive system, urinary tract, limb, genital tract, abdominal wall defects and oro-facial clefts.

[b] Infants or fetuses born between 1997 and 2014 diagnosed with a known chromosomal anomaly or monogenic anomaly.

[c] Both cases (1) and controls (0) included only male infants.

Table 4
Results of multivariable logistic regression with control group 2 (adjusted for age of the mother, sex of the child, level of education, season of conception, smoking, folic acid use and area-level SES-score).

	Air pollutants (median) (OR (CI))						
	N = 5560	NO_2	NO_x	PM_{10}	$PM_{2.5}$	$PM_{10-2.5}$	Absorbance
Anomalies of the nervous system	0 5294						
	1 266	0.99 (0.96–1.03)	1.00 (0.98–1.02)	1.12 (0.91–1.37)	1.24 (0.85–1.80)	1.24 (0.82–1.87)	1.84 (0.67–5.06)
Eye anomalies	0 5457						
	1 103	1.00 (0.94–1.06)	0.99 (0.95–1.03)	0.92 (0.64–1.31)	0.95 (0.48–1.88)	0.73 (0.36–1.51)	0.53 (0.09–3.26)
Heart defects	0 4251						
	1 1309	0.99 (0.97–1.01)	1.00 (0.99–1.01)	1.00 (0.90–1.11)	1.19 (0.97–1.45)	0.92 (0.74–1.15)	1.08 (0.63–1.85)
Anomalies of the respiratory tract	0 5524						
	1 36	0.98 (0.89–1.08)	1.00 (0.93–1.06)	0.96 (0.54–1.71)	0.77 (0.22–2.72)	0.63 (0.17–2.31)	0.82 (0.05–14.44)
Oro-facial clefts	0 5148						
	1 412	0.98 (0.95–1.01)	0.99 (0.97–1.01)	0.91 (0.76–1.10)	0.84 (0.58–1.22)	1.05 (0.74–1.49)	0.67 (0.27–1.69)
Anomalies of the digestive system	0 5056	0.98 (0.96–1.01)	0.99 (0.97–1.01)	0.92 (0.77–1.09)	0.78 (0.55–1.10)	0.89 (0.64–1.24)	0.48 (0.20–1.15)
	1 504						
Anomalies of the urinary tract	0 5028						
	1 532	0.99 (0.97–1.02)	0.99 (0.98–1.01)	1.01 (0.87–1.18)	1.19 (0.89–1.58)	0.86 (0.62–1.19)	1.40 (0.65–3.02)
Limb anomalies	0 4125						
	1 1435	1.02 (1.00–1.04)[d]	1.01 (1.00–1.02)	0.98 (0.88–1.09)	**0.73 (0.58–0.92)**	0.98 (0.79–1.22)	0.72 (0.41–1.26)
Abdominal wall defects	0 5508						
	1 52	1.06 (0.98–1.14)	1.03 (0.98–1.08)	1.40 (0.94–2.06)	1.49 (0.72–3.11)	1.65 (0.69–3.93)	5.41 (0.79–36.93)
Genital anomalies	0 5103						
	1 457	**1.04 (1.01–1.07)**	1.02 (1.00–1.04)	1.18 (1.00–1.39)	**1.37 (1.01–1.87)**	**1.45 (1.05–2.02)**	**2.27 (1.00–5.18)**[d]
Hypospadias[c]	0 2634						
	1 446	**1.04 (1.01–1.07)**	1.02 (1.00–1.04)	1.15 (0.97–1.37)	1.29 (0.94–1.78)	**1.46 (1.05–2.03)**	1.96 (0.85–4.56)
Multiple congenital anomalies	0 5106						
	1 454	0.99 (0.96–1.02)	0.99 (0.98–1.01)	0.96 (0.81–1.13)	0.94 (0.67–1.32)	1.03 (0.74–1.44)	0.99 (0.43–2.29)

1 = cases[a], 0 = control group 2[b].

Associations in bold are significant at $p < 0.05$.

[a] Infants or fetuses born between 1997 and 2014 with a non-chromosomal and non-monogenic birth defect including anomalies of the nervous system, eye, heart, respiratory tract, digestive system, urinary tract, limb, genital tract, abdominal wall defects and oro-facial clefts.

[b] Infants or fetuses born between 1997 and 2014 with a non-chromosomal and non-monogenic anomaly (5560- number of cases), excluding the anomaly of interest in the subgroup.

[c] Both cases (1) and controls (0) included only male infants.

[d] The lower limit of the CI was smaller than 1, but due to rounding given as 1.00.

pollution exposure during gestation and congenital anomalies and warrants future research that should also focus on possible mechanisms. Our work also supports the premise that further research should study a wide range of congenital anomaly subgroups, as recommended by a recent literature review (Vrijheid et al., 2011). A better understanding of the underlying mechanisms might help prevent the birth of infants with a congenital anomaly.

Abbreviations

EUOCAT NNL, European Registration of Congenital Anomalies and Twins Northern Netherlands; ESCAPE, European Study of Cohorts for Air Pollution Effects; LUR, land use regression; PM, particulate matter; NO_2, nitrogen dioxide; NOx, nitrogen oxide; LB, live births; FD, fetal deaths; TOPFA, termination of pregnancy after prenatal diagnosis of a fetal anomaly

Conflicts of interest

The authors declare that they have no conflicting interests related to this manuscript.

Funding

EUROCAT NNL is funded by the Dutch Ministry of Welfare, Health and Sports. The funder had no role in study design, data collection, data analysis, data interpretation, or writing the report. The corresponding author had full access to all the data in this study.

Acknowledgements

We thank Jackie Senior for editing the manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ijheh.2018.07.008.

References

Agay-Shay, K., Friger, M., Linn, S., Peled, A., Amitai, Y., Peretz, C., 2013. Air pollution and congenital heart defects. Environ. Res. 124, 28–34. https://doi.org/10.1016/j.envres.2013.03.005.

Baccarelli, A., Bollati, V., 2009. Epigenetics and environmental chemicals. Curr. Opin. Pediatr. 21, 243–251.

Beelen, R., Hoek, G., Vienneau, D., Eeftens, M., Dimakopoulou, K., Pedeli, X., Tsai, M.-Y., Künzli, N., Schikowski, T., Marcon, A., 2013. Development of NO2 and NOx land use regression models for estimating air pollution exposure in 36 study areas in Europe – the ESCAPE project. Atmos. Environ. 72, 10–23. https://doi.org/10.1016/j.atmosenv.2013.02.037.

Chen, E.K.-C., Zmirou-Navier, D., Padilla, C., Deguen, S., 2014. Effects of air pollution on the risk of congenital anomalies: a systematic review and meta-analysis. Int. J. Environ. Res. Publ. Health 11, 7642–7668. https://doi.org/10.3390/ijerph110807642.

Dadvand, P., Rankin, J., Rushton, S., Pless-Mulloli, T., 2011. Ambient air pollution and congenital heart disease: a register-based study. Environ. Res. 111, 435–441. https://doi.org/10.1016/j.envres.2011.01.022.

Eeftens, M., Beelen, R., de Hoogh, K., Bellander, T., Cesaroni, G., Cirach, M., Declercq, C., Dėdelė, A., Dons, E., de Nazelle, A., Dimakopoulou, K., Eriksen, K., Falq, G., Fischer, P., Galassi, C., Gražulevičienė, R., Heinrich, J., Hoffmann, B., Jerrett, M., Keidel, D., Korek, M., Lanki, T., Lindley, S., Madsen, C., Mölter, A., Nádor, G., Nieuwenhuijsen, M., Nonnemacher, M., Pedeli, X., Raaschou-Nielsen, O., Patelarou, E., Quass, U., Ranzi, A., Schindler, C., Stempfelet, M., Stephanou, E., Sugiri, D., Tsai, M.-Y., Yli-Tuomi, T., Varró, M.J., Vienneau, D., Klot, S. von, Wolf, K., Brunekreef, B., Hoek, G., 2012. Development of land use regression models for $PM_{2.5}$, $PM_{2.5}$ absorbance, PM_{10} and PM_{coarse} in 20 European study areas; results of the ESCAPE project. Environ. Sci. Technol. 46, 11195–11205. https://doi.org/10.1021/es301948k.

Eeftens, M., Beelen, R., Fischer, P., Brunekreef, B., Meliefste, K., Hoek, G., 2011. Stability of measured and modelled spatial contrasts in NO(2) over time. Occup. Environ. Med. 68, 765–770. https://doi.org/10.1136/oem.2010.061135.

Effects of Air Pollution on Children's Health and Development, 2005. WHO, Copenhagen, Denmark.

Elliott, P., Briggs, D., Morris, S., de Hoogh, C., Hurt, C., Jensen, T.K., Maitland, I., Richardson, S., Wakefield, J., Jarup, L., 2001. Risk of adverse birth outcomes in populations living near landfill sites. BMJ 323, 363–368.

Farhi, A., Boyko, V., Almagor, J., Benenson, I., Segre, E., Rudich, Y., Stern, E., Lerner-Geva, L., 2014. The possible association between exposure to air pollution and the risk for congenital malformations. Environ. Res. 135, 173–180. https://doi.org/10.1016/j.envres.2014.08.024.

Gilboa, S.M., Mendola, P., Olshan, A.F., Langlois, P.H., Savitz, D.A., Loomis, D., Herring, A.H., Fixler, D.E., 2005. Relation between ambient air quality and selected birth defects, seven county study, Texas, 1997-2000. Am. J. Epidemiol. 162, 238–252. https://doi.org/10.1093/aje/kwi189.

Gulliver, J., Morris, C., Lee, K., Vienneau, D., Briggs, D., Hansell, A., 2011. Land use regression modeling to estimate historic (1962-1991) concentrations of black smoke and sulfur dioxide for Great Britain. Environ. Sci. Technol. 45, 3526–3532. https://doi.org/10.1021/es103821y.

Karssenberg, D., Schmitz, O., Salamon, P., de Jong, K., Bierkens, M.F.P., 2010. A software framework for construction of process-based stochastic spatio-temporal models and data assimilation. Environ. Model. Software 25, 489–502. https://doi.org/10.1016/j.envsoft.2009.10.004.

Knol, F., 1998. From High to Low; from Low to High: the Development of Social Status of Neighbourhoods between 1971 and 1995 the Hague. Sociaal Cultureel Planbureau (in Dutch).

Liang, Z., Wu, L., Fan, L., Zhao, Q., 2014. Ambient air pollution and birth defects in Haikou city, Hainan province. BMC Pediatr. 14 (283). https://doi.org/10.1186/s12887-014-0283-6.

Linhart, Y., Bashiri, A., Maymon, E., Shoham-Vardi, I., Furman, B., Vardi, H., Mazor, M., 2000. Congenital anomalies are an independent risk factor for neonatal morbidity and perinatal mortality in preterm birth. Eur. J. Obstet. Gynecol. Reprod. Biol. 90, 43–49.

Mazzoli-Rocha, F., Fernandes, S., Einicker-Lamas, M., Zin, W.A., 2010. Roles of oxidative stress in signaling and inflammation induced by particulate matter. Cell Biol. Toxicol. 26, 481–498. https://doi.org/10.1007/s10565-010-9158-2.

Padula, A.M., Tager, I.B., Carmichael, S.L., Hammond, S.K., Yang, W., Lurmann, F.W., Shaw, G.M., 2013. Traffic-related air pollution and selected birth defects in the San Joaquin Valley of California. Birth Defects Res. A. Clin. Mol. Teratol 97, 730–735. https://doi.org/10.1002/bdra.23175.

Pedersen, M., Giorgis-Allemand, L., Bernard, C., Aguilera, I., Andersen, A.-M.N., Ballester, F., Beelen, R.M.J., Chatzi, L., Cirach, M., Danileviciute, A., Dedele, A., Eijsden, M. van, Estarlich, M., Fernández-Somoano, A., Fernández, M.F., Forastiere, F., Gehring, U., Grazuleviciene, R., Gruzieva, O., Heude, B., Hoek, G., de Hoogh, K., van den Hooven, E.H., Håberg, S.E., Jaddoe, V.W.V., Klümper, C., Korek, M., Krämer, U., Lerchundi, A., Lepeule, J., Nafstad, P., Nystad, W., Patelarou, E., Porta, D., Postma, D., Raaschou-Nielsen, O., Rudnai, P., Sunyer, J., Stephanou, E., Sørensen, M., Thiering, E., Tuffnell, D., Varró, M.J., Vrijkotte, T.G.M., Wijga, A., Wilhelm, M., Wright, J., Nieuwenhuijsen, M.J., Pershagen, G., Brunekreef, B., Kogevinas, M., Slama, R., 2013. Ambient air pollution and low birthweight: a European cohort study (ESCAPE). Lancet. Respir. Med 1, 695–704. https://doi.org/10.1016/S2213-2600(13)70192-9.

Schembari, A., Nieuwenhuijsen, M.J., Salvador, J., de Nazelle, A., Cirach, M., Dadvand, P., Beelen, R., Hoek, G., Basagaña, X., Vrijheid, M., 2014. Traffic-related air pollution and congenital anomalies in Barcelona. Environ. Health Perspect. 122, 317–323. https://doi.org/10.1289/ehp.1306802.

Somers, C.M., Yauk, C.L., White, P.A., Parfett, C.L.J., Quinn, J.S., 2002. Air pollution induces heritable DNA mutations. Proc. Natl. Acad. Sci. Unit. States Am. 99, 15904–15907. https://doi.org/10.1073/pnas.252499499.

Spinder, N., Bergman, J.E.H., Boezen, H.M., Vermeulen, R.C.H., Kromhout, H., de Walle, H.E.K., 2017. Maternal occupational exposure and oral clefts in offspring. Environ. Health 16 (83). https://doi.org/10.1186/s12940-017-0294-5.

Vrijheid, M., Martinez, D., Manzanares, S., Dadvand, P., Schembari, A., Rankin, J., Nieuwenhuijsen, M., 2011. Ambient air pollution and risk of congenital anomalies: a systematic review and meta-analysis. Environ. Health Perspect. 119, 598–606. https://doi.org/10.1289/ehp.1002946.

World Health Statistics, 2013. WHO; Geneva; Switzerland.