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The influence of industry-related air pollution on birth outcomes in an industrialized area[☆]



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ABSTRACT

Recent studies suggest that air pollution, from among others road traffic, can influence growth and development of the human foetus during pregnancy. The effects of air pollution from heavy industry on birth outcomes have been investigated scarcely.

Our aim was to investigate the associations of air pollution from heavy industry on birth outcomes.

A cross-sectional study was conducted among 4488 singleton live births (2012–2017) in the vicinity of a large industrial area in the Netherlands. Information from the birth registration was linked with a dispersion model to characterize annual individual-level exposure of pregnant mothers to air pollutants from industry in the area. Associations between particulate matter (PM₁₀), nitrogen oxides (NO_x), sulphur dioxide (SO₂), and volatile organic compounds (VOC) with low birth weight (LBW), preterm birth (PTB), and small for gestational age (SGA) were investigated by logistic regression analysis and with gestational age, birth weight, birth length, and head circumference by linear regression analysis.

Exposures to NO_x, SO₂, and VOC (per interquartile range of 1.16, 0.42, and 0.97 µg/m³ respectively) during pregnancy were associated with LBW (OR 1.20, 95%CI 1.06–1.35, OR 1.20, 95%CI 1.00–1.43, and OR 1.21, 95%CI 1.08–1.35 respectively). NO_x and VOC were also associated with PTB (OR 1.14, 95%CI 1.01–1.29 and OR 1.17, 95%CI 1.04–1.31 respectively). Associations between exposure to air pollution and birth weight, birth length, and head circumference were statistically significant. Higher exposure to PM₁₀, NO_x, SO₂ and VOC (per interquartile range of 0.41, 1.16, 0.42, and 0.97 µg/m³ respectively) was associated with reduced birth weight of 21 g to 30 g.

The 90th percentile industry-related PM₁₀ exposure corresponded with an average birth weight decrease of 74 g.

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1. Introduction

Air pollution is a complex mixture of different gaseous and particulate components and can cause several health effects, such as respiratory and cardiovascular disease. Recent evidence suggests that air pollution can also influence the growth and development of the human foetus during pregnancy, resulting in an increased risk for infant death, stillbirth, low birth weight (LBW), preterm birth (PTB), and small for gestational age (SGA). These adverse birth

outcomes may influence growth and development during childhood. For example, LBW is associated with elevated rates of respiratory problems during infancy (Boardman et al., 2001). In addition, effects of LBW on coronary heart disease and the related disorders stroke, hypertension and non-insulin-dependent diabetes during later-life have been observed (Barker, 2004). For example, PTB is associated with a reduced insulin sensitivity during childhood which is a risk factor for type 2 diabetes mellitus (Hofman et al., 2004).

A systematic review in 2018 on 28 studies estimated per 10 µg/m³ increase in particulate matter with diameters of less than 10 µm (PM₁₀) and less than 2.5 µm (PM_{2.5}) pooled odds ratios (ORs) for PTB of 1.09 (95% confidence interval (CI) 1.03–1.16) and 1.24 (95% CI 1.08–1.41), respectively (Klepac et al., 2018). Nitrogen dioxide (NO₂) did not show a significant association with PTB in this review.

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The studies in this review used different approaches for exposure assessment, namely ambient air pollution modelling, personal monitoring, air sampling, ecological biomonitoring, and various traffic indicators (e.g. inverse distance weighting), that may have influenced the results. Another systematic review in 2017 on 23 studies estimated per interquartile range (IQR) increment increase in PM_{2.5} pooled ORs for PTB and term LBW of 1.03 (95% CI 1.01–1.05) and 1.03 (95% CI 1.02–1.03), respectively (Li et al., 2017). A recent systematic review in 2019 on 40 studies estimated per 20 µg/m³ increment increase in PM₁₀ pooled ORs for PTB and LBW of 1.05 (95% CI 1.02–1.07) and 1.06 (95% CI 1.02–1.09) respectively (Guo et al., 2019). Also NO_x per 20 ppm increment increase showed a significant pooled OR for PTB of 1.02 (95% CI 1.01–1.03) and LBW of 1.03 (95% CI 1.01–1.05). Regarding sulphur dioxide (SO₂) exposure per 5 ppb increment increase, only the association for LBW was significant with a pooled OR of 1.21 (95% CI 1.08–1.35). There is emerging evidence that PM₁₀ and NO₂ may also have adverse effects on head circumference and birth length as birth outcomes (Fu et al., 2019; Huang et al., 2019; Malmqvist et al., 2017; van den Hooven et al., 2012).

The majority of studies on maternal exposure to air pollution and adverse birth outcomes have focused on single pollutants (Jedrychowski et al., 2017). However, a multiple-pollutant approach may be more relevant because people are exposed to a complex mixture of pollutants. Collinearity between air pollutants is often observed which makes it hard to disentangle the effect of each pollutant in multiple-pollutant regression model analyses. In case of severe collinearity the pollutants must be regarded as indicators of the mixture of air pollution rather than particular causative factors of adverse birth outcomes.

Studies about industry-related air pollution as a potential source for adverse birth outcomes are scarce, although the potential effect of localised air pollution from industry on health is often a major public concern. A Spanish ecological study showed an excess of PTB for mothers living within 3.5 km of galvanization industries (relative risk (RR) 1.09, 95% CI 1.00–1.18) and hazardous waste industries (RR 1.07, 95% CI 1.00–1.15), compared to mothers living in municipalities without industry. Comparable risks were also observed for LBW for the aforementioned industries and several other industries (Castelló et al., 2013). A cross-sectional study in Taiwan among pregnant women showed an association between residence in areas with higher air pollution from petrochemical industries and preterm delivery (OR_{adjusted} 1.18, 95% CI 1.04–1.34), compared to pregnant women in the control area (Yang et al., 2002). In a study of an intervention (labour strike) with elimination of industry-related air pollution, mothers who were pregnant around the time of the temporary closure of a steel mill in Utah (USA) were less likely to deliver prematurely than mothers who were pregnant well before or after the closure (RR 0.86, 95% CI 0.75–0.98). The occurrence of low birth weight among term infants was similar throughout the entire study period (Parker et al., 2008).

In most studies the contribution of industry-related air pollution cannot be easily disentangled from traffic-related air pollution due to multiple sources in the same geographic region. Therefore, the aim of this study is to investigate the influence of air pollution from large industrial sites on birth outcomes. This study targets a region in the Netherlands with the unique situation of a high concentration of industries within a region with low traffic density.

2. Methods

2.1. Study design and population

A cross-sectional study was conducted among singleton live

births during 2012–2017 in the vicinity of the large industrial area along the channel from the cities Terneuzen to Sas van Gent in the Southwest of the Netherlands (municipality Terneuzen) and in surrounding areas without heavy industries (municipalities Hulst and Sluis). At the time of the study several heavy industries were active in this area, such as a large petrochemical factory, fertilizer factories, a bromine plant, and terminals for storing and shipping of dry bulk products, among others, fertilizer. The study area borders on Belgium, where heavy industry is also present. The exposure to air pollution was calculated using a dispersion model with emission data of Dutch and Belgian industries.

Information on birth outcomes was obtained from the birth registration of the Zeeland Public Health Service in the Netherlands. Municipal Public Health Services in the Netherlands are required by law to gain insight into the health of the local population including newborns. Beside birth weight, and gestational age, the municipal Public Health Services collect also information on socio-economic status and risk factors such as smoking of mothers. Potential covariates were selected based on previous studies (Li et al., 2017; Seabrook et al., 2019; Woodruff et al., 2009).

The Law for Protection of Personal Data requires protection of personal privacy. These procedures are laid down in the Code of Conduct for Medical research (at www.federa.org), established by the Council of the Federation of Medical Scientific Societies. These procedures were strictly adhered and the data were analysed anonymously.

Two data files were used for this study: a birth outcomes file with IDs and a home address file without IDs. After calculation of the air pollution exposure at the home addresses with a dispersion model, the exposure - address file was enriched with the IDs and the addresses were deleted by a Trusted Third Party to ensure confidentiality of personal information. Thereafter we merged the enriched file and the birth outcomes file. There were further no identifiers such as postalcodes. This study has been approved by the medical ethical committee from the Erasmus MC, University Medical Centre, The Netherlands (reference MEC-2018-1275).

2.2. Exposure assessment

A variety of components were emitted by plants in the industrial area along the canal Terneuzen to Sas van Gent in the Southwest of the Netherlands and by plants in the ports of Ghent and Antwerp in Belgium, such as particulate matter (PM), nitrogen oxide (NO_x), sulphur dioxide (SO₂), and volatile organic compounds (VOC) such as benzene, ethylene, and 1,3-butadiene. Emission data of these plants were obtained from the Emission Register in the Netherlands (<http://www.emissieregistratie.nl/>) and the Flanders Environment Agency in Belgium (<https://en.vmm.be/>). The Netherlands National Institute for Public Health and the Environment (RIVM) coordinates the annual compilation of the Emission Register on behalf of the Dutch Ministry of Infrastructure and Environment. Emission factors were derived from measurements, calculations of an emission model or from (the international) literature. The emission data from the Flanders Environment Agency were supplied by the companies via integral annual environmental reports (IMJV). Emission data of Belgian plants within 15 km of the Dutch border were included in this study. The obtained emission data covers annual emission rates for the years 2011–2017.

Several air pollution components were emitted by the plants, therefore, we selected the most relevant components. The total emission (kg/year) of an air pollution compound was divided by the European Commission immission limit values for the protection of human health (www.ec.europa.eu) or, if not available, the

maximum permissible concentration (MPC) in air from the RIVM (<https://rvszoekstysteem.rivm.nl>). The following air pollution components were considered for selection: 1,2-dichloroethane, acetonitrile, acrylonitrile, benzene, butanone, chlorobenzene, cumene, dichloromethane, ethylene, ethylbenzene, ethylene oxide, ethanol, particulate matter, propylene oxide, mercury, naphthalene, nitrogen oxides, styrene, sulphur dioxide, toluene, vinyl chloride, and xylene. These components were emitted in relevant quantities and immission limit values were available. In the Netherlands for dioxins only an emission limit value is applicable, and one plant with dioxin emission had dioxins quantities far below the limit. The three air pollution compounds with the highest ratios were selected, namely: PM₁₀, SO₂, and NO_x. PM_{2.5} was not chosen because before the year 2015 the Emission Register lacked PM_{2.5} data for the study area. VOC without methane (no limit value available) was selected because non-negligible quantities of VOC were emitted, such as ethylene, and ethylene oxide.

For the PM₁₀, NO_x, SO₂ and VOC dispersion calculations of 149 (23 plants), 488 (52 plants), 219 (33 plants) and, 848 (75 plants) emission sources were used respectively as input.

The Operational Priority Substances (OPS) dispersion model (version 4.5.2.1) (Van Jaarsveld, 2004), developed by the RIVM, was used to calculate annual concentration levels at individual homes. If the pregnancy period involved two different years, the weighted average concentration of these two years was calculated. The OPS model estimates the exposure to specific compounds attributable to industry, in addition to background exposure due to other exposure sources including traffic and agriculture. The model requires emission data (emission strength, emission height, diameter source, coordinates source, heat capacity and substance) and hourly-based meteorological data (among others: temperature, relative humidity, wind speed, wind direction, precipitation and global/solar) as input for the calculations. The meteorological data were retrieved from the Royal Netherlands Meteorological Institute (KNMI). The OPS model also requires a receptor file. The geographic information system QGIS (version 2.18) was used to geocode (by means of a plugin) the home addresses of the pregnant mothers. Geocoding was conducted by using the combination of street name, house number, and place of residence as well as using the combination of postal code and house number. If both methods resulted in different outcomes, the correct x, y coordinate was found by using Google Maps. In this way 100% geocoding was obtained. The x,y coordinates of the home addresses were used for the receptor file in the OPS model. The OPS model has been validated extensively and a good agreement was found between measured and modelled exposure to SO_x and NO_x (Bijwaard and Eleveld, 2002; Van Jaarsveld, 2004; van Jaarsveld and de Leeuw, 1993).

In order to differentiate between industry and traffic sources of air pollution, the traffic-related exposure was estimated based on traffic density information (annual average). In the study area the exposure to air pollution from traffic was relatively low (less than 5000 vehicles per day or the distance between road and house is more than 100 m). Five (trunk) roads (N61, N62, N252, N258 and N290) and some city streets in the village Terneuzen have more than 5000 vehicles per day. To avoid interference of traffic exposure, newborns were excluded from the analysis if the distance between home address and these major urban roads and motorways was less than 100 m.

The study area borders at the river Westerschelde. The river Westerschelde and the channel Terneuzen – Sas van Gent are busy waterways for professional transport by ships. These (sea going) ships contribute significantly to the emission of sulphur dioxide, nitrogen oxides, fine particulate matter, vanadium, and nickel compounds into the air. A study in the Netherlands showed that the NO_x contribution from intensive sea shipping is measurable up to

approximately 250 m from the axis of the channel (Mooij and Mennen, 2007). Other compounds, such as SO₂, fine particulate matter, vanadium, and nickel, contribute less to the concentrations in the living environment. To avoid interference of ship-based exposure, newborns were excluded from the analysis if the distance between the axis of the waterway and home address was less than 250 m.

2.3. Birth outcomes, sociodemographic information and risk factors

Adverse birth outcomes and birth variables. The birth registration of the Zeeland Public Health Service (2012–2017) in the Netherlands contains information about gestational age at birth, birth weight, birth length and head circumference. LBW was defined as weight less than 2500 g at birth. PTB was defined as less than 37 weeks of gestation. SGA was defined as birth weight below the national 10th percentile for babies of the same gender and gestational age in the Dutch reference population (www.perined.nl). The gestational age was determined by last menstrual period.

The birth variables were infant gender (male, female), parity (order of birth), and month of delivery. Month of delivery was categorized in season of delivery (December–February, March–May, June–August, September–November) with June–August (summer) defined as the reference level.

Socio-demographic characteristics. Socio-demographic variables were maternal age at birth (years), ethnicity (Dutch, non western immigrant, western immigrant) and highest maternal educational level mother. The highest educational level of the mother was categorized in: 1) primary school or less (8 years of education or less), 2) lower general secondary education (12 years of education), 3) higher general secondary education (14 years of education) and 4) college or university (more than 14 years of education).

Health behaviour. Health behaviours of interest were alcohol use during pregnancy (yes, no) and smoking during pregnancy (yes, no).

2.4. Statistical analyses

Pearson correlation coefficients were used to determine pairwise associations between the four air pollutants components. Associations between air pollution exposure and LBW, PTB and SGA were analysed with multivariate logistic regression analyses. For birth weight, birth length and head circumference linear regression analysis was used. The validity of the regression models was checked by graphical residual analysis of normality. Collinearity between variables was tested with the variance inflation factor (VIF). Since a considerable proportion (40%) of the study population had one or more incomplete covariates (see Table 1), missingness at random was investigated to justify the use of imputation. Analyses showed some modest associations between exposure and missing values for the covariates ethnicity, age, and parity. This could introduce bias, depending on whether the covariates were important confounders. Since ethnic minorities (of older age, and with higher parity) more often resided in exposed areas, we investigated the associations between exposure and missing values for ethnicity, adjusted for age and parity. With mutual adjustment for these covariates no significant associations were found between missingness in covariates with exposure, justifying the assumption of missingness at random.

Comparison of regression analyses of exposure on outcome in the total study population without adjustment for covariates and regression analyses with complete cases only and full adjustment for all covariates showed very similar estimates. Hence, missing values did not bias exposure-response associations and imputation

Table 1
Statistical summary of birth outcomes, social-demographic characteristics and behaviour factors of the mother (n = 4488).

Characteristic		Missing
Gender child		
Male, n (%)	2258 (50.3)	
Female, n (%)	2230 (49.7)	
Birth outcomes		
Low weight (<2500 g), n (%)	233 (5.2)	
Preterm birth (<37 weeks of gestation), n (%)	240 (5.3)	
Small for gestational age, n (%)	528 (11.8)	19
Gestational age (days), mean (SD)	276 (11.3)	
Weight (g), mean (SD)	3383 (526.7)	
Length (cm), mean (SD)	50.0 (2.4)	510
Head circumference (cm), mean (SD)	34.4 (1.5)	927
Parity, % (n)		608
Primiparous	1834 (47.3)	
Multiparous	2046 (52.7)	
Mother's age at delivery (years), n (%)		966
< 20	91 (2.6)	
20–24	449 (12.7)	
25–34	2475 (70.3)	
35–39	417 (11.8)	
>39	90 (2.6)	
Mother's ethnicity, n (%)^a		965
Native Dutch	2853 (81.0)	
Immigrant western	439 (12.5)	
Immigrant non western	231 (6.6)	
Highest education mother, n (%)^a		1277
Lower general secondary education or less	538 (16.8)	
Higher general secondary education	1528 (47.6)	
College, university	1145 (35.7)	
Smoking use mother during pregnancy, n (%)		410
No	3512 (86.1)	
Yes	566 (13.9)	
Alcohol use mother during pregnancy, n (%)		456
No	3951 (98.0)	
Yes	81 (2.0)	

^a Percentages do not add up to 100% due to rounding error.

was justified. Multiple imputation (n = 5) was performed for the characteristic of the mother, based on the correlation between the variable with missing values and other mother characteristics, air pollution exposure and birth outcomes (Graham, 2009; Sterne et al., 2009). The missing value patterns did not display systematic bias with either exposure or outcome measures and therefore, the data were imputed according to the Markov Chain Monte Carlo method. Detailed information on the population characteristics of the mothers based on the original data set and imputed data set is presented in Supplementary Material, Table S1. Analyses were performed using both the original data set without covariates and the imputed data sets with covariates.

The statistical analyses were conducted with the statistical package IBM SPSS version 24 (SPSS Inc., Chicago, IL, USA). Results will be presented with 95% confidence intervals.

3. Results

From January 1, 2012 to December 31, 2017 in the study region 4866 live births were registered. Non-singleton pregnancies (n = 107) and newborns with a home address close to major urban roads/motorways and waterways (n = 281) were excluded, leaving 4488 live births in the current study.

Table 1 shows the descriptive statistics of birth outcomes, socio-demographic characteristics, and health behaviours of the mothers. Birth length and head circumference were less routinely measured at birth. The same applies to mother's age at delivery, mother's ethnicity, and mother's education.

Table 2 shows that most of the mothers in the study population

Table 2
Exposure to industry-related air pollution (2012–2017).

Component	Median	Interquartile range	Minimum – Maximum
PM ₁₀ (µg/m ³)	0.38	0.41	0.5–3.80
NO _x (µg/m ³)	2.53	1.16	0.49–9.50
SO ₂ (µg/m ³)	0.78	0.42	0.21–2.33
VOC (µg/m ³)	1.95	0.97	0.34–9.04

had a modestly increased exposure to PM₁₀, NO_x, VOC, and SO₂ from industrial emissions compared to the background concentration from all other sources. The geographical exposure pattern is depicted in Fig. 1 for NO_x and for other compounds in supplementary file (Supplementary Figs. S1–S3).

The air pollution compounds were (highly) correlated (Pearson correlation coefficients ranged from 0.46 to 0.85, see Fig. 2). The birth outcomes were also highly correlated. The highest correlations were observed for birth weight with birth length and birth weight with head circumference (Pearson correlation coefficient of 0.79 and 0.71, respectively). The lowest correlation was found for gestational age with head circumference and gestational age with birth length (Pearson correlation coefficient of 0.45 and 0.57, respectively).

Tables 3 and 4 show statistical analyses with the total study population without adjustment for covariates and with imputed complete cases with adjustment for all covariates. The results with and without adjustment for covariates showed very similar estimates.

Adjusted logistic regression analyses in Table 3 showed that exposures to NO_x, SO₂, and VOC (per interquartile range of 1.16, 0.42, and 0.97 µg/m³ respectively) were significantly associated with LBW (OR 1.20, 95%CI 1.06–1.35, OR 1.20, 95%CI 1.00–1.43, and OR 1.21, 95%CI 1.08–1.35 respectively). If LBW was adjusted for gestational age the associations became insignificant. Exposures to NO_x and VOC were also associated with PTB (OR 1.14, 95%CI 1.01–1.29 and OR 1.17, 95%CI 1.04–1.31 respectively). Various other associations, although not significant, had similar ORs.

All four components of air pollution higher exposure was consistently associated with lower gestational age and smaller newborns (see Table 4). Linear regression analyses with adjustment for covariates showed that higher exposure during pregnancy to NO_x, SO₂ and VOC (per interquartile range of 1.16, 0.42, and 0.97 µg/m³ respectively) was significantly associated with a 0.34, 0.67, and 0.37 days lower gestational age, respectively. Higher exposure to the four components was associated with a reduced birth weight of 21.16 g to 29.93 g, and a reduced birth length varying from 0.1 cm to 0.2 cm. If birth weight was adjusted for gestational age, the association for SO₂ and VOC became insignificant. Higher exposure to PM₁₀, NO_x on SO₂ (per interquartile range of 0.41, 1.16, and 0.42 µg/m³ respectively) was also associated with a smaller head circumference of 0.07 cm to 0.12 cm.

The sensitivity analysis with two-pollutant regression analyses showed that reported associations compared to single pollutant models were reduced. In all two-pollutant models exposure to SO₂ remained statistically significantly associated with gestational age and head circumference of newborns (Supplementary Table S2). A three-pollutant model showed similar results for SO₂ (data not shown).

4. Discussion

This study showed that higher exposure to NO_x, SO₂ and VOC from industrial sources (per interquartile range of 1.16, 0.42, and 0.97 µg/m³ respectively) was significantly associated with LBW (OR 1.20, 1.20 and 1.21 respectively). NO_x and VOC were also associated

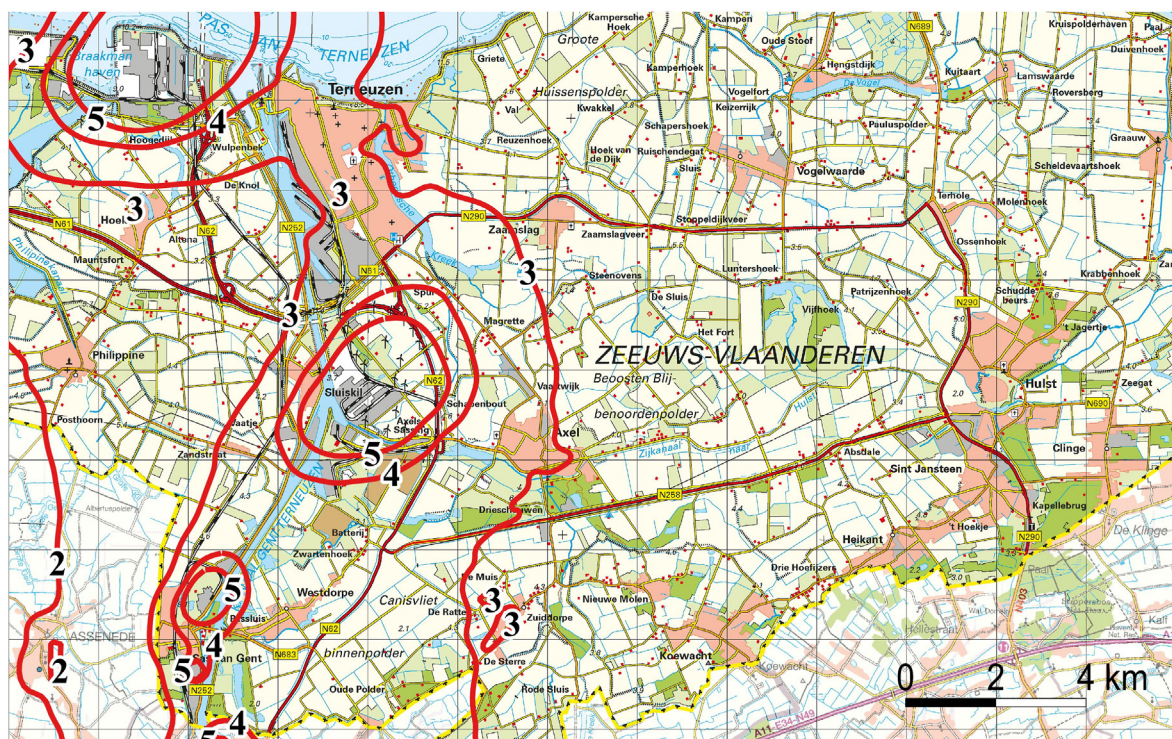


Fig. 1. Modelled NO_x iso-concentration contours (per µg/m³), depicted with red lines. Numbers presents the mean annual industry-related exposure without background concentration (2012–2017). Map reprinted from Kadaster in the Netherlands (<https://nationaalgeoregister.nl/>) under a CC-BY-4.0 license, 2019. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

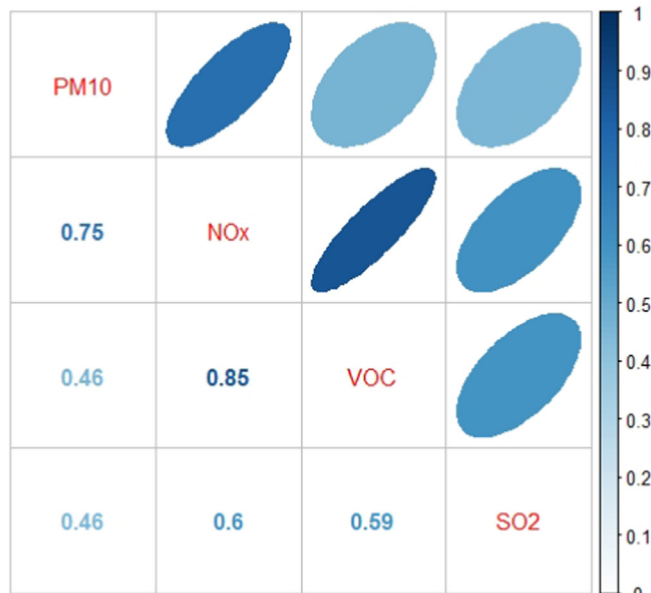


Fig. 2. Correlation (Pearson) matrix for air pollution components (n = 4488).

with PTB (OR 1.14 and 1.17 respectively). Higher exposure during pregnancy to PM₁₀, NO_x, SO₂ and VOC (per interquartile range of 0.41, 1.16, 0.42, and 0.97 µg/m³ respectively) was significantly associated with reduced birth weight (varying from 21 g to 30 g) and a reduced birth length (0.1 cm to 0.2 cm). Higher exposure during pregnancy to NO_x, SO₂ and VOC (per interquartile range) was significantly associated with lower gestational age (varying from 0.3 to 0.7 days). Higher exposure to PM₁₀, NO_x, and SO₂ (per

interquartile range) was significantly associated with a smaller head circumference (0.07 cm to 0.12 cm).

The air pollution components were highly correlated and therefore it is possible that the effect of the analysed pollutant is the effect of another pollutant(s). Therefore, the pollutants should be considered more as indicators of the air pollution mixture and not as specific causal factors for adverse birth outcomes. The multi-pollutant model analyses suggest that SO₂ is the most important component. In a Canadian cohort study SO₂ was also the best predictor of both PTB and LBW (Seabrook et al., 2019).

Comparable studies about the influence of industry-related air pollution on birth outcomes are rare. To the best of our knowledge there are no other studies that describe association of modelled individual air pollution exposure from industry and birth outcomes. Other studies have compared populations living in industrial areas with a control population. An individual patient data meta-analysis on 14 population-based mother-child cohort studies in 12 European countries (Pedersen et al., 2013) and a child birth cohort study in the Netherlands (van den Hooven et al., 2012) reported effects of air pollution exposure from traffic and other sources on birth outcomes, albeit at substantially higher exposure levels than in the current study. A possible explanation for the higher exposure-response relationship in our study is our sole focus on industry-related exposure, excluding exposure due to high traffic and busy waterways. The composition of industrial PM₁₀ and VOC exposure in our study population may differ from traffic-related exposure in other studies.

For comparison purposes, the effects of active smoking during pregnancy (yes/no) on the continuous birth outcomes were estimated and compared with the effect of air pollution. Maternal smoking was associated with a birth weight change of -266 g (95% CI -316 – -217) (adjusted for confounders). The 90th percentile PM₁₀ exposure in the study area corresponded with an added

Table 3
Associations between exposure to industry-related air pollution (per interquartile range) and discrete birth outcomes in logistic regression analyses.

Air pollution exposure	Preterm birth	Low birth weight	Low birth weight ^b	Small for gestational age
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
	(n = 4488)	(n = 4488)	(n = 4488)	(n = 4469)
Unadjusted regression models				
PM ₁₀ (per 0.41 µg/m ³)	1.10 (0.97–1.24)	1.12 (1.00–1.27)	1.10 (0.95–1.27)	1.06 (0.97–1.16)
NO _x (per 1.16 µg/m ³)	1.12 (0.99–1.26)	1.20 (1.07–1.35)	1.17 (1.02–1.35)	1.01 (0.93–1.11)
SO ₂ (per 0.42 µg/m ³)	1.16 (0.98–1.38)	1.19 (1.00–1.41)	1.08 (0.88–1.34)	0.97 (0.86–1.09)
VOC (per 0.97 µg/m ³)	1.16 (1.04–1.30)	1.23 (1.10–1.37)	1.17 (1.02–1.34)	1.02 (0.93–1.11)
Adjusted regression models^a				
PM ₁₀ (per 0.41 µg/m ³)	1.11 (0.98–1.26)	1.11 (0.98–1.25)	1.10 (0.94–1.29)	1.04 (0.95–1.14)
NO _x (per 1.16 µg/m ³)	1.14 (1.01–1.29)	1.20 (1.06–1.35)	1.17 (1.00–1.37)	1.00 (0.92–1.10)
SO ₂ (per 0.42 µg/m ³)	1.19 (1.00–1.41)	1.20 (1.00–1.43)	1.07 (0.85–1.33)	0.97 (0.86–1.10)
VOC (per 0.97 µg/m ³)	1.17 (1.04–1.31)	1.21 (1.08–1.35)	1.15 (1.00–1.33)	0.99 (0.91–1.09)

Bold text indicates OR is statistically significant (p < 0.05).

^a Adjusted for infant's gender, parity, birth season, maternal age, maternal education level, maternal ethnicity, smoking use mother during pregnancy and alcohol use mother during pregnancy.

^b Adjusted also for gestational age.

Table 4
Associations between exposure to industry-related pollution (per interquartile range) and continues birth outcomes in linear regression analysis.

Air pollution exposure	Gestational age (days)	Birth weight (g)	Birth weight ^b (g)	Birth length (cm)	Head circum. (cm)
	B (95% CI)	B (95% CI)	B (95% CI)	B (95% CI)	B (95% CI)
	(n = 4488)	(n = 4488)	(n = 4488)	(n = 3978)	(n = 3561)
Unadjusted regression models					
PM ₁₀ (per 0.41 µg/m ³)	-0.29 (-0.63–0.05)	-26.96 (-42.73–-11.19)	-19.03 (-31.79–-6.28)	-0.15 (-0.23–-0.08)	-0.10 (-0.15–-0.05)
NO _x (per 1.16 µg/m ³)	-0.37 (-0.69–-0.05)	-24.02 (-39.14–-8.91)	-13.87 (-26.10–-1.64)	-0.16 (-0.23–-0.09)	-0.07 (-0.12–-0.02)
SO ₂ (per 0.42 µg/m ³)	-0.66 (-1.10–-0.23)	-27.34 (-47.74–-6.94)	-9.15 (-25.67–7.37)	-0.15 (-0.25–-0.05)	-0.12 (-0.18–-0.05)
VOC (per 0.97 µg/m ³)	-0.41 (-0.73–-0.08)	-25.38 (-40.66–-10.09)	-14.24 (-26.61–-1.87)	-0.15 (-0.22–-0.07)	-0.07 (-0.12–-0.01)
Adjusted regression models^a					
PM ₁₀ (per 0.41 µg/m ³)	-0.22 (-0.56–0.13)	-21.74 (-37.21–-6.26)	-15.85 (-28.26–-3.45)	-0.12 (-0.19–-0.04)	-0.09 (-0.14–-0.04)
NO _x (per 1.16 µg/m ³)	-0.34 (-0.67–-0.01)	-21.53 (-36.27–-6.79)	-12.51 (-24.36–-0.66)	-0.13 (-0.20–-0.06)	-0.07 (-0.12–-0.02)
SO ₂ (per 0.42 µg/m ³)	-0.67 (-1.11–-0.23)	-29.93 (-49.65–-10.20)	-11.85 (-27.70–4.01)	-0.15 (-0.25–-0.06)	-0.12 (-0.18–-0.05)
VOC (per 0.97 µg/m ³)	-0.37 (-0.70–-0.04)	-21.16 (-35.92–-6.40)	-11.13 (-22.95–0.69)	-0.12 (-0.19–-0.05)	-0.05 (-0.10–0.00)

Bold text indicates regression coefficient is statistically significant (p < 0.05).

^a Adjusted for infant's gender, parity, birth season, maternal age, maternal education level, maternal ethnicity, smoking use mother during pregnancy and alcohol use mother during pregnancy.

^b Adjusted also for gestational age.

concentration of ≥0.90 µg/m³, which indicates an average birth weight decrease of 74 g at the 90th percentile of the modelled PM₁₀ distribution. This is more than a quarter of the effect of smoking.

This study has certain strengths and limitations. First, a strength of the study is the use of birth outcomes as objective register-based measure with linkage to exposure estimates from a dispersion model. This prevents reporting bias in presented associations. A second strength is that exposure to air pollution was based on a dispersion model. A validation study showed a good agreement for both SO_x and NO_x between measured and modelled concentrations with the OPS dispersion model (Van Jaarsveld, 2004). A dispersion model takes factors, such as stack height, exact distance between stack and the home address of the mothers, weather and climate, into account. Third, also emissions from foreign industries were included in this study. Fourth, extensive emission data was used for the dispersion calculations (see Methods section). Although available information only allowed estimation of annual mean concentrations, this is probably a fair reflection of industry-based air pollution from heavy industries with continuous production.

A limitation is the fact that outdoor air pollution estimated at the home address was used as an exposure estimate without considering, for example, exposure at the workplace and during travel. Second, some studies suggests that birth outcomes may be particularly sensitive to various components (e.g. organic compounds, nitrate, elemental carbon, trace metals) from different

sources of PM pollution (Bell et al., 2010; Laurent et al., 2014). The industry in the study area with its different processes emit PM₁₀ with different compositions. This may influence the results with regard to PM₁₀. Third, the study was not powered sufficiently to conduct a full mixture analysis above the two-pollutant models in the sensitivity analysis. Fourth, because of a substantial proportion of subjects with missing values for covariates (around 1500) the data was imputed. In general, covariates in regression analyses provide better estimators, but can also provide a bias if a covariate is correlated with exposure (for example, if education is correlated with exposure). Analyses with and without covariates showed that the covariates had only a small influence on the results.

5. Conclusion

Exposure to air pollution from industry was related with adverse birth outcomes. The 90th percentile PM₁₀ exposure from the industry in the study area corresponded with an average birth weight decrease of 74 g.

Author contributions

Arnold Bergstra: Conceptualization, Methodology, Software, Formal analysis, Investigation, Writing- Original draft, Visualization. Bert Brunekreef: Writing- Reviewing and Editing. Alex

Burdorf: Conceptualization, Methodology, Investigation, Writing-Reviewing and Editing, Supervision.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envpol.2020.115741>.

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