Neonatal blood pressure in association with prenatal air pollution exposure, traffic, and land use indicators: An ENVIR*ON*AGE birth cohort study

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ABSTRACT

Elevated blood pressure (BP) in early life may lead to cardiovascular morbidity and mortality in later life. Air pollution exposure has been associated with increased BP in adults and children, but the contribution of prenatal air pollution exposure has rarely been assessed. In addition, we are not aware of any study on neonatal BP and maternal residential traffic and land use indicators during pregnancy. We investigated the association between newborn BP and prenatal air pollution, traffic and land use indicators, using data from 427 term (gestational age > 36 weeks) births from the ENVIR*ON*AGE birth cohort. Newborn BP was measured using an automated device within 4 days after birth. Daily maternal residential air pollutants during pregnancy, including particulate matter with an aerodynamic diameter $\leq 2.5\,\mu m$ ($PM_{2.5}$) and $\leq 10\,\mu m$ (PM_{10}), black carbon (BC), and nitrogen dioxide (NO_2), were modelled using a high-resolution spatial-temporal model. The association between newborn BP and air pollution during the last 15 weeks of pregnancy was assessed using distributed lag models. Each $5\,\mu g/m^3$ increment in prenatal $PM_{2.5}$ exposure was associated with a 2.4 mm Hg (95% CI, 0.5 to 4.2) higher systolic and a 1.8 mm Hg (95% CI, 0.2 to 3.5) higher diastolic BP at birth. Overall estimates for PM_{10} were similar but those for NO_2 and BC did not reach significance. Associations between newborn BP and exposures during the last 4 to 5 weeks of pregnancy were significant for all pollutants. An IQR (20.3%) increment in percentage residential greenness in a 5 km radius was associated with a 1.2 mm Hg (95% CI, −2.5 to 0.1; $p = 0.07$) lower systolic and a 1.2 mm Hg (95% CI, −2.4 to −0.0; $p = 0.05$) lower diastolic BP. An IQR (4.1%) increment in percentage industrial area in a 5 km radius was associated with a 1.0 mm Hg (95% CI, 0.1 to 1.9; $p = 0.03$) higher diastolic BP. Residential traffic indicators did not significantly associate with newborn BP. Prenatal air pollution exposure, greenness, and industrial area at maternal residence may affect offspring BP from birth onwards.

1. Introduction

Blood pressure (BP) substantially rises with ageing across the life span. BP tracks from childhood to adolescence and adulthood, and high BP is associated with cardiovascular disease in later life (Hao et al., 2017; Lim et al., 2012). Air pollution has frequently been associated with increased risk of cardiovascular morbidity and mortality (Bourdrel et al., 2017; Claeys et al., 2017). Both recent and long-term exposure to air pollution is associated with BP in adults (Giorgini et al., 2016) and children (Bilenko et al., 2015; Dong et al., 2014; Pieters et al., 2015;

Sughis et al., 2012; Zeng et al., 2017). Biological explanations by which recent and long-term exposure to air pollution is linked to BP include autonomic imbalance, pro-oxidative and systemic inflammatory responses, and changes in hemodynamically active mediators (Giorgini et al., 2016) and microvasculature (Provost et al., 2017). Also residential traffic and land use indicators have been linked with changes in BP (Agyemang et al., 2007; Fuks et al., 2014; Grazuleviciene et al., 2014; Markevych et al., 2014). In a large-scale meta-analysis, traffic load on major roads within 100 m of the residence was associated with increased systolic BP (SBP) and diastolic BP (DBP) (Fuks et al., 2014).

Residential proximity to green spaces has been associated with lower BP in both children and adults (Agyemang et al., 2007; Grazuleviciene et al., 2014; Markevych et al., 2014).

Nano-sized particles from ambient air pollution enter the circulation (Saenen et al., 2017) and are able to cross the placenta (Veras et al., 2008; Bové et al., 2019). Because *in utero* life represents a critical time window in the early programming of possible diseases later in life (Barker, 1995), unravelling the connection between prenatal air pollution exposure and neonatal BP may provide new insights in the etiology of diseases linked with early-life air pollution exposure. To the best of our knowledge, only one study (van Rossem et al., 2015) reports on the link between prenatal air pollution and neonatal BP, and no studies have investigated newborn BP in association with maternal residential traffic and land use indicators.

In this study, we assessed the associations between newborn BP and air pollution concentrations, traffic exposure, and land use indicators at maternal residence during pregnancy. Distributed lag models (DLMs) were used for analyses with air pollutants, facilitating the identification of vulnerable pregnancy windows.

2. Methods

2.1. Study design

Study participants were selected from the ongoing ENVIR*ON*AGE (ENVIRonmental influence *ON* early AGEing) birth cohort study. The ENVIR*ON*AGE birth cohort has been described in detail previously (Janssen et al., 2017). In brief, ENVIR*ON*AGE is a population-based prospective birth cohort study located in Limburg, Belgium. Mother-infant pairs are recruited from the East-Limburg Hospital in Genk for an epidemiological follow-up from birth till young adulthood, aiming to unravel adverse environmental interactions with human health. The study protocol of the ENVIR*ON*AGE birth cohort was approved by the ethics committees of Hasselt University and East-Limburg Hospital.

Participating mothers provided written informed consent when they arrived at the hospital for delivery and completed study questionnaires to provide detailed information on variables such as maternal education, smoking status, place of residence, physical activity and newborn's ethnicity. Maternal education was coded "low" (no diploma or primary school), "middle" (high school) or "high" (college or university degree). Former smokers were defined as those who had quit smoking before pregnancy and current smokers as having smoked before and during pregnancy. Classification of ethnicity is based on the native country of the neonates' grandparents as either European (at least two grandparents were European) or non-European (at least three grandparents were of non-European origin). Other maternal and perinatal parameters were collected from medical records such as maternal age, parity, pre-pregnancy body mass index (BMI), newborn's sex, birth date, time of delivery, birth weight and length, gestational age, ultrasonographic data, method of delivery, and pregnancy complications. Parity was categorized into 1, 2, and ≥ 3 children. Pre-pregnancy BMI was measured at the first prenatal visit. Gestational age was calculated on the basis of the first day of the mother's last menstrual period combined with the first ultrasonographic examination. All newborns were healthy and free of anomalies as confirmed by paediatricians through both prenatal ultrasound examination and postnatal assessment immediately after birth.

2.2. Study population

A total of 762 mother-newborn pairs were recruited between 19 January 2014 and 19 December 2016. During the hospital stay BP was measured by one and the same person between 48 and 96 h after delivery. BP measurements were missing for 229 newborns because the person taking the measurements was not present due to holidays or weekends (n = 164), the mother left the hospital prior to the expected

date (n = 42), the newborn was under observation or transferred to the neonatal intensive care unit because of prematurity or other reasons (n = 22), or the measurement could not be performed due to restlessness of the newborn (n = 1). Other reasons for exclusion from the study were: incomplete BP measurement (n = 78), missing maternal BP (n = 5), missing covariate information (n = 9), gestational age < 37 weeks (n = 12), and missing exposure information (n = 2). In total, the data of 427 mother-newborn pairs remained for the study analysis.

2.3. BP measurement

Newborn's BP was measured with an advanced oscillometric measurement device (Vital Signs Monitor 6000 Series, Welch Allyn Inc., Skaneateles Falls, NY). To ensure accurate measurements, appropriate cuffs were used according to the limb circumference of the newborn (Stebor, 2005). BP was measured in the morning (between 09.00 a.m. and 11.00 a.m.) according to a standardized protocol: BP was taken in between feedings while the newborn was lying in a supine rest position. Newborn BP was taken five times consecutively on the right upper arm with a 2-min interval according to the guidelines of the European Society of Hypertension (Parati et al., 2008). The condition of the newborn during BP measurements was recorded into five categories: deep sleep, light sleep, quiet awake, active awake or crying.

Maternal BP was measured using an automated oscillometric measurement device (Omron 705IT, Omron Corporation, Kyoto, Japan). The measurement was taken on the right upper arm in a sitting position after resting for 5 min. Five consecutive measurements were taken 1 min apart. For newborn as well as maternal BP, the average of the last three measurements was used for the current analysis.

2.4. Air pollution exposure

Daily air pollutant concentrations at the mother's home address were obtained from the Belgian Interregional Environment Agency. A spatial-temporal interpolation method was used to construct residential-based estimates of ambient exposure to air pollutants including particulate matter (PM) with an aerodynamic diameter $\leq 2.5\,\mu m$ ($PM_{2.5}$) and $\leq 10\,\mu m$ (PM_{10}), black carbon (BC), and nitrogen dioxide (NO_2) (Janssen et al., 2008). This interpolation method uses land-cover data obtained from satellite images (CORINE land-cover data set) and pollution data of fixed monitoring stations. Coupled with a dispersion model (Lefebvre et al., 2013) that uses emissions from point sources and line sources, this model chain provides daily exposure values in a high-resolution receptor grid. Overall model performance was evaluated by leave-one-out cross-validation including 34 monitoring points for $PM_{2.5}$, 58 for PM_{10}, 14 for BC, and 67 for NO_2. Validation statistics of the interpolation tool gave a spatiotemporal explained variance of > 0.80 for $PM_{2.5}$ and PM_{10} (Maiheu et al., 2012), 0.74 for BC (Lefebvre et al., 2011), and 0.78 for NO_2 (Maiheu et al., 2012).

Average trimester exposures during pregnancy were calculated (forward) starting from the day of conception, whereas average weekly exposures were calculated (backward) starting from the day of birth (week 1 including day of birth and 6 days before, week 2 including the 7th to the 13th day before birth, and so on). Address changes during pregnancy were taken into account in the calculation of trimester and weekly averages. Daily mean ambient temperatures measured at the station of Diepenbeek were provided by the Royal Meteorological Institute (Ukkel, Belgium) and were used to calculate trimester and weekly mean temperatures during pregnancy.

2.5. Traffic and land use indicators

Residential addresses of the mothers at birth were geocoded. Distances to the nearest major road with available traffic counts and traffic density were determined using the geographic information

system (GIS) (ArcGIS 9.3). Traffic density in a 200 m buffer around the mother's residence was equal to the length of each road in the buffer multiplied by the traffic count on each specific road. Traffic densities within the buffer were multiplied by a weight decreasing with distance following a Gaussian curve. Finally the sum was made for the distance-weighted traffic densities in all buffers within 200 m of the residence. More details on the calculation of traffic indicators can be found elsewhere (Bijnens et al., 2017).

Residential landscape was assessed by land use data (CORINE land-cover 2000; European Environment Agency, Copenhagen, Denmark) including greenness (semi-natural, forested, and agricultural areas) and industrial areas within a 5 km radius from the residential address.

A GIS-based noise model including the Flemish street and railway networks was used to estimate residential traffic noise during pregnancy in 5 dB(A)-intervals, as described by Bijnens et al. (2017). Weighted equivalent noise levels in dB(A) for traffic over day-time (based on the weighted yearly average noise level between 7 a.m. to 7 p.m., and 7 p.m. to 11 p.m.) and at night (yearly average noise level between 11 p.m. and 7 a.m.) were modelled. Exposure to traffic noise was categorized as ≤ 55 dB, > 55 to ≤ 60 dB, and > 60 dB.

2.6. Statistical analysis

All analyses were performed with the statistical software R, version 3.3.2 (R Project for Statistical Computing). The final study population was compared with excluded mother-newborns pairs using a Student's *t*-test for continuous variables and a Pearson's chi-squared test for categorical variables.

Associations between newborn BP and prenatal air pollution exposure were explored by entering average trimester-specific exposures in a linear regression model (three trimesters in the same model, separate models for different pollutants). Models were adjusted for the following *a priori* selected covariates: a linear term for time, seasonality (a seasonal sine and cosine with a 365-day cycle), birth weight, newborn's sex, newborn's ethnicity, gestational age, newborn's age, newborn's condition at the BP measurement, maternal age, maternal pre-pregnancy BMI, maternal education, maternal smoking status, parity, and maternal BP (systolic or diastolic corresponding to the modelled outcome). Regression coefficients were expressed as partial Pearson correlations (with *p*-values), using the ppcor package in R (Kim, 2015).

Because significant associations were only observed for third trimester exposures, we performed a more detailed investigation of weekly average exposures during the last 15 weeks of pregnancy by using distributed lag (non-linear) models (DL(N)Ms). A DL(N)M is defined through a "cross-basis" function, which allows the simultaneous estimation of a (non-linear) exposure-response association and non-linear effects across lags, the latter termed lag-response association (Gasparrini et al., 2010). In the main analysis, we assumed a linear exposure-response function, and the lag structure was modelled using a natural cubic spline with 3 degrees of freedom (df), setting the knots at equally spaced values in the original lag scale (1 to 15 weeks). Final effect size estimates (with 95% CI) represent the overall cumulative (lag1-15) change in BP for a 5 $\mu g/m^3$ increment in $PM_{2.5}$, PM_{10}, and NO_2, and for a 0.5 $\mu g/m^3$ increment in BC during the last 15 weeks of pregnancy. DL(N)Ms were ran using the dlnm package in R (Gasparrini, 2011).

The same models (except for the DLM cross-basis) were used to assess associations between newborn BP and traffic and land use indicators. Distance to major roads and distance-weighted traffic density variables were log-transformed and effect size estimates (with 95% CI) were calculated for a doubling in the traffic indicator. Land use indicator estimates are presented for an interquartile range (IQR) increase in percentage area.

Potential nonlinearity in the associations between newborn BP and exposure to air pollutants was explored by using natural cubic spline DLNMs with 3 df to model the exposure-response functions (using the default placement of knots at equally-spaced quantiles). In another secondary analysis, we ran two-pollutant models by entering exposure pairs (including pollutants as well as land use indicators) in the same model. For air pollutants, trimester averages (instead of DLM cross-bases) were used in two-pollutant models. We also assessed adjustment for day- and night-time noise exposure in two-pollutant models. Finally, we assessed effect modification by ethnicity, maternal education, maternal smoking, pregnancy complications, method of delivery, and condition of the baby at BP measurement. Stratified analyses were only performed for subgroups with at least 100 individuals.

In sensitivity analyses for DLM models, we defined the lag structure using an unconstrained DLM, a model in which the weekly mean exposures (n = 15) are entered as separate variables (Schwartz, 2000; Zanobetti et al., 2000). Because of the correlation between air pollution concentrations for contiguous weeks, the unconstrained DLM may result in unstable estimates for the individual lags, but this model is more flexible and less prone to bias for the estimate of the overall effect (Schwartz, 2000). Secondly, we tested whether results were robust to the inclusion of a cross-basis for weekly mean temperature during the last 15 weeks of pregnancy, using a natural cubic spline with 5 df for the temperature-BP function (with knots at equally spaced values of the actual temperature range) and a natural cubic spline with 3 df for the lag structure (with knots at equally spaced values in the original lag scale). We also adjusted our model for month of measurement instead of the sine and cosine term. Finally, we accounted for total pregnancy exposure in a DLM including weekly average air pollution concentrations up to 36 weeks before birth, using 5 df for the lag structure.

3. Results

3.1. Descriptives

Characteristics of the final study population (n = 427) and excluded mother-newborn pairs (n = 335) were similar (Table S1), except for the higher gestational age (39.4 ± 1.1 *versus* 38.6 ± 2.4 weeks, *p* < 0.0001) and birth weight (3426 ± 459 *versus* 3287 ± 617 g, *p* = 0.0004) in the final study population (due to missing BP measurements for newborns transferred to the neonatal intensive care and exclusion of remaining preterm births).

Mean ± SD gestational age was 39.3 ± 1.0 weeks and mean birth weight was 3426 ± 459 g (Table 1). Most (85.2%) of the newborns were of European origin. Mean ± SD newborn SBP and DBP were 67.5 ± 9.1 and 40.4 ± 8.2 mm Hg respectively. Newborn's condition at BP measurement was recorded as deep sleep (73.1%), light sleep (16.9%), quiet awake (7.3%), active awake (2.6%) or crying (0.2%). Mean ± SD maternal age was 29.6 ± 4.6 years, and mean ± SD maternal pre-pregnancy BMI was 24.7 ± 4.5 kg/m². Half (50.4%) of the mothers were primiparous. Mean ± SD maternal SBP and DBP were 118.6 ± 11.2 and 73.6 ± 9.4 mm Hg respectively. Of the participating mothers, 9.8% smoked during pregnancy and 25.8% stopped smoking before pregnancy. Most of the mothers had a medium (37.7%) or high education (50.4%).

The median (5th–95th percentiles) weekly exposures during the last 15 weeks of pregnancy were 8.8 μg/m³ (4.0–25.9) for $PM_{2.5}$, 14.6 μg/m³ (7.8–31.2) for PM_{10}, 0.8 μg/m³ (0.3–2.0) for BC, and 14.7 μg/m³ (7.0–25.5) for NO_2. The median (5th–95th percentiles) residential proximity to major roads was 323 m (27–1803), the median residential greenness within 5 km buffer was 67% (41–82) and the median industrial area was 4.1% (0.9–12.3) (Table 2). Median (5th–95th percentiles) weekly temperature was 11.7 °C (2.7–20.1). Spearman correlation coefficients (r) between air pollution concentrations (trimester 3 averages), temperature (trimester 3 average), traffic, and land use indicators are presented in Table S2. For air pollutants, correlations were highest between $PM_{2.5}$ and PM_{10} (r = 0.89) and between BC and NO_2 (r = 0.84). Correlations with temperature were strongest for $PM_{2.5}$ (r = −0.75) and weakest for PM_{10} (r = −0.50). Distance to major

Table 1

Characteristics of mother-newborn pairs (n = 427).

Characteristic		Mean ± SD or n (%)
Newborns		
Systolic blood pressure, mm Hg		67.5 ± 9.1
Diastolic blood pressure, mm Hg		40.4 ± 8.2
Birth weight, g		3426 ± 459
Sex	Boys	230 (53.9)
Ethnicity	European-Caucasian	364 (85.2)
Gestational age, weeks	37	22 (5.1)
	38	67 (15.7)
	39	108 (25.3)
	40	158 (37.0)
	41	72 (16.9)
Age at BP measurement, days	1	35 (8.2)
	2	232 (54.3)
	3	143 (33.5)
	4	17 (4.0)
Condition at BP measurement	Deep sleep	312 (73.1)
	Light sleep	72 (16.9)
	Quiet awake	31 (7.2)
	Active awake	11 (2.6)
	Crying	1 (0.2)
Mothers		
Systolic blood pressure, mm Hg		118.6 ± 11.2
Diastolic blood pressure, mm Hg		73.6 ± 9.4
Age, years		29.6 ± 4.6
Pre-pregnancy BMI, kg/m^2		24.7 ± 4.5
Education[a]	Low	51 (11.9)
	Middle	161 (37.7)
	High	215 (50.4)
Smoking status[b]	Never	275 (64.4)
	Former	110 (25.8)
	Current	42 (9.8)
Parity	1	215 (50.4)
	2	153 (35.8)
	≥3	59 (13.8)
Pregnancy complications[c]	Yes	59 (13.8)
Caesarean section	Yes	19 (4.4)

[a] Maternal educational level was coded "low" when mothers did not obtain any diploma, "middle" when they obtained a high school diploma, and "high" when they obtained a college or university degree.

[b] Maternal smoking status was categorized as "never smoker", "former smoker" when quitted smoking before pregnancy, and "smoker" when smoking continued during pregnancy.

[c] Pregnancy complications was defined as the experience by the mother of one or more of the following conditions during pregnancy: gestational diabetes, hypertension, infectious disease, pre-eclampsia, vaginal bleeding, and hyperthyroidism or hypothyroidism.

Table 2

Distribution of the weekly average air pollutant concentrations and temperature during the last 15 weeks of pregnancy, and distribution of traffic and land use indicators.

	Percentiles				
	5th	25th	50th	75th	95th
PM$_{2.5}$, µg/m^3	4.0	6.2	8.8	14.5	25.9
PM$_{10}$, µg/m^3	7.8	11.1	14.6	20.3	31.2
BC, µg/m^3	0.3	0.6	0.8	1.2	2.0
NO$_2$, µg/m^3	7.0	10.6	14.7	19.8	28.5
Temperature, ˚C	2.7	6.6	11.7	16.3	20.1
Distance to major road, m	27.3	106.2	322.8	747.2	1803.2
Distance-weighted traffic density, vehicles × km/day	58.2	101.8	146.7	341.0	1367.4
Greenness, %	41.0	54.1	67.0	74.4	82.3
Industrial area, %	0.9	2.6	4.1	6.7	12.3

PM$_{2.5}$, PM$_{10}$ = particulate matter with an aerodynamic diameter ≤ 2.5 and 10 µm respectively; BC = black carbon; NO$_2$ = nitrogen dioxide.

roads correlated well with distance-weighted traffic density (r = −0.68) and greenness correlated well with industrial area (r = −0.77), but correlations between traffic and land use indicators were weak (r from −0.11 to 0.11). Correlations of air pollutants with land use indicators (r from −0.65 to 0.49) were stronger than those with traffic indicators (r from −0.20 to 0.25), and these correlations were strongest for NO$_2$ (r from −0.65 to 0.49) and weakest for PM$_{2.5}$ (r from −0.25 to 0.16).

3.2. Main analysis

Adjusting for covariates and exposure during other trimesters, average third trimester PM$_{2.5}$, PM$_{10}$, BC, and NO$_2$ exposure was significantly associated with newborn SBP and DBP, with partial Pearson correlation coefficients ranging from 0.11 to 0.13 (Fig. 1). No associations were observed for first and second trimester exposures (Supplemental Figs. S1 and S2).

The lag-specific (weekly) DLM estimates of the association between newborn SBP and air pollutant exposures during the last 15 weeks of pregnancy are shown in Fig. 2. A significantly higher newborn SBP was observed in association with PM$_{2.5}$, PM$_{10}$, and NO$_2$ air pollution during the last 5 gestational weeks, and with BC during the last 4 gestational weeks. Similar results were found for newborn DBP (Supplemental Fig. S3). A 5 µg/m^3 increment in PM$_{2.5}$ exposure during the last 15 weeks of pregnancy was associated with an estimated cumulative change of 2.4 mm Hg (95% CI, 0.5 to 4.2) in SBP and 1.8 mm Hg (95% CI, 0.2 to 3.5) in DBP (Table 3). The corresponding changes for a 5 µg/m^3 increment in PM$_{10}$ were 2.1 mm Hg (95% CI, 0.8 to 3.4) for SBP and 1.5 mm Hg (95% CI, 0.3 to 2.7) for DBP. Estimated cumulative changes in newborn SBP and DBP did not reach significance for BC and NO$_2$.

Residential traffic indicators (distance to major road and distance-weighted traffic density) did not significantly associate with newborn BP (Table 3). An IQR (20.3%) increment in percentage residential greenness within 5 km radius of the residence was associated with a 1.2 mm Hg (95% CI, −2.5 to 0.1; *p* = 0.07) lower neonatal SBP and a 1.2 mm Hg (95% CI, −2.4 to −0.0; *p* = 0.05) lower DBP. An IQR (4.1%) increment in percentage industrial area within 5 km radius was associated with a 1.0 mm Hg (95% CI, 0.1 to 1.9; *p* = 0.03) higher neonatal DBP.

3.3. Secondary and sensitivity analyses

The 3-dimensional DLNM plots of the associations modelled using a nonlinear exposure-response function (Supplemental Figs. S4 and S5) suggested a flattening out of the slope (*e.g.* for PM and DBP) or even a negative slope (*e.g.* for PM and SBP) at very high concentrations. For concentrations below the 95th percentile, however, associations were fairly linear, and confidence intervals for estimates at higher concentrations were wide. Results from two-pollutant models (Supplemental Fig. S6) showed that estimates for PM$_{2.5}$ and PM$_{10}$ remained similar and (nearly) significant when BC, NO$_2$ or land use indicators were added to the model. In contrast, estimates for BC, NO$_2$, and land use indicators, were no longer significant in combination with another pollutant or land use indicator. None of the effect estimates was affected by adjustment for noise exposure.

Restricting the analyses to European newborns (n = 364) resulted in slightly stronger associations for all pollutants and land use indicators (Supplemental Fig. S7). Restricting the analyses to newborns from never smoking mothers (n = 275) resulted in considerably stronger associations than observed in the main models, whereas estimates for newborns from current and former smoking mothers (n = 152) were close to zero. Excluding mothers with pregnancy complications or caesarean section (resulting in n = 368 and n = 408 respectively) had little effect on estimates, but restricting the analyses to sleeping babies (n = 384) resulted in slightly stronger associations. Although cumulative estimates for BC and NO$_2$ did not reach
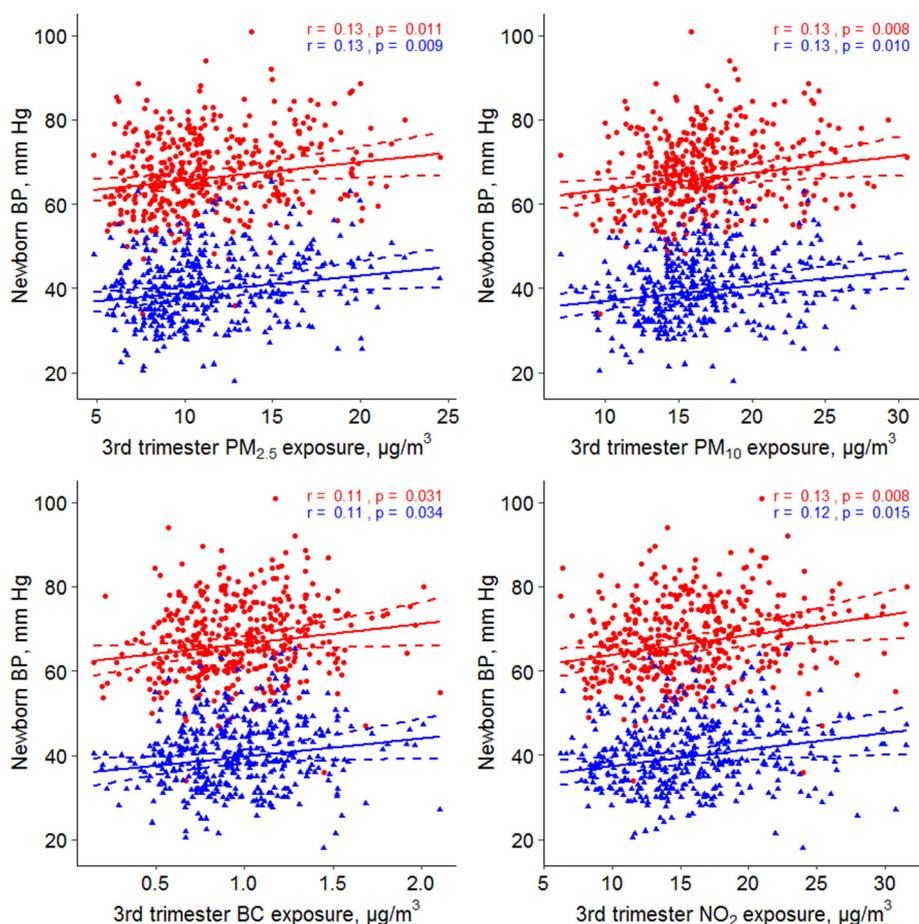
Fig. 1. Scatterplot of newborn systolic (red circles) and diastolic (blue triangles) blood pressure *versus* average $PM_{2.5}$, PM_{10}, BC, and NO_2 exposure during the 3rd trimester of pregnancy together with adjusted regression lines (solid lines) and 95% confidence intervals (dashed lines). Models were adjusted for long-term trends and seasonality, birth weight, newborn's sex, newborn's ethnicity, gestational age, newborn's age, newborn's condition, maternal age, maternal pre-pregnancy BMI, maternal education, maternal smoking status, parity, maternal blood pressure, and average $PM_{2.5}$, PM_{10}, BC, or NO_2 exposure during the first and second trimesters. $PM_{2.5}$, PM_{10} = particulate matter with an aerodynamic diameter ≤ 2.5 and $10\,\mu m$ respectively; BC = black carbon; NO_2 = nitrogen dioxide; r = partial Pearson correlation coefficient. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

significance in the main analysis, significant effects of these pollutants were observed in some subgroup analyses. In sensitivity analyses for DLM models, the use of an unconstrained lag structure, the adjustment for ambient temperature and month of BP measurement, and the DLM including average weekly exposures up to 36 weeks before birth resulted in similar cumulative (lag1-15) estimates (Supplemental Fig. S8).

4. Discussion

A higher BP in the first days of the neonate's life was associated with higher air pollution concentrations, higher percentage industrial area, and lower greenness at maternal residence. Flexible exposure-lag-response models (DLMs) revealed that newborn BP is susceptible to exposure to $PM_{2.5}$, PM_{10}, BC, and NO_2 during the last four to five weeks of pregnancy.

Associations between air pollution exposure and BP have been reported in adults (Cai et al., 2016) and children (Bilenko et al., 2015; Dong et al., 2014; Pieters et al., 2015; Sughis et al., 2012; Zeng et al., 2017). Only three previous studies have investigated offspring BP in association with prenatal air pollution exposure (Breton et al., 2016; van Rossem et al., 2015; Zhang et al., 2018), with only one of these focusing on newborn BP (van Rossem et al., 2015). van Rossem et al. (2015) reported a higher neonatal SBP in association with higher BC exposures during the third trimester (1.0 mm Hg; 95% CI, 0.1 to 1.8 for a $0.32\,\mu g/m^3$ increase in mean 90-day residential BC) (van Rossem et al., 2015). Associations between SBP and $PM_{2.5}$ were significant for average exposures up to 30 days before birth, but not for longer-term (60- to 90-days) averages (van Rossem et al., 2015). In a study on 3- to 9-year old children, Zhang et al. (2018) found that a $5\,\mu g/m^3$ increment in $PM_{2.5}$ during the third trimester of pregnancy was associated with a 3.49 (95% CI, 0.71 to 6.26) percentile increase in child SBP or a 1.47

(95% CI, 1.17 to 1.85) times higher risk of elevated BP. In children of around 11 years, exposure to NO_2 in the third trimester of pregnancy was associated with a higher SBP, but no association was found for $PM_{2.5}$ (Breton et al., 2016).

Residential greenness has been linked with BP in adults (Agyemang et al., 2007; Grazuleviciene et al., 2014) and children (Markevych et al., 2014), but we are not aware of any previous studies investigating newborn BP in association with maternal residential traffic and land use indicators during pregnancy. Similar to our results, Bijnens et al. (2017) demonstrated that a higher BP in adults was associated with lower residential greenness in the early life environment, but not with distance to major roads. Maternal stress could be an underlying mechanisms in the association between surrounding greenness and offspring BP. Contact with green space has been reported to be beneficial to mental health, particularly levels of stress (van den Berg et al., 2010), and higher levels of green space in residential neighbourhoods are linked with lower perceived stress and healthier cortisol levels (Roe et al., 2013). Furthermore, BP in 5- to 7-year old children has been linked with the presence of multiple psychosocial stressors during pregnancy (van Dijk et al., 2012). Lower levels of residential greenness may also reflect a higher exposure to traffic-related noise, which has been found to be associated with higher BP in adults (Foraster et al., 2014) and children (Liu et al., 2014). Estimates for land use indicators (and air pollutants), however, were robust to the adjustment for residential noise exposure in our study. Lastly, the association between greenness and newborn BP may be mediated by air pollutant exposure, as suggested by the decrease in the effect size for greenness when air pollutants (especially NO_2) are added to the model.

Are our current observations on the link between BP at birth and prenatal air pollution exposure supported by experimental animal studies? Exposure of pregnant mice to $PM_{2.5}$ during pregnancy induced in
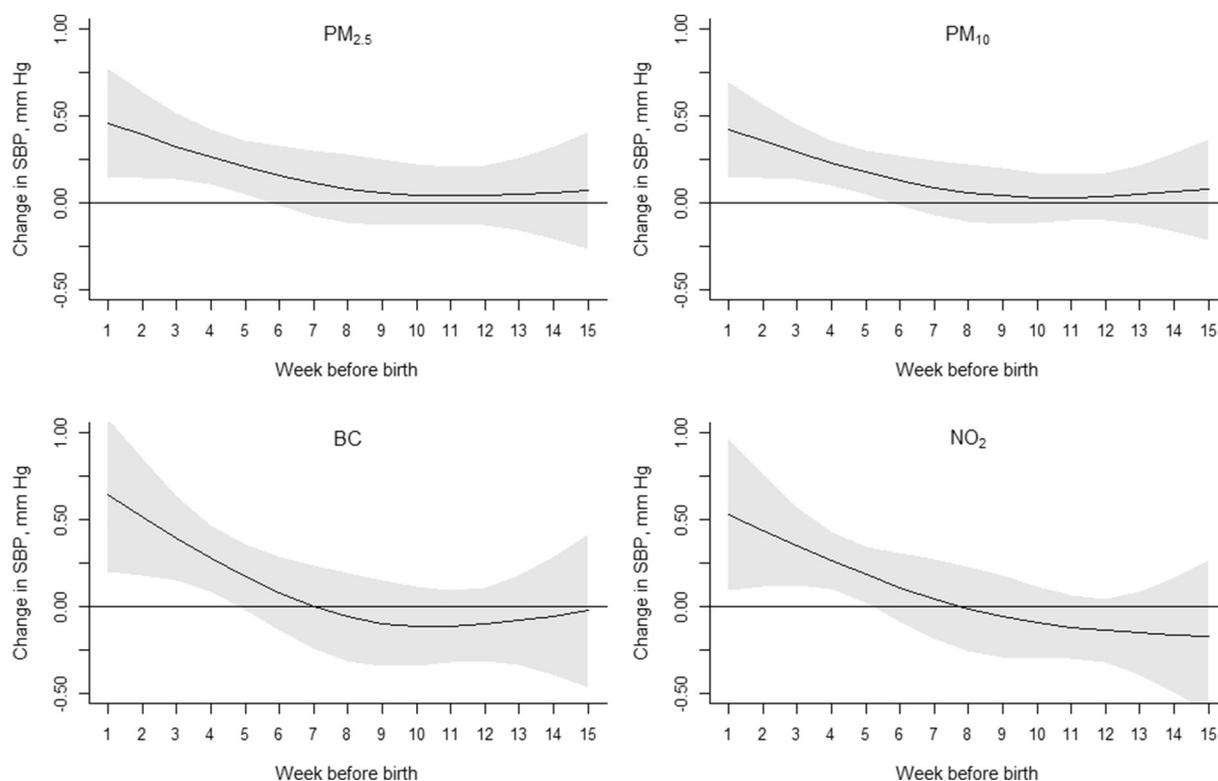
Fig. 2. Lag-specific DLM estimates of the association between newborn systolic blood pressure (SBP) and weekly average exposure to air pollutants during the last 15 weeks of pregnancy. Estimates are presented for a 5 µg/m³ increment in PM$_{2.5}$, PM$_{10}$, NO$_2$, and for a 0.5 µg/m³ increment in BC. Models were adjusted for long-term trends and seasonality, birth weight, newborn's sex, newborn's ethnicity, gestational age, newborn's age, newborn's condition, maternal age, maternal pre-pregnancy BMI, maternal education, maternal smoking status, parity, and maternal blood pressure. PM$_{2.5}$, PM$_{10}$ = particulate matter with an aerodynamic diameter ≤ 2.5 and 10 µm respectively; BC = black carbon; NO2 = nitrogen dioxide.

Table 3
Effect size estimates of newborn systolic (SBP) and diastolic blood pressure (DBP) associated with incremental changes in residential environmental exposures including air pollution of the last 15 weeks of pregnancy, traffic, and land use indicators.

Exposure	SBP, mm Hg	DBP, mm Hg
Air pollution		
PM$_{2.5}$ (+5 µg/m³)	2.4 (0.5; 4.2)	1.8 (0.2; 3.5)
PM$_{10}$ (+5 µg/m³)	2.1 (0.8; 3.4)	1.5 (0.3; 2.7)
BC (+0.5 µg/m³)	1.4 (−0.3; 3.1)	1.1 (−0.5; 2.7)
NO$_2$ (+5 µg/m³)	1.0 (−0.1; 2.1)	0.7 (−0.3; 1.7)
Traffic indicators		
Distance to major road (doubling)	−0.06 (−0.49; 0.37)	−0.01 (−0.40; 0.39)
Distance-weighted traffic density (doubling)	0.26 (−0.31; 0.83)	0.05 (−0.47; 0.57)
Land use in a 5 km radius		
Greenness (+20.3%)	−1.2 (−2.5; 0.1)	−1.2 (−2.4; −0.0)
Industrial area (+4.1%)	0.6 (−0.4; 1.6)	1.0 (0.1; 2.0)

For air pollution, the estimates represent the cumulative change in blood pressure (mm Hg) for a 5 µg/m³ increment in PM$_{2.5}$, PM$_{10}$, and NO$_2$, and for a 0.5 µg/m³ increment in BC during the last 15 weeks of pregnancy. For traffic indicators, the estimates are presented for a doubling in distance to major road and distance-weighted traffic density, and for land use indicators, the estimates are for an IQR (interquartile range) increment in area percentage (20.3% for greenness and 4.1% for industrial area). Models were adjusted for long-term trends and seasonality, birth weight, newborn's sex, newborn's ethnicity, gestational age, newborn's age, newborn's condition, maternal age, maternal pre-pregnancy BMI, maternal education, maternal smoking status, parity, and maternal blood pressure. PM$_{2.5}$, PM$_{10}$ = particulate matter with an aerodynamic diameter ≤ 2.5 and 10 µm respectively; BC = black carbon; NO$_2$ = nitrogen dioxide.

the offspring cardiac systolic and diastolic dysfunction as a result of cardiac remodelling by increase of left ventricle end-systolic and end-diastolic diameters (Gorr et al., 2014). Furthermore, the same research team demonstrated that *in utero* exposure to PM$_{2.5}$ triggers acute inflammatory response, chronic matrix remodelling, and alterations in Ca^{2+}-handling proteins resulting in global cardiac dysfunction in adult mice (Tanwar et al., 2017). Long-term exposure of mice to ambient levels of air pollution has also been associated with alterations in placental functional morphology (Veras et al., 2008).

Like polluted ambient air, environmental tobacco smoke is largely composed of an aerosol of particles derived from combustion (Pope III et al., 2009). In line with our observations on ambient prenatal air pollution exposure, several studies have demonstrated an increase in newborn SBP or DBP in association with *in utero* exposure to tobacco smoking (Bruin et al., 2010; Cohen et al., 2010; Geerts et al., 2007; Oken et al., 2005). Moreover, maternal smoking during pregnancy increases offspring BP in late adolescence (Hogberg et al., 2012). Furthermore, smoking during pregnancy leads to long-lasting 'reprogramming' of infant's BP control mechanisms (Cohen et al., 2010).

Neonatal BP increases may reflect early life changes in the large arteries and microvasculature, changes in autonomic imbalance and/or endothelial dysfunction due to increased oxidative stress. Previously, our research group reported larger nitrosative stress in placental tissue due to air pollution exposure, but this was driven by exposures earlier in pregnancy (Saenen et al., 2016). The health implication of increased neonatal BP and its potential persistence later in childhood remains to be elucidated in the follow-up part of the ENVIR*ON*AGE birth cohort at the age of 4 years, which includes exhaustive cardiovascular phenotyping such as arterial stiffness, elasticity, and microvasculature measurements. Studies tracking BP over time (Fuentes et al., 2002; Hao et al., 2017; Oikonen et al., 2016) and the Bogalusa Heart Study (Bao et al., 1995) in the USA demonstrated that childhood BP levels at or

above the 80th percentile, *i.e.* not necessarily in hypertensive ranges, were associated with an increased prevalence of elevated BP during adulthood.

A strength of our study is the relatively large sample size, representative for the reproductive segment of the Flemish population of Belgium (Janssen et al., 2017). In order to eliminate investigator-dependent bias, all BP measurements were performed by one researcher, using an appropriate cuff size and the same validated and automated device for all newborns. BP measurements were performed within 96 h after birth in a standardized way between feedings and the newborns mostly (90%) in a sleeping state. Another strength of this study is the availability of daily residential air pollution concentrations from pre-conception onwards which enables us to explore the impact of air pollution exposures during different exposure windows (Janssen et al., 2017). The use of DLM on weekly air pollution averages provides a more detailed picture of the exposure-lag-response association compared to the use of trimester-specific averages (Wilson et al., 2017), which enabled the identification of the last four weeks as a critical and sensitive period for the association between air pollutants and newborn BP.

Despite all the efforts to organize the BP measurements in between feedings and when the newborn is asleep, we were not able to successfully measure BP in 40% of the newborns recruited during the study period. Characteristics of these mother-newborn pairs, however, were similar to those from the included pairs, except for the higher birth weight in the final study population (which did not include preterm births). Another limitation is the potential misclassification of exposure. Our results are based on outdoor exposure at the maternal residence and thus not accounting for personal exposure, exposures at work or time spent outside the residence. Therefore, the air pollution levels assessed at the home address may not accurately reflect the actual exposures levels. It should, however, be mentioned that the model used for estimating the residential exposure has recently been shown to associate with a urinary biomarker of internal dose of nano-sized black carbon particles (Saenen et al., 2017).

5. Conclusion

Third trimester prenatal air pollution exposure, especially during the last five weeks of pregnancy, is associated with increased systolic and diastolic BP in the newborn. Maternal residential greenness during pregnancy is likely to decrease BP of the newborn, whereas living near an industrial area may increase neonatal BP.

Acknowledgment

Declaration of interests

All authors have completed the Unified Competing Interest form http://icmje.org/conflicts-of-interest/ (available on request from the corresponding author) and declare: no support from companies for the submitted work; no relationships with companies that might have an interest in the submitted work in the previous 3 years; no other financial relationships that may be relevant to the submitted work.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.05.047.

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